TREATMENT OF RENAL TUMOURS
A SUMMARY OF THE SIOP-RTSG 2016 UMBRELLA GUIDELINES (VERSION II)

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This document is dedicated to and free available for the treatment of children with renal cancer. If your country considers to use it, please consider to initiate your country within the SIOP-RTSG Association, and to register your patients in the SIOP-RTSG registry, in order to enhance the knowledge based on international cohort studies. (Please contact us: SIOP-Umbrella-DM@prinsesmaximacentrum.nl)
At the moment (November 2022, 25 countries (Europe, Asia and South America) are participating in UMBRELLA). See at https://siop-rtsg.org/

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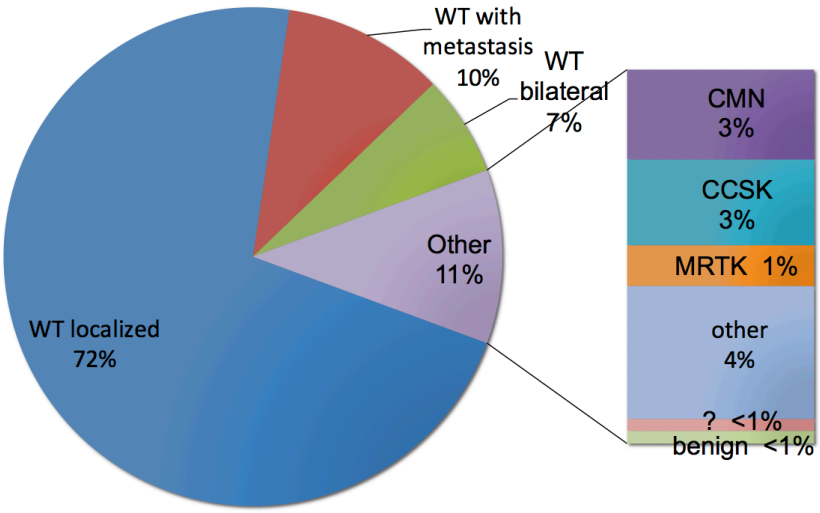
1. Background and Rationale

Childhood renal tumours are relatively uncommon, accounting for ~5% of all paediatric malignancies. Thus, nearly 1000 children are diagnosed in Europe each year. Of these tumours, around 80–90% are thought to be Wilms tumours, whereas other renal tumours (non-Wilms tumours), including clear cell sarcoma of the kidney (CCSK), renal cell carcinoma (RCC), malignant rhabdoid tumour of the kidney (MRTK), and congenital mesoblastic nephroma (CMN) are even less common. The exact incidence of non-Wilms tumours is unclear, owing to the probable under-registration of patients with these tumours in renal tumour protocols.

In Europe the vast majority of children are treated according to Renal Tumour Study Group of the International Society of Paediatric Oncology (SIOP-RTSG) protocols with pre-operative chemotherapy, surgery, and post-operative treatment dependent on stage and histology. Overall survival for WT approaches 90%, but a subgroup of WT, with high-risk histology and/or relapsed disease, still have a much poorer prognosis. Outcome is similarly poor for the rare non-WT, particularly for young children with MRTK, metastatic CCSK, and metastatic RCC.

The SIOP–RTSG has developed a protocol for diagnosis and treatment of childhood renal tumours, UMBRELLA SIOP-RTSG 2016 (referred to as the UMBRELLA protocol), to continue international collaboration in the treatment of childhood renal tumours. The UMBRELLA protocol succeeds the SIOP−2001 protocol. The name UMBRELLA signifies the ambitious aim to collect information concerning all paediatric primary renal tumours in a comprehensive multidimensional data registry, which includes embedded review of diagnostics, standardized biobanking, and treatment recommendations. The UMBRELLA protocol will support integrated biomarker and imaging research, with a particular focus on assessing the independent prognostic value of genomic changes within the tumour (chromosomal gain of 1q and the extent of its intratumoral heterogeneity) and the volume of the blastemal component that survives preoperative chemotherapy.
Childhood renal tumours are relatively uncommon, accounting for ~5% of all paediatric malignancies. Of these tumours, around 80–90% are thought to be Wilms tumours, whereas other renal tumours (non-Wilms tumours), including clear cell sarcoma of the kidney (CCSK), renal cell carcinoma (RCC), malignant rhabdoid tumour of the kidney (MRTK), and congenital mesoblastic nephroma (CMN) are even less common. The exact incidence of non-Wilms tumours is unclear, owing to the probable under-registration of patients with these tumours in renal tumour protocols.



Distribution of renal tumours in childhood. (CMN: congenital mesoblastic nephroma, CCSK: Clear cell sarcoma of the kidney, MRTK: Malignant Rhabdoid tumour of the kidney)

The UMBRELLA protocol addresses both Wilms tumours and non-Wilms tumours and there is a more comprehensive version available on the https://siop-rtsg.org/index.php/cb-login

2. Patient group

Treatment guidelines for Wilms tumours in the UMBRELLA protocol include recommendations for localised, metastatic (stage IV), and bilateral disease (stage V), for all age groups, and for relapsed disease. These recommendations were established by a multidisciplinary panel of leading experts on renal tumours within the SIOP–RTSG, including paediatric oncologists, radiologists, pathologists, surgeons, radiation oncologists, statisticians, and scientists involved in basic research. Thorough communications were undertaken with colleagues with similar expertise involved in the Children's Oncology Group (COG), to ensure all relevant evidence was applied when deciding how to implement the results of the SIOP−2001 randomized trial, which investigated the safety of omitting doxorubicin in treating stage II–III intermediate-risk Wilms tumours, and to refine recommendations for patients with Wilms tumour. Over the past 15 years, wide-ranging discussions on global strategies for children with renal tumours have evolved between SIOP–RTSG and COG during meetings and workshops. These conversations have resulted in sharing of data and knowledge, which has been used in the design of the current UMBRELLA guideline for diagnostics and treatment.

2.1. Clinical and laboratory Work-up

Full history:

- Symptoms/signs and reason for referral (screening, by chance, coincidence with other disease, tumour related symptoms) and duration of symptoms
- Performance status, general signs and symptoms and duration of symptoms
- History of in vitro fertilization and assisted reproductive fertility techniques and birth weight

- Existence of a syndrome/malformations and their specification including history of syndrome related surgeries including urological surgeries and other treatments
- History of prior malignancies/cancer treatment and coexisting diseases
- Family history of syndromes and malignancies
- Previous cancer treatment

Clinical assessment:

- Age, gender, bodyweight, length and dysmorphic signs
- Assessment by Lansky/Karnofsky Scale
- Blood pressure
- Body temperature and signs of infection
- Tumour palpability: position and size if palpable

Laboratory investigations:

- Blood/Serum:
    - Full blood cell count (FBC)
    - Creatinine, Blood urea nitrogen (BUN), LDH, liver enzymes, serum calcium
    - Coagulation parameters (factor about 5% of WT acquire von Willebrand's disease)
    - Blood group including Rhesus factor
    - Viral screening as a baseline
- Urine:
    - Urine metabolites of catecholamines (VMA/HVA) to exclude neuroblastoma
    - Protein, glucose, cells

2.2. Imaging diagnostics

2.2.1. Imaging techniques:

- **Abdominal Ultrasound:** Ultrasound is the mandatory first line imaging procedure in children with a suspected abdominal mass. The operator should be a radiologist or peadiatrician with training and experience in paediatric ultrasound and paediatric oncology. The complete abdomen must be examined with probes adjusted to the size of the child: in general, in this age group with a transducer of at least 5 MHz. The use of a high frequency probe (≥ 10 MHz) is mandatory for detailed examination of the contralateral kidney (also in prone and lateral position) in search for a bilateral tumour, nephrogenic rests or abnormalities that may affect renal function. The liver parenchyma must be screened for metastases. Ultrasound is the modality of choice for examining the renal vein and inferior vena cava in search for intravenous tumour thrombus, both with 2D-ultrasound and colour-Doppler and for real-time evaluation of the relationship of the tumour with adjacent organ.

- **Abdominal MRI:** Abdominal MRI is the first-choice complementary imaging procedure to ultrasound. Because of the lack of ionizing radiation and the excellent soft tissue contrast, MRI is preferred to CT. The complete abdominal cavity must be examined (from liver dome to pelvis included). The examination protocol should be performed by MR-radiographers trained in paediatric abdominal MRI. Sedation or general anaesthesia is recommended in young children according to local practice. Administration of gadolinium is recommended but not mandatory. MRI should

preferably be scheduled before biopsy of the tumour. **Register 3 dimensions before and after preoperative cytotoxic treatment for response assessment.**

- **Abdominal CT (only if MRI is not available):** Abdominal CT is the second-choice complementary imaging procedure to ultrasound. Administration of intravenous iodinated contrast is mandatory. A volumetric acquisition of 1 (portal venous) phase must be performed. The whole abdominal cavity must be assessed (complete liver and pelvis included).

- **Chest X-Ray:** Chest X-ray with AP (or PA) will be performed at diagnosis as a mandatory baseline procedure. A chest X-ray performed for positioning of the central venous line may serve as baseline test. During follow-up after end of therapy, chest x-ray will be performed in both AP (or PA) and lateral views.

- **Chest CT:** An unenhanced chest CT scan is a mandatory diagnostic procedure to assess lung metastasis. Intravenous contrast is not mandatory (but may be used if it is combined with an abdominal CT scan instead of abdominal MRI). Only, if pulmonary metastasis is detected at diagnosis, chest CT will be repeated before abdominal surgery.

- **Optional and functional diagnostics imaging:** MIBG (If neuroblastoma cannot be ruled out, but VMA/HVA screening is the first step), MRI of the head (in MRTK, CCSK and/or focal neurology), Bone Scan/whole body MRI or PET-scan (CCSK), Echocardiography (in all patients planned to receive doxorubicin), MAG3-Scintigraphy (optional to evaluate the side-specific function of remaining renal tissue in specific cases before surgery).

2.2.2. Classification of lung lesions:

Nodule(s) of ≥ 3-5 mm are classified as lung metastases. These patients are to be treated with preoperative AVD. Re-assessment of the lung lesions prior to tumour nephrectomy is indicated in order to direct postoperative treatment according to response.

Nodules of 1-2 mm are not classified as lung metastases and will be treated with 4 weeks of preoperative AV, as are localized tumours. They need to be reassessed prior to nephrectomy with chest CT.

Lung nodules with the following characteristics will be recorded

- Non-calcified
- Round shaped
- Sharply marginated

Pulmonary lesions different from lung metastases:

- Linear-shaped pulmonary opacities consistent with atelectasis.
- Ground glass, ill-defined or diffuse alveolar pulmonary opacities consistent with inflammatory or infectious disease.
- Calcified pulmonary nodules consistent with granulomas.
- Triangular or trapezoidal perifissural or subpleural densities, consistent with lymph nodes.

Classification of round solid nodules with sharp margins according to diameter:

1 – 2 mm
3 – 5 mm
6 – 10 mm
> 10 mm

2.2.3. Cutting Needle Biopsy

Cutting/Core needle biopsies can be used to verify the radiologic diagnosis of renal tumours with 1.6% relevant complications such as tumour bleeding, rupture and needle track recurrence. Indications, in case of radiological and/or clinical doubt.

Summary of recommended indications for diagnostic core needle biopsy of renal neoplasms in children, adolescents and young adults **without features of genetic predisposition**.

	Features typical of WT (i.e., NOT requiring biopsy) **ALL** criteria required	Biopsy NOT recommended if ANY of these criteria met	Biopsy recommended if ANY of these criteria met	Indication to be discussed in Tumour board meetings if ANY of these criteria
Clinical Criteria	Age greater than or equal to 6 months but less than 7 years No infectious syndrome	Age under 3 months (upfront surgery indicated)	Age 10 years and older Age between 7 and 10 years tumour volume* <200ml	Age greater than or equal to 3 months but less than 6 months Infectious syndrome Urinary tract infection
Radiological criteria	Obvious renal origin Unilateral tumour Solid or mixed (solid and cystic) tumour No calcification Metastases absent or limited to lungs and age over 2y	Totally cystic tumor (primary surgery, if indicated) Bilateral kidney tumors and / or Nephroblastomatosis (age greater than or equal to 6 months but less than 7 years, presumptive chemotherapy if age compatible)	Uncertain renal origin Atypical metastases: Bones (any age) CNS (any age) Pulmonary (under 2 years)	Intra-tumour calcifications Tumour volume under 80 mL Major necrotic adenopathy Bilateral kidney tumours and 7 years or older
Biochemical criteria	Normal urinary catecholamines Normal serum calcium LDH less than 4x upper limit of normal		Elevated urinary catecholamines Hypercalcemia and age under 4 y	LDH over 4x upper limit of normal

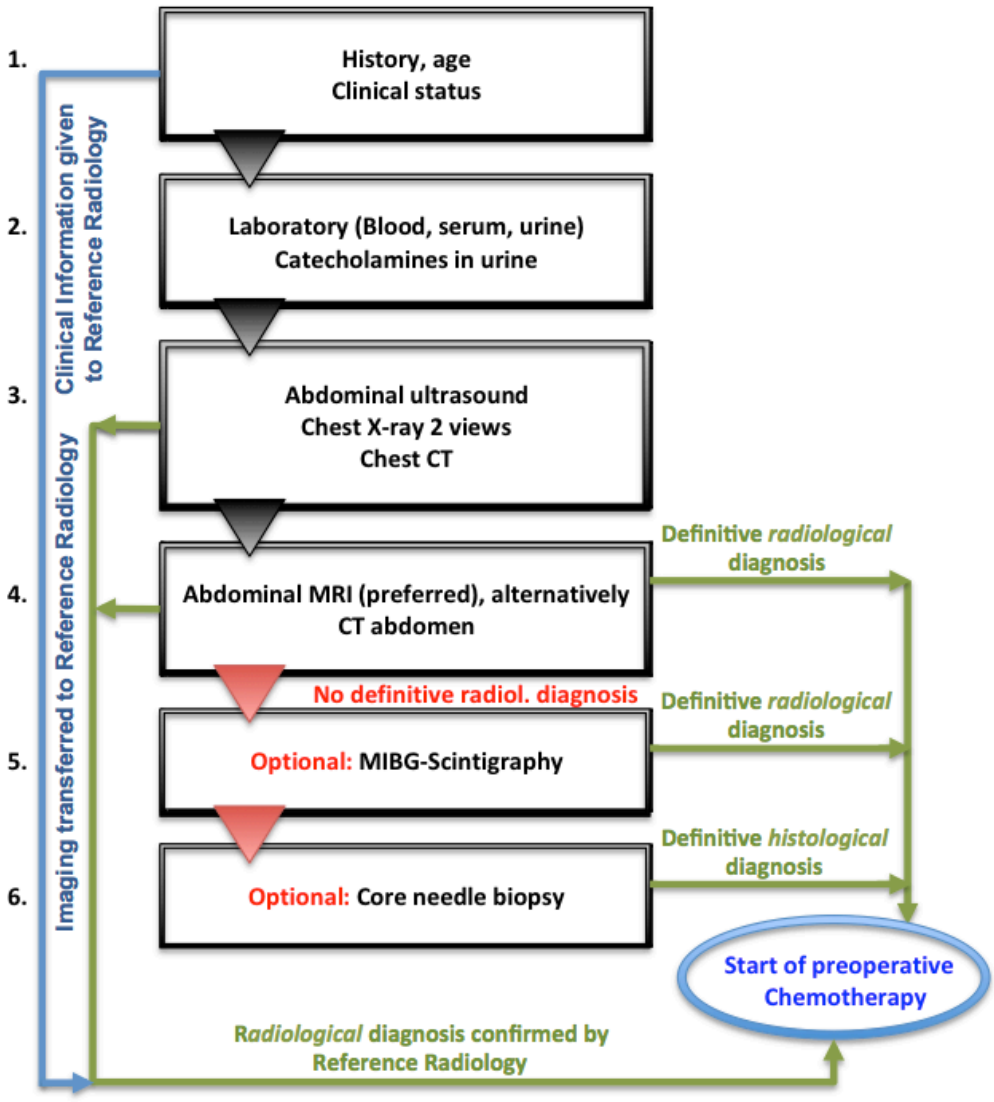
Note : (*) Tumour volume = length (cm) x width (cm) x thickness (cm) x 0.523

Jackson TJ, Brisse HJ, Pritchard-Jones K, Nakata K, Morosi C, Oue T, Irtan S, Vujanic G, van den Heuvel-Eibrink MM, Graf N, Chowdhury T; SIOP RTSG Biopsy Working Group. How we approach paediatric renal tumour core needle biopsy in the setting of preoperative chemotherapy: A Review from the SIOP Renal Tumour Study Group. Pediatr Blood Cancer. 2022 Sep;69(9):e29702.

Procedural Recommendations:

- Under general anaesthesia
- Ultrasound or CT guidance – make sure to sample solid and viable tumour, avoid sampling of necrotic or cystic areas
- Co-axial technique is mandatory
- Retroperitoneal biopsy tract only (do not use transperitoneal access)
- Use cutting needles with a size of 18 or 16 Gauge to guarantee sufficient tissue for pathologic differentiation.
- *Open* biopsies are not advised (consequence is that it will automatically become stage III)

2.2.4. Flow diagram of initial diagnostic work-up*



**Patients included in the UMBRELLA protoco will benefit from central radiology and pathology review*

2.2.5. Timeframe of diagnostic work-up:

All renal tumour patients older than 6 months and younger than 16 years will be treated with chemotherapy before surgery. This indicates that 2 diagnostic moments are important, i.e. at presentation (day 0) and before surgery (day 28 in stage I-III, and day 42 in stage IV).

Standard investigations during the pre-operative phase in clinically localized disease

	Investigations	(Day 0)	Day 15	Day 28
Stage I-III	*Abdominal ultrasound*	*X*	*X*[4]	*X*
	CT chest including a standard chest X-Ray AP or PA view	*X*		
	MRI abdomen (DWI[1]*) (alternative: CT, if MRI is not available)*	*X*		*X*
	MRI cerebrum[2]	*Histological proven MRTK or CCSK*		
	Core needle biopsy[3]	*X*		
	Urine VMA/HVA, (MIBG scintigraphy)*	*X*		
	Full Blood Count prior each course of chemotherapy			
	Serum (ASAT, ALAT, Urea, creatinine, creatinine clearance, electrolytes)	*X*		*X*
	Viral screen, Blood group Rhesus, coagulation	*X*		

[1] research, [2] in case of MRTK and CCSK; brain US to consider in infants, [3] only in case of serious doubt of WT (based on age, clinical presentation and imaging, see also radiology chapter). Response according to RECIST criteria (www.recist.com). [4] before chemotherapy at week 3, if tumour increases : stop chemotherapy and consider early surgery.
** Only if imaging is not conclusive for Wilms tumour or VMA is elevated*

Standard diagnostics during the pre-operative phase in stage IV

	Investigations	***(Day 0)***	***Day 15***	***Day 28***	***Day 42***
Stage IV	*Abdominal ultrasound*	*X*		*X*[4]	*X*
	CT chest including a standard chest X- Ray AP ***or*** *PA view*	*X*			*X (only CT)*
	MRI abdomen (DWI[1]*) (alternative CT, if MRI is not available)*	*X*			*X*
	MRI cerebrum[2]	*Histological proven MRTK or CCSK*			
	Core needle biopsy[3]	*X*			
	Urine VMA, HVA (MIBG scintigraphy)*	*X*			
	Full Blood Count prior each course of chemotherapy				
	Serum (ASAT, ALAT, Urea, creatinine, electrolytes)	*X*		*X*	*X*
	Viral screen Blood group Rhesus, coagulation	*X*			
	Cardiac ultrasound	*X*			*X*

[1] research, [2] in case of MRTK and CCSK; brain US to consider in infants, [3] only in case of serious doubt of WT (based on age, clinical presentation and imaging). Response according to RECIST criteria. [4] if tumour increases stop chemotherapy and consider early surgery.

Postoperative investigations after renal surgery in patients that received pre-operative chemotherapy

	Investigations	*Week 1 after surgery*	*Week 6*	*Week 10*	*Week 24 (if applicable)*	*End of therapy*
Stage I-IV	*Abdominal ultrasound*	*X*	*(X)*	*X*	*(X)*	*X*
	CT chest [4]			*X*[2,3]		*X*[4]
	MRI abdomen (alternative CT, if MRI is not available)	*No longer needed, US is sufficient*				
	Full Blood Count prior each course of chemotherapy and additionally according to local practice					
	Serum (Urea, creatinine, electrolytes, ASAT, ALAT)	*X*	*X*	*X*	*X*	*X*
	Cardiac ultrasound [5]			*X*		*X*
	MRI cerebrum [7]	*X*				X
	Technetium bone scan or whole body MRI or FDG-PET [8]	*X*				X
	Audiogram [9]	*X*		*X*		X
	Clinical geneticist[10]	*X*				

[2] in case of stage IV and only chest CT, [3] only in case of non-CR in stage IV after surgery and only chest CT, [4] Chest CT if still persistent disease after neoadjuvant chemotherapy otherwise X-Ray, [5] from 200 mg/m^2 doxorubicin on, [7] in MRTK and CCSK, [8] in CCSK and RCC, [9] in case of carboplatin, [10] In case of bilateral disease or rhabdoid tumour.

Postoperative investigations in patients after primary surgery (i.e. without pre-operative chemotherapy)

	Evaluation	*Diagnosis (Day 0)*	*Week 1 after surgery*	*Week 6*	*Week 10*	*Week 24 (if applicable)*	*End of therapy*
Stage I-IV	*Central Radiology Review*	*X* [2]			*X* [3]		
	CT chest	*X*			*X* [2,3]		*X* [4]
	*Standard chest X-Ray AP **or** PA view*	*X*					
	Abdominal Ultrasound		*X*	*X*	*X*		*X*
	MRI abdomen	*X (before surgery)*					*X*
	Full Blood Count prior each course of chemotherapy and additionally according to local practice.						
	Serum (Urea, creatinine, electrolytes)	*X*	*X*	*X*	*X*	*X*	*X*
	Cardiac ultrasound [5]	*X*				*X*	*X*
	MRI cerebrum [7]		*X*				X
	Technetium bone scan or wholebody MRI or FDG-PET [8]		*X*				X
	Audiogram [9]		*X*		*X*		X
	Clinical geneticist[10]		*X*				

[2] in case of stage IV and only chest CT, [3] only in case of non-CR in stage IV at week 6 and only chest CT, [4] Chest CT if still persistent disease after neoadjuvant chemotherapy otherwise X-Ray, [5] after diagnosis from 200 mg/m^2 doxorubicin on, [7] in MRTK and CCSK, [8] in CCSK and RCC, [9] in case of carboplatin, [10] In case of bilateral disease or rhabdoid tumour.

2.3. Pathology

The **intact** surgical specimen should be brought to the laboratory **without being opened by the surgeon**. It should be dealt with by the pathologist as soon as it arrives in the lab to minimise degradation of RNA especially. The specimen should be examined as follows:

1. ***Weigh***, ***measure*** and ***photograph*** the whole specimen. Look carefully for ruptures and fissures and locate any suspicious areas and/or ink them 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 their site.
3. ***Identify renal vein, artery and ureter*** and take transverse section block of each at/near the resection margin.
4. ***Ink*** the surface of the whole specimen and renal sinus with Indian ink and let it dry **before** opening the specimen. This is a critical step and should always be done, otherwise it might be impossible to stage the tumour accurately 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 and record the macroscopic appearance. **It is critical to accurately measure the tumour in all three dimensions - this will be used for calculating volume of tumour and blastema.**
7. **Assess the percentage of a necrotic tumour**.
8. Describe and photograph the multicystic cut surface, if present.
9. ***Samples required*** for biology studies should be taken (please see below)
10. **The specimen** should be ***fixed*** in 10% 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.
11. **The samples for histological examination should include**:
    a) at least one longitudinal slice of tumour and kidney surface, completely sampled

    In addition, please sample the following:
    b) macroscopically different areas of the tumour
    c) 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)
    d) sinus lymph nodes when present
    e) other lymph nodes
    f) 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
    g) each nodule away from the main mass (in multifocal tumours)
    h) tumour-kidney interface
    i) tumour-kidney capsule
    j) areas of the capsule that are suspected of being invaded by the tumour
    k) areas of perirenal fat suspected for tumour infiltration (important for assessment whether the tumour is completely resected)
    l) areas of adhesions of the tumour to surrounding tissues
    i) at least 2 blocks with normal kidney and blocks from abnormal looking areas in the renal tissue

In summary

- **Weigh and accurately measure the specimen and tumour (in all 3 dimensions)**
- **Sample tumour according to the Guidelines (above)**
- **Assess the percentage of chemotherapy-induced changes on gross and histological examination**
- **Assess the percentages of viable tumour components.**

3. Overall guidelines for chemotherapy

No treatment course including ActinomycinD, Doxorubicin, Carboplatin, Cyclophosphamide or Etoposide should be initiated if the absolute neutrophil count is < 1.000/µl or the platelet count is < 100.000/µl.

3.1. Drugs and dosage:

a. **Actinomycin D**

Formulation: Dry powder vials to dissolve with sterile water, containing 0.5 mg dactinomycin

Application: Intravenous infusion

Not given in children weighing less than 5 kg.

No single dose should exceed 2000 µg (2mg).

Known important incompatibilities: doxorubicin, allopurinol, colchicine, probenecid, sulfinpyrazon

Side effects and main toxicities: Nausea, vomiting, stomatitis, mucositis, diarrhoea, myelosuppression, immunosuppression, fever, alopecia, transient increase of liver function (up to global liver failure, veno-occlusive disease (VOD) (2% of cases), hypocalcaemia, allergic reaction.

b. **Vincristine**

Formulation: Ready-to-use vials, one vial contains vincristinesulfate 1mg (= 0.895 mg Vincristine) plus lactose

Application: Intravenous infusion

No single dose should exceed 2mg.

Known incompatibilities: All solutions with a pH other than 3.5 to 5.0.

Side effects and main toxicities: ONLY FOR INTRAVENOUS INFUSION, peripheral neuropathy, central neurotoxicity, constipation, VOD, poly-, dysuria, inadequate ADH secretion, transient myelosuppression, reversible hair loss, necrosis after paravenous injection, in combination with cyclosporin A potential for severe neurotoxicity. Cross-reactivity with doxorubicin, daunorubicin, Actinomycin D, metramicin and mitomycin.

c. **Doxorubicin**

Formulation: Dry powder and saline solution for dissolving, one vial contains 100mg doxorubicinhydrochlorid

Application: Infusion over 2-6 hours

Total cumulative dose given should not exceed 300 mg/m^2.

Important incompatibilities: allopurinol, aluminium, cephalotin, gancyclovir, diazepam, fluorouracil, furosemide, heparin, hydrocortisone, methotrexate, natrium-hydrogencarbonat, piperacilin, theophylin.

Side effects and main toxicities: Transient myelosuppression, reversible hair loss, cardiotoxicity (acute arrhythmias and late cardiomyopathy), nausea and vomiting, mucositis, transient increase in liver function tests, allergic reactions, paravasation necrosis, in cases of doses excessive of a maximum cumulative dose 400mg/m2 the risk of cardiomyopathy arises without existing risk factors. In acute cardiomyopathy within 24

to 48 hours arrhythmias, extra systoles, ECG changes which are in general reversible. A minor side effect is red discoloration of the urine.

d. **Etoposide** (VP-16) or **Etoposide phosphate**

Formulation: Dry powder vials to dissolve with sterile water, 5% dextrose or normal saline.

Application: Infusion

Total cumulative dose given should not exceed 2700 mg/m^2. Except for patients with stage IV, arm B and C and for patients with relapse.

Important incompatibilities: amphotericin B, cefepime, chlorpromazine, imipenem, methylpred-nisolone, mitomycin. Interaction with coumadin and derivatives.
Side effects and main toxicities: myelosuppression, reversible hair loss, fever, hypotension, anaphylactic reactions, nausea and vomiting, diarrhea, mucositis, hepatic enzyme elevation, secondary malignant disease, rarely myalgia, central nervous system disturbances, peripheral neuropathy, in isolated cases acute leukaemia, cardiac dysrhythmias, heart attacks, Stevens-Johnson-Syndrome.

e. **Carboplatin**

Formulation: Vials with 5ml, 15ml, 45ml containing carboplatinum 50mg, 150 mg, 450mg. Solution in dextrose 5%

Application: Infusion

Important incompatibilities: aluminium, amphotericin B, Sodium-Bicarbonate
Side effects and main toxicities: Nausea, vomiting, painful gastrointestinal sensations, allergic reactions (pruritus, fever, redness, very rarely anaphylactic reaction with bronchospasm and cardio-depressive effects), transient myelosuppression, change of taste, rarely optic neuritis, auditory and peripheral neuropathy, ototoxicity, transient increase of liver function tests.

Nephro-toxicity is of importance at high doses and in patients with prior renal dysfunction. Precautions: reduction of the dose in proportion to creatinine clearance. **Total cumulative dose given should not exceed 3600 mg/m^2, except for patients with relapse, where the cumulative dose may be higher depending on primary treatment with carboplatin.** Dose reduction according to Calvert formula: Dose [mg] = 4 x (GFR [ml/min] +15 x BSA [m^2]) or for children according to the formula (modification after Newell): Dose [mg] = 4 x (GFR [ml/min] +0,36 BW [kg]). This results in an AUC for Carboplatin of 4 mg x min/ml/day.

f. **Cyclophosphamide**

Formulation: Vials of 100mg, 200mg, 500mg, 1,000mg available, dry powder vials plus saline solution vials.

Application: Infusion

Total cumulative dose 5400 – 11400 (18000 maximum in HR schema for stage IV) mg/m^2 (depending on schema)**.**

Important incompatibilities: amphotericin B, benzyl alcohol, induction of microsomal liver enzymes by phenobarbital, phenytoin, benzodiazepines, chloralhydrate or dexamethasone resulting in increased activity of cyclophosphamide, increased

cardiotoxicity with simultaneous application of anthracyclines.
Side effects and main toxicities: Transient myelosuppression, reversible hair loss, nausea and vomiting, haemorrhagic cystitis due to accumulation of acrolein in the urine, water retention, cardiotoxicity in high doses, VOD in high dose approaches, secondary malignancy, infertility. **Mesna** (Uromitexan®) needs to be given.

g. **Ifosfamide**

Formulation: Dry powder vials to dissolve with sterile water or vials with 4% Ifosfamide solution, vials as dry powder available 200, 500, 1,000, 2,000, 3,000 mg

Application: Infusion

Total cumulative dose given should not exceed 36 g/m².

Important incompatibilities: none
Side effects and main toxicities: transient myelosuppression, reversible hair loss, nausea and vomiting, haemorrhagic cystitis, encephalopathy (10% with agitation, nightmares, loss of consciousness and/or seizures), transient increased liver function tests, Fanconi-syndrome, CNS toxicity in up to 12% in phase II studies, in isolated cases cardiotoxicity. **Mesna** (uromitexan ®) needs to be given.

h. **Irinotecan**

Formulation: Vials 40 mg (2ml), 100 mg (5ml) or and 100mg (5ml)

Application: Infusion

Important incompatibilities: neuromuscular blocking agents, CYP3A-inducing anticonvulsant drugs (e.g., carbamazepine, phenobarbital, phenytoin) leads to reduced exposure to irinotecan, co-administration of ketoconazole resulted in a decrease in the AUC, drugs known to inhibit (e.g., ketoconazole) or induce (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin) drug metabolism by CYP3A4.
Side effects and main toxicities: The most significant adverse effects of irinotecan are severe diarrhea and extreme suppression of the immune system. **Recommendation regarding diarrhoe**: 5-7 days of cefixim and loperamide. Irinotecan recipients with a homozygous (both of the two gene copies) polymorphism in UGT1A1 gene, to be specific, the *28 variant, should be considered for reduced drug doses.

i. **Melphalan**

Formulation: Dry powder vials to dissolve with solution vials, vials as dry powder available: 50 mg

Application: Infusion over 1 hour (high dose chemotherapy regimen)

Important incompatibilities: Nalidixic acid: haemorrhagic enterocolitis, kidney function reduction if cyclosporine is given after stem cell transplantation.
Side effects and main toxicities: myelosuppression, reversible hair loss, nausea and vomiting, transient increased liver function tests, icterus, veno-occlusive disease (VOD), myalgia, rhabdomyolysis, exanthema, haemolytic anemia, interstitial pneumonia, lung fibrosis, arrhythmias.

Drugs should be stored and reconstituted according to the instructions given by the manufacturer. Adequate hydration should be given to all patients receiving chemotherapy, especially those under 1 year of age, as one factor to avoid veno-occlusive disease (VOD).

G-CSF

In case of severe neutropenia (very high risk treatment, relapse treatment), G-CSF can be given (5 µg/kg/daily; subcutaneous) starting 5 to 6 days after the last dose of chemotherapy and given until ANC ≥ 1000 and past the nadir of myelosuppression or a minimum of 1 week. **G-CSF** s**hould be stopped for 48 hours before starting of the next chemotherapy.**

3.2. Toxicity

3.2.1. Haematological toxicity

Hemoglobin level, WBC and platelet counts should be performed before each course of chemotherapy.

- **Neutropenia:** absolute neutrophil count (ANC) has to be above 1000/mm^3 to start a course with actinomycin D or doxorubicin, cyclophosphamide, ifosfamide, carboplatin. Vincristine may be continued without taking the ANC into account if the patient is clinically well.
- **Thrombocytopenia:** platelet count has to be > 100.000/mm^3 to start a treatment course. The course in progress should be interrupted if the platelet count falls below 50.000/mm^3 and in case of such a sudden fall, the patient should be monitored carefully for signs of VOD or sepsis/line infection, with daily full blood count and liver function tests. Transfusion of platelets is indicated always in case of haemorrhages.
- **Anemia alone** should be treated by transfusion if necessary (Hb <7 g/l). Anemia is not a reason to modify the treatment schedule.

If a course of treatment results in a nadir WBC count below 1500/mm^3 or in a nadir ANC below 1000/mm^3, associated with mucositis and/or fever or in a nadir platelet count below 50.000, associated with marked enlargement of the liver or haemorrhages:
The doses on the next course can be reduced to 2/3 and if the next course of chemotherapy is well tolerated full doses will be tried again in subsequent ones.

3.2.2. Neutropenic fever

Definition: Temperature (rectal) > 38,5° C or 4 x > 38,0° C within 24h with interval of more than 4h and neutrophil count < 500/µl

Diagnosis: Blood cultures each central line separately! Stool cultures, urinalysis
Throat, skin and mucosa (incl. anal) cultures
Virus isolation from lesions, stool and urine
Chest X-ray if respiratory symptoms, sonography of abdomen

Beside intensive diagnostics it is mandatory to start systemic antibiotic therapy immediately. The combination of antibiotics has to be selected according to typical pathogens of the hospital/institution. If pulmonary symptoms persist despite broad-spectrum antibiotic therapy for 72 hours bronchial lavage may be considered according to national guidelines. In case of suspected fungal disease add antifungal treatment. G-CSF can be given according to international recommendations.

3.2.3. Isolated gastrointestinal complications

- Vomiting particularly occurs for a few hours after the injection of actinomycin D or doxorubicin. It can usually be treated symptomatically and rarely requires treatment modifications.
- Diarrhea with or without vomiting particularly may occur after irradiation of the whole abdomen, in young children, and after irinotecan. This may require the treatment to be withheld for a few days and sometimes irradiation has to be abandoned. Supportive treatment may be required. In case of diarrhea after irinotecan loperamide might be needed.
- Constipation is common with vincristine. One has to see that loose stools are produced by prescribing laxatives. The drugs should be omitted in case of paralytic ileus and restarted at a 50% dose.

3.2.4. Hepatic complications:

Hepatic complications may occur with actinomycin D, vincristine or doxorubicin. Risk factors are nephroblastoma of the right kidney and irradiation of the whole abdomen or the right flank associated with mainly actinomycin D. Patients with signs of liver dysfunction should be monitored carefully.

Patients with venous occlusive disease (VOD), also referred to as SOS (sinusoidal obstruction syndrome) do need supportive treatment including the administration of defibrotide. Defibrotide is an anticoagulant with a multiple mode of action. Actinomycin D should not be given until the main abnormalities have returned to normal and half the dose should be given for the first following course. If the symptoms reappear during actinomycin D treatment, this drug should be withdrawn permanently. Vincristine may enhance hepatopathy.

If there are problems in interpreting or applying the protocol in children with hepatic disease, the National PI should be contacted for advice.

3.2.5. Exposure to infection with varicella or herpes:

Patients who develop varicella or herpes should receive aciclovir or valaciclovir and chemotherapy should not be started until one week after the control of the rash.

3.2.6. Cardiac toxicity:

There are no generally accepted guidelines for dose modifications of doxorubicin available. Monitoring with echocardiography should be done before the first administration of doxorubicin and thereafter at least every 100 mg/m^2 cumulative dose. Interruption of doxorubicin must be considered if fractional shortening falls below 28% or a reduction of > 10% is seen between two consecutive administrations. If seen, do not delay chemotherapy by giving VA alone. Repeat echo after 3 weeks and if improved, proceed with doxorubicin, but perform echocardiography before each administration of doxorubicin. A reduction above 20% of baseline is a reason to withhold doxorubicin until the fractional shortening has normalized to its initial value. Beware of anemia that may influence the fractional shortening.

Cardiac toxicity is more prone to occur in a patient who has received thoracic radiotherapy and has a left sided nephroblastoma stage III.

We recommend measuring Fractional Shortening, Ejection Fraction and if possible, the End Systolic Wall Stress to evaluate increasing afterload, which is a consequence of the wall muscle thinning, due to cardiomyocyte damage.

3.2.7. Neurological toxicity:

Muscular weakness and hyporeflexia are the main side effects of vincristine. Jaw pain, pain on swallowing and hoarseness may occur. In case of peripheral nerve palsies, foot drop, and severe neuritis one or two injections of vincristine should be omitted and the next dose decreased to 2/3. Vincristine neuropathy is more common in elderly patients.

In case of ifosfamide induced CNS toxicity Methylenblue (MB) is the treatment of choice until resolution or a significant improvement of symptoms is achieved. An EEG should be performed to confirm the typical anomalies related to ifosfamide. MB administration does not affect ifosfamide pharmacokinetics. The recommended dose of intravenous MB for treatment of ifosfamide-induced encephalopathy is 50 mg every 4 hours (1% aqueous solution over 5 minutes), whereas the dose for secondary prophylaxis of ifosfamide-induced encephalopathy is 50 mg every 6 hours, either intravenously or orally.

3.2.8. Bladder and renal toxicity:

Cyclophosphamide and ifosfamide can cause haemorrhagic cystitis if the details for its prescription are not met. The regular use of Mesna is indicated at 120 – 150% of the cytostatic drug dosage. In case of macroscopic and repetitive haematuria chemotherapy needs to be stopped. To increase diuresis infusion hyperhydration (3 l/m^2) and a diuretic drug (furosemide, mannitol) should be considered.

Dose modifications due to increasing serum-creatinin-levels or in case of tubulopathy should be considered.
Generally, the following steps are conceivable for ifosfamide:

1. Application of ifosfamide over 24 hours instead of short infusion
2. Dose reduction of ifosfamide of about 1/3
3. Give cyclophosphamide in exchange for ifosfamide

Similar strategies are possible in case of ifosfamide induced CNS-toxicity.

In case of carboplatin and reduction of the creatinine-clearance dose should be adjusted according to the Calvert or Newell formula.

3.2.9. Gonadotoxicity:

Gonatotoxicity occurs mainly after alkylating agents and radiotherapy of the abdomen. Fertility counselling and fertility preservation according to international standard guidelines should always be considered in patients at risk. This is especially necessary in those patients with whole abdominal irradiation (after spill), high total cumulative dosages of cyclophosphamide and before high-dose chemotherapy with stem cell rescue.

3.2.10. Major intolerance during pre-operative therapy

If during the pre-operative chemotherapy period the following complications occur, the patients should proceed to nephrectomy once they have recovered from the toxicity, assuming surgery is deemed feasible with acceptable risk, otherwise alternative pre-operative chemotherapy drugs may be considered. Usually, post-operative chemotherapy should still be given according to tumour stage and histology, unless the tumour is low risk histology and low stage and/or the clinical situation makes it unacceptable to continue further chemotherapy.

Alternative chemotherapy drugs to be considered should be discussed with the national coordinator. In some instances, (e.g. Act D) it may be acceptable to re-expose with reduced doses, for other drugs where cumulative dose is the key driver of toxicity (e.g. doxorubicin), the drug should be discontinued permanently.

a. Profound thrombocytopenia (thrombocytes < $50x10^9$/l) with or without haemorrhage associated with VOD/SOS: abdominal pain with diarrhea, ascites, edema, marked enlargement of liver, oliguria, fever and jaundice
b. Or with cutaneous erythema with desquamation compatible with Stevens Johnson syndrome
c. Severe neurological complications as intolerable paraesthesia with paralysis, convulsion, or amaurosis.

Overall regular monitoring of kidney function, cardiac ultrasound and audiology, during treatment, is recommended in cases treated with chemotherapy that increase the risk of toxicity.

3.3. Chemotherapy dose adjustments for infants and/or < 12 kg body weight

	< 5 kg (66% of kg dose)	**5 - 12 kg (dose in kg)**	**≥ 12 kg (full dose)**
Vincristine*	0.033 mg/kg	0.05 mg/kg	1.5 mg/sqm
Actinomycin D §	Omit #	30 µg/kg	45 µg/kg
Doxorubicin	1.1 mg/kg	1.7 mg/kg	50 mg/ m^2
Carboplatin	4.4 mg/kg	6.7 mg/kg	200 mg/ m^2 (TCD: x3 per course)
Cyclophosphamide	10 mg/kg	15 mg/kg	450 mg/ m^2 (TCD: x3 per course)
Ifosfamide	Omit # (because of neuro-toxicity)	66 mg/kg	2000 mg/ m^2 (TCD: x3 per course)
Etoposide (VP-16)	Omit # (because of ethanol) , Etopophos($) possible, 3.3 mg/kg	5 mg/kg	150 mg/ m^2 (TCD: x3 per course)
Melphalan		6.7 mg/kg	200 mg/ m^2
Irinotecan	1.1 mg/kg	1.7 mg/kg	50 mg/ m^2 (TCD: x5 per course, max: 100mg)

*No reduction of vincristine dose after primary surgery in stage I favorable histology; #: discuss with the national coordinator; § Actinomycin D is contraindicated for children <5kg and for children less than 3 months of age (defined as 91 days). **I**n some countries and on a case-per-case situation actinomycin-D can be proposed after a discussion in a MDT with cautious supportive care. **Doses in relapsed patients are partly different and explained in the chapter about relapses ; $ Calculation of Etopophos = 1.136 x VP1.**

If possible radiotherapy should be avoided in these young infants, because of the increased risk of serious long-term toxicity.

3.4. Supportive Treatment

Laxatives should be prescribed when vincristine is given to prevent constipation.

A **diet** containing no lactose, saccharose and gluten can be given as a prophylactic measure during abdominal irradiation.

Pneumonitis prevention: patients receiving the (very) high-risk regimens, during relapse treatment and those who are treated with lung irradiation should receive prophylactic oral cotrimoxazole or pentamidine nebulization for prevention of pneumocystis jiroveci pneumonia.

G-CSF: especially in the high-risk regimens it might be necessary to use G-CSF if bone marrow recovery if not sufficient before the next course. In the high-risk regimen for stage IV WT, G-CSF is highly recommended. Also in case of severe infection in aplastic patients one could decide to use G-CSF. For patients treated according to non-high-risk regimens, supportive treatment with growth factors is permitted but not considered as essential.

Transfusion: erythrocyte and platelet transfusions may be given according to national or centre recommendations.

4. Treatment guidelines for Wilms tumours

4.1. Staging

Upfront distinguish between local stage, stage IV and stage V. This determines pre-operative treatment. After surgery, staging based on the tumor and LN, as well as and histological subtype determines postoperative treatment.

For histological classification and staging (see appendix 2)

4.2. Localized Wilms Tumours (stage I – III)

4.2.1. Treatment recommendations localized WT

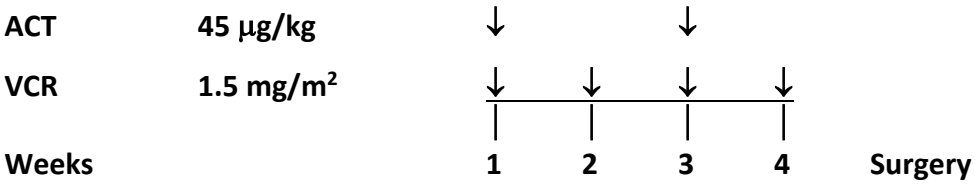
- In children below the age of 6 months, primary surgery is advised, but only after an interdisciplinary evaluation of the individual risks of tumour rupture against preoperative chemotherapy. All other patients are advised to be treated with VA
- Fine needle aspiration or tru-cut (core) biopsy, should be considered in case of serious doubt of WT.

4.2.2 Pre-operative chemotherapy

Two drugs (vincristine (VCR) and actinomycin D (ACT-D) x 4 weeks

- Vincristine: 1.5 mg/m^2 (max 2 mg) weeks 1, 2, 3, 4 (5th dose can be given if week 5 falls before planned surgery)
- Actinomycin D: 45 µg/kg (max 2 mg), weeks 1, 3

Both drugs are given by intravenous bolus.



Reassessment of the tumour by imaging at week 4

Surgery should be planned for week 5-6. In case of any delay (which is not advised) an extra dose of VCR is recommended.

4.2.3 Post-operative treatment

After surgery, the different histological subtypes of nephroblastoma and local stage of the tumour can be determined. Combined with the volume of the tumour (pre-operative scan), these prognostic factors will dictate post-operative treatment. In this SIOP protocol, tumour volume has been added as a risk stratification factor for a subgroup of nephroblastomas. Patients with a tumour volume of > 500 ml after preoperative chemotherapy and non-stromal or non-epithelial intermediate risk histology and local stage II or III will be treated more intensively with AVD. This decision is based on analyses of patients from SIOP 2001, which

demonstrated that tumour volume in that subset of patients, is a significant risk factor in case of only receiving postoperative VA. For patients with stage I intermediate risk or any stage with epithelial and stromal subtype, large tumour volume (500 ml) after pre-operative chemotherapy did not significantly affect the outcome.

		Tumour volume after preoperative chemotherapy	Stage I	Stage II	Stage III
Low Risk (only CN)		All	No further treatment	AV2	AV2
Intermediate Risk		≤ 500 ml	AV1	AV2	AV2 + RT
Intermediate Risk*		> 500 ml	AV1	AVD	AVD + RT
High Risk	**BT**	All	AVD	HR-1	HR-1 + RT
	DA	All	AVD	HR-1 + flank RT	HR-1 + RT

*Overview of postoperative treatment. (*with the exception of stromal and epithelial type, they are always treated independent of tumour size: AV1 in stage I and AV2 in stage II and III); CN: completely necrotic; A= actinomycin D, V= vincristine, D =doxorubicin (cumulative dose 250 mg/m²), HR = high risk histology; BT: blastemal type; DA: diffuse anaplasia; RT: radiotherapy; Note that for Stage 1 tumours with low risk histology, no postoperative chemotherapy is given. All tumours in this category should be send for urgent pathological central review (< 2 weeks for result)*

Stage I, Low Risk Histology: No further treatment

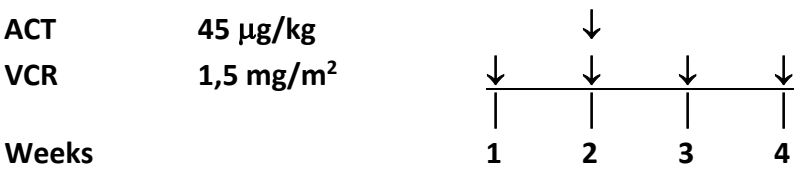
In WT with low risk histology and stage I no further treatment is given. It is important to have the result of central pathology review before any decision about postoperative treatment is made. In case of delay one further vincristine can be given.

Stage I, Intermediate Risk Histology: Regimen AV1

Important note: This treatment is given to all patients with local stage I and intermediate risk histology.

- Vincristine: 1.5 mg/m^2 (max 2mg) weekly for 4 weeks (4 doses in total). The first dose is to be given once peristalsis is established following surgery and within 21 days of the last dose of pre-operative chemotherapy.
- Actinomycin D: 45 µg/kg (max 2mg), at week 2 (day 7) of postoperative regimen. Delayed until the absolute neutrophil count is >1.0 x10^9/l or platelet count >100 x 10^9/l.

Both drugs are given by intravenous bolus.



Stage I, High Risk Histology: Regimen AVD

Important note: This treatment is also given for patients with stage II and III with focal anaplasia, mixed or regressive type and tumour volume > 500 ml after preoperative chemotherapy.

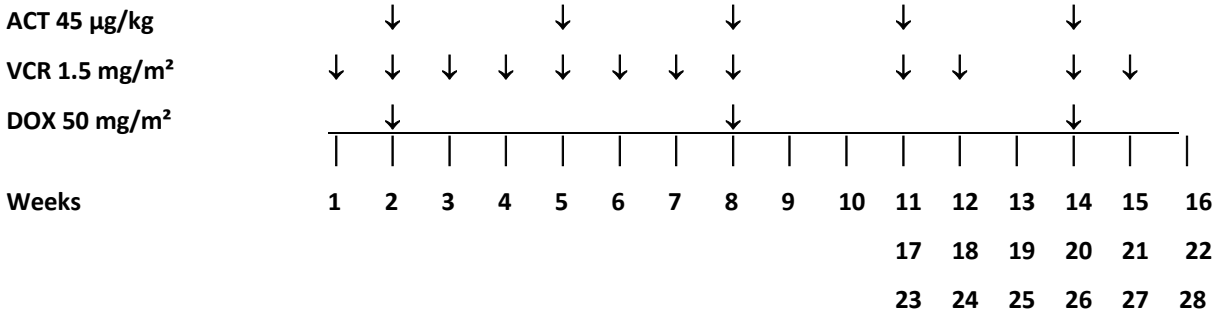
The total duration of the postoperative chemotherapy is 27 weeks.

- Vincristine: 1.5 mg/m^2 (max 2 mg) commenced when peristalsis established following surgery and within 21 days of pre-operative chemotherapy. Give weekly for 8 weeks (8 doses) and then on day one of weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27 (20 doses in total)
- Actinomycin D: 45 µg/kg (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

Both drugs are given by intravenous bolus.

- Doxorubicin: 50 mg/m^2 in 2-6 hours infusion every 6 weeks to start in week two concurrently with the first dose of Actimomycin D and the second dose of Vincristine. Subsequent doses are given at weeks 8, 14, 20 and 26 (5 doses in total – maximal **total cumulative dose: 250 mg/m^2**)

Actinomycin D and Doxorubicin should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l.



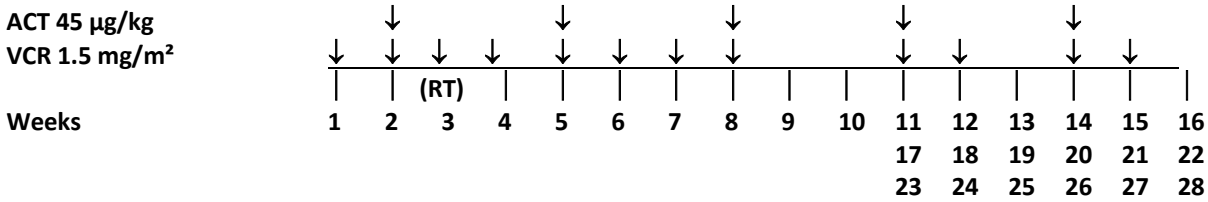
Stage II/III Low and Intermediate Risk Histology: Regimen AV-2

Important note: This treatment is given for all patients with local stage II and III. In case of focal anaplasia, mixed and regressive type with a tumour volume > 500 ml after preoperative chemotherapy doxorubicin is added to AV-2 (treatment with AVD as for high-risk stage I).
The total duration of the postoperative chemotherapy is 27 weeks.

- Vincristine: 1.5 mg/m^2 (max 2 mg) commenced when peristalsis established following surgery and within 21 days of pre-operative chemotherapy. Give weekly for 8 weeks (8 doses) and then on day one of weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27 (20 doses in total)
- Actinomycin D: 45 µg/kg (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

Both drugs are given by intravenous bolus. Reduce Actinomycin by 1/3 when radiotherapy is given within 14 days of administration.

Treatment should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l.



Note: Stage III tumours do need local radiotherapy

Stage II/III High Risk Histology: High Risk Regimen HR-1

Total duration of postoperative treatment is 34 weeks.

There are two alternating courses of chemotherapy given at 21-day intervals. Both combinations consist of 2 drugs. The first course starts as soon as the patient has recovered from surgery and clinical condition allows. This should be the case within 21 days after end of preoperative chemotherapy. Each cycle commences when absolute neutrophil count is > 1.0x10^9/l and platelet count >100 x 10^9/l provided rising WBC values.

- **Course 1:** Cyclophosphamide and Doxorubicin

  Cyclophosphamide: 450 mg/m^2 on days 1, 2 and 3 of weeks 1, 7, 13, 19, 25 and 31 (6 courses in total), infusion time 1 hour.

  Doxorubicin: 50 mg/m^2 on day 1 of weeks 1, 7, 13, 19, 25 and 31 (6 courses in total), infusion time 4-6 hour.

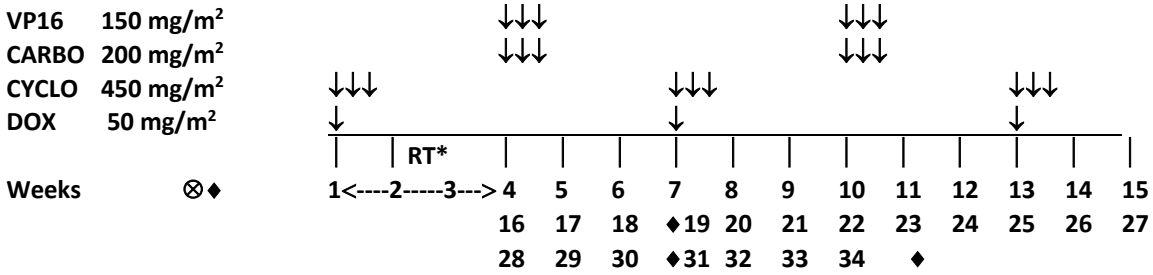
  Doxorubicin can be started after the first dose of cyclophosphamide.

- **Course 2:** Etoposide and Carboplatin

  Etoposide (VP16): 150 mg/m^2 on days 1,2,3 of weeks 4, 10, 16, 22, 28 and 34 (6 courses in total), infusion time 1 hour.

  Carboplatin: 200 mg/m^2 (or AUC = 2.65 see 14.2.1e) on days 1,2,3 of weeks 4, 10, 16, 22, 28 and 34 (6 courses in total), infusion time 1 hour. Consider dose reduction for carboplatin to 150 mg/m^2 in case of hematotoxicity after previous course.

Treatment should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l. G-CSF can be given if delays of treatment or grade 4 neutropenia did occur after the first 2 – 4 cycles. Use of prophylactic cotrimoxazole is recommended for HR regimens as PJP prophylaxis.



♦ = Echocardiography: at start of treatment, before week 19, 31 and at end of treatment
⊗ = GFR (measure at every third course, or more frequently if there is evidence of renal dysfunction
* = local irradiation not in stage II in case of blastemal subtype

Note: Only stage II tumours with diffuse anaplasia do need local radiotherapy (not stage II blastemal type. All stage III tumours do need local radiotherapy

4.3 Metastatic Wilms Tumours (stage IV)

4.3.1. General remarks

Biopsy of lesions suspected of **metastasis at other sites than the lungs**, including extra-abdominal lymph nodes, should be considered if reasonably feasible.
All lesions have to be re-assessed prior to nephrectomy. In case of incomplete response surgical clearance should be attempted where feasible and safe without risk of long-term morbidity.
If there is a discrepancy between the histology group of the renal tumour versus that of the resected nodules/metastases, the therapeutic strategy should be adapted to the "highest" risk of histology.
In principle and where possible flank and pulmonary irradiation should be administered at the same time (if indicated) to minimize toxicity of overlapping fields.

4.3.2. Pre-operative chemotherapy

Preoperative treatment for **patients having lung nodules** is stratified according to the size of lung nodules (see below). The same reasoning applies **not** to other nodules (e.g. liver, etc.).
Nodules of 1-2 mm are **not** classified as lung metastases and will be treated with 4 weeks of preoperative AV, as are localized tumours. They need to be reassessed prior to nephrectomy with chest CT.
Nodule(s) of ≥ 3-5 mm are classified as lung metastases. These patients are to be treated with **preoperative AVD**. Re-assessment of the lung lesions prior to tumour nephrectomy is indicated in order to direct postoperative treatment. In case of persisting nodules, it is recommended – wherever possible - to perform excision of nodules at time of tumor nephrectomy, in order to examine the histology and achieve a clearance of the chest disease if reasonable possible. If a complete clearance is not achievable, it is recommended to remove representative and accessible nodules. This will help directing therapy in the post-operative phase. If the histology of resected nodules rules out viable or necrotic tissue, consider treating as localized tumour. If histology shows viable or necrotic metastasis or biopsy is not feasible, continue according to Stage IV recommendations according to stage of local tumour, histology group and complete/incomplete resection of nodules (see below).

If a complete clearance of nodules is achieved at tumour nephrectomy in patients with LR or IR histology, this group of patients can receive a reduced cumulative dose of doxorubicin during postoperative treatment (AVD150).
Nodules ≥ 5 mm, are classified as lung metastases. These patients are to be treated with **preoperative AVD** chemotherapy and radiologically reassessed prior to nephrectomy to direct postoperative treatment according to the recommendations for Stage IV.
Patients having **metastasis at any other site** are to be treated with **preoperative AVD** and reassessed prior to nephrectomy. In case of incomplete response surgical clearance should be aimed for if feasible, safe and without long-term morbidity.

4.3.3. Pre-operative Reassessment of metastasis

Reassessment imaging of local tumour and metastases/nodules should be performed after preoperative chemotherapy and before surgery using the same technique as at diagnosis.
This table per se is not decisional for the treatment strategy but is useful for clinical-radiological qualification and analysis of outcome.

Target lesion (≥ 5 mm)	Non-target lesion (initially < 3 mm)*	Overall response
CR	CR	**CR**
No lesions > 2 mm and no new lesion	Non PD or SD and no new lesions	**VGPR**
> 30% response and no new lesion	Non PD and no new lesions	**PR**
SD and no new lesion	Non PD and no new lesions	**SD**
> 20% increase or new lesions	PD or new lesions	**PD**

Definition of metastatic response after preoperative chemotherapy: WT-Absolute-RECIST-Merge ("WARM") CT slice thickness 1mm, otherwise 2 x CT-slice thickness. Target lesions must be at least twice the size of the CT-slice thickness. Relative response is calculated based on the sum of all target-lesion's diameters initially and at re-assessment. In case of doubt, contact national Principal Investigator (PI).).* For target lesions of 3-5 mm, the only response categories are CR and non-CR. Example rounding: 5.4 mm is rounded down to 5 mm and 5.5 mm is rounded up to 6 mm.

4.3.4. Surgery

Nephrectomy and metastasectomy must be carried out as detailed in the surgery guidelines. Intralesional excisions with potential tumour spill must be avoided at all instances.

4.3.5. Post-operative chemotherapy

Surgical and radiotherapy guidelines are given in the other sections.

4.3.5.1. Post-operative chemotherapy for patients with nodules of <3 mm at time of tumor nephrectomy

Post-operative chemotherapy is given according to the results of the chest CT after pre-operative AV:

- If the chest CT shows **no nodules**, then postoperative treatment is given according to local stage and histology as in localized disease. Imaging controls of the chest is recommended every 8 - 12 weeks for the first two years after diagnosis
- In case of **persisting** nodules, at least a representative resection of nodules **should** be performed if feasible.
    - Only if histology rules out any viable or necrotic tumour, continue with treatment for localized disease according to stage and histology.
    - If biopsy shows viable or necrotic tumour treat with AVD 250 (meaning 150 mg/m^2 of cumulative dose of doxorubicin as no preoperative doxorubicin was given and reassess at W10. If persisting micronodules at that time whole lung RT is recommended
    - In case of diffuse anaplasia and blastemal type whole lung irradiation is indicated if metastases are histologically verified.
    - If biopsy is not feasible, continue with treatment for localized disease according to histology with a minimum of AV2, regardless of stage. Reassess at W10 and contact PI if persisting nodules.
- In case of **increasing size** of nodules, at least a representative resection of nodules **has** to be performed if feasible.
    - Only if histology rules out any viable or necrotic tumour, continue with treatment for localized disease according to histology with a minimum of AV2.
    - If biopsy shows viable or necrotic tumour treat with AVD 250 (meaning 150 mg/m^2 of cumulative dose of doxorubicin as no preoperative doxorubicin was given and reassess at W10. If persisting micronodules at that time whole lung RT is recommended
    - In case of diffuse anaplasia whole lung irradiation is indicated if metastasis are histologically verified (please contact the national PI).
    - If biopsy is not feasible, continue with treatment for localized disease according to histology, regardless of stage. Reassess at W10 and contact PI if persisting nodules.

4.3.5.2. Post-operative chemotherapy for patients with nodules of ≥ 3 mm

There are four post-operative scenarios:

A **Metastasis/nodules absent (CR or VGPR as defined in table) or completely removed by the surgeon and IR or LR histology.**

A1 Lung nodules ≥ 3 and ≤ 5mm at diagnosis and LR/IR histology.
A2 Lung nodules > 5 mm at diagnosis and LR/IR histology.

A3 Complete surgical removal of only non-malignant tissue: If viable or necrotic malignant tissue is ruled out and other non-malignant histology has been shown (no proof of previous metastases) and complete resection of lesions is performed, proceed with postoperative treatment according to local stage.

B Metastasis/nodules ≥ 3mm at diagnosis incompletely removed or multiple inoperable nodules and LR histology of the primary tumour.

C Metastasis/nodules ≥ 3mm at diagnosis incompletely removed or multiple inoperable nodules and IR histology of the primary tumour.

D Patients with high-risk histology of the primary tumour (including those that are in CR after preoperative chemotherapy and surgery).

Post-operative treatment of group A1

Group A1: Local Stage I/II/III, low and intermediate Risk Histology. Metastatic Clearance (CR) of lung nodules ≥3-5mm obtained by chemotherapy or completely removed by surgeon.

Recommended treatment: **Regimen AVD150**

Of Note: If complete response is achieved by resection of nodules and viable tumour is found **radiotherapy** is recommended. Otherwise contact PI. AVD150 is still recommended provided there has been radiological response to preoperative AVD. Patients with local stage III IR receive flank/abdominal irradiation.

Post-operative treatment of group A2

Group A2: Local Stage I/II/III, low and intermediate Risk Histology; Clearance (CR/VGPR) of nodules > 5 mm at diagnosis obtained by chemotherapy or completely removed by surgeon.

Recommended Treatment: **Regimen AVD250**

Of Note: If complete response is achieved by resection of nodules and viable tumour is found **radiotherapy** is recommended. Otherwise contact PI. AVD250 is still recommended provided there has been radiological response to preoperative AVD. Patients with local stage III IR receive flank/abdominal irradiation.

Post-operative treatment of group A3

Group A3: Local Stage I/II/III, low or intermediate risk histology with complete surgical clearance of other non-malignant histology:

Recommended Treatment**: According to local stage for localized disease**.

Note: Patients with local stage III IR receive flank/abdominal irradiation. No pulmonary irradiation is indicated.

Post-operative treatment of group B

Group B: Local Stage I/II/III, Low Risk Histology with residual nodules/metastasis after chemotherapy and surgery:

It is recommended to resect (one)/multiple representative nodules. Postoperative treatment is recommended according to histology. The following options are possible:

- If no proof of metastases (i.e. viable or necrotic malignant tissue has been ruled out), consider proceeding with treatment according to local stage (provided multiple, representative nodules have been resected and remaining nodules seem doubtful for metastases).
- If no viable tumour but necrotic nodules in a representative number of metastases, proceed with **regimen AVD250** postop for 27 weeks with cumulative dose of doxorubicin of 250 mg/m^2. Repeat CT assessment in week 10. If nodules are still visible: reconsider complete resection. No pulmonary radiotherapy.
- If viable tumour in resected lung nodules, proceed with **regimen AVD250.** and **radiotherapy to the lungs** In that case it is not a LR tumour and a switch to CDCV regimen may be considered.
- If representative lung nodules cannot be resected, proceed with **regimen AVD250** postop for 27 weeks with cumulative dose of doxorubicin of 250 mg/m^2 and carry out reassessment CT at week 10. If nodules are still visible, reconsider resection of at least 1 nodule. In addition, **consider lung irradiation** since the lung nodules may not be LR histology.

Of note: Local and lung irradiation should be given simultaneously to avoid overlapping fields. Irradiation may be postponed to week 10 for this purpose.

Post-operative treatment of group C

Group C: Local Stage I/II/III, Intermediate Risk Histology with residual metastatic disease.

It is recommended to resect (one)/multiple nodules. The indication of obtaining a complete surgical remission is depending on the number, size and location of the nodules. At least, if the number of nodules at diagnosis and at surgery is limited (<10 at diagnosis, < 6 at surgery) a complete resection of lung nodules should be discussed with reference surgeons.

Postoperative treatment is recommended according to histology and achieved clearance of metastasis. The following options are possible:

- If no proof of metastases (i.e. viable or necrotic malignant tissue has been ruled out), consider proceeding with **treatment according to localized disease** (provided multiple nodules have been resected and remaining nodules seem doubtful for metastases). If multiple nodules disappeared after preoperative AVD and remaining nodules are non-malignant, postoperative AVD250 can still be indicated.
- If no viable tumour but necrotic nodules in a representative number of nodules is found, proceed with **regimen AVD250** postop for 27 weeks with cumulative dose of doxorubicin of 250 mg/m^2. Carry out chest CT in week 10. If nodules are still visible: reconsider complete resection or pulmonary radiotherapy. In case of persistent viable lung metastasis at week 10 pulmonary radiotherapy is indicated.
- If viable tumour in resected nodules is found, proceed with **4 drugs regimen** postoperatively for 34 weeks and reassess at post-OP week 10. **Pulmonary radiotherapy** is indicated even if CR can be achieved at week 10.

- If representative nodules cannot be resected, proceed with **4 drugs regimen** postop for 34 weeks and reassess at post-OP week 10. **Pulmonary radiotherapy** is indicated if persisting nodules. In case of local stage III it is highly recommended to combine radiotherapy to the flank and to the lung to avoid overlapping fields. This can be delayed to post op week 10 if necessary.

Of note: Other sites of metastasis than the liver and lungs receive **radiotherapy** independent of response, if they cannot be resected completely. Patients with local stage III IR receive **flank/abdominal irradiation**.

Post-operative treatment of group D

Group D: Local Stage I/II/III with high-risk histology regardless of metastatic status and histologically proven metastasis.
This group has a particularly poor outcome despite intensive 4-drug treatment and therefore there has been reconsideration of the approach to treatment. Only few patients per year will fall into this group D and therefore local centres should ask the PI of stage IV to get advice for the best current treatment approach. Experts' opinion of the SIOP-RTSG board considers the approach as depicted in Appendix 6 as the best available treatment option, but alternative treatment options can be discussed.

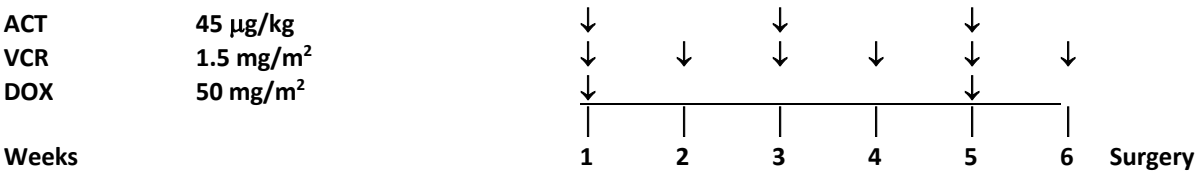
4.3.6. Treatment schedules for Stage IV

Preoperative AVD

Group: All Stage IV with lung nodules ≥2 mm (See 15.3.1)
Three drugs (vincristine (VCR), actinomycin D (ACT) and doxorubicin) x 6 weeks

- Vincristine: 1.5 mg/m^2 (max 2 mg) weeks 1, 2, 3, 4, 5, 6
- Actinomycin D: 45 µg/kg (max 2 mg) weeks 1, 3, 5
- Doxorubicin: 50 mg/m^2 weeks 1, 5

Vincristine and actinomycin D are given by intravenous bolus, doxorubicin as a 4-6 hours infusion.



Treatment in weeks 1, 3 and 5 is blood count dependent and delay is indicated if neutrophils are <1000/µl and/or blood values are still decreasing. In case of severe and unexpected thrombocytopenia consider VOD-diagnostics and treatment.

In exceptional cases, a week 7 dose of vincristine can be administered if there is some delay of surgery. However, nephrectomy should preferably be performed in week 7 and not later than week 8. Reassessment imaging of local tumour and metastases should be performed at week 6 using the same technique as at diagnosis.

Regimen AVD150

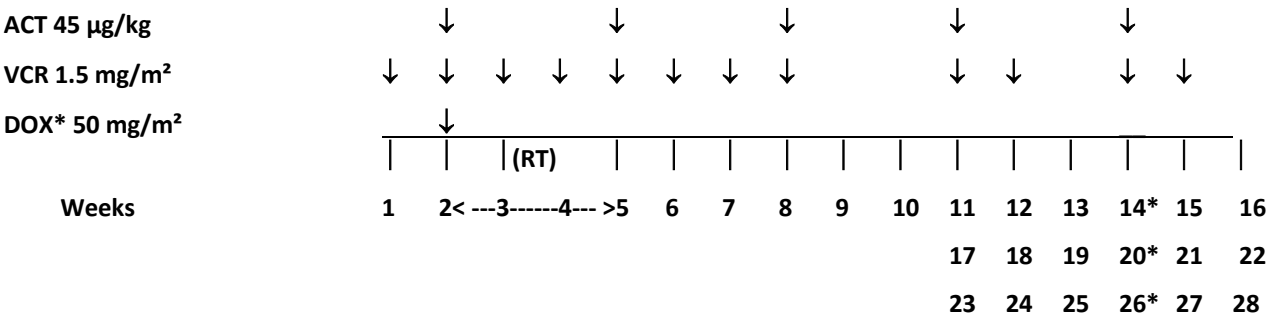
Group A1 Patients

The total duration of the postoperative chemotherapy is 27 weeks.

- Vincristine: 1.5 mg/m^2 (max 2 mg) to be started when when peristalsis is established following surgery and within 21 days of pre-operative chemotherapy. Give weekly for 8 weeks (8 doses) and then on day one of weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27 (20 doses in total)
- Actinomycin D: 45 µg/kg (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

Both drugs are given by intravenous bolus.

- Doxorubicin: 50 mg/m^2 in 4-6 hours infusion once in week 2 concurrently with the first dose of Actimomycin D and the second dose of Vincristine. Subsequent doses are not given! (1 dose in total - total cumulative dose including pre-operative treatment: 150 mg/m^2



* No doxorubicin in weeks 8, 14, 20 and 26, cumulative dose 150 mg/m^2

Echocardiogram in week 1 and at end of treatment

Actinomycin D and doxorubicin should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l. Chemotherapy cycles can be adapted to avoid use of Doxorubicin within 14 days of radiotherapy. Reduce dose of ACT by 1/3 when RT is given within 14 days of this administration. Avoid ACT and doxorubicin from 1 week before until 2 weeks after radiotherapy and then apply full dose.

Note: Patients with local stage III receive abdominal/flank irradiation. No pulmonary irradiation is indicated unless viable malignant tissue is found in the completely resected lung nodules. Irradiation of metastases at other sites than lungs is indicated, if not fully resected or if viable metastasis.

Regimen AVD250:

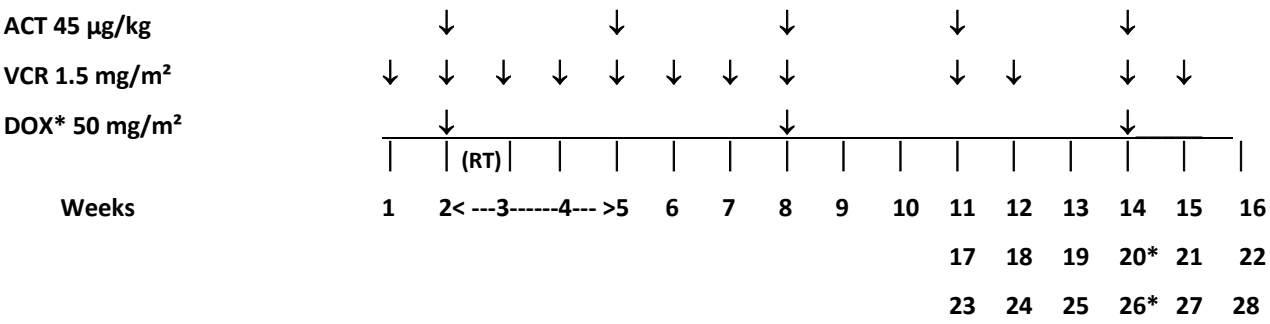
Groups: A2, B, and C only in the case of resection of representative and exclusively necrotic nodules

The total duration of the postoperative chemotherapy is 27 weeks.

- Vincristine: 1.5 mg/m^2 (max 2 mg) commenced when peristalsis established following surgery and within 21 days of pre-operative chemotherapy. Give weekly for 8 weeks (8 doses) and then on day one of weeks 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26, 27 (20 doses in total)
- Actinomycin D: 45 µg/kg (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

Both drugs are given by intravenous bolus.

- Doxorubicin: 50 mg/m^2 in 4-6 hours infusion every 6 weeks to start in week 2 concurrently with the first dose of Actimomycin D and the second dose of Vincristine. Subsequent doses are given at weeks 8 and 14 (3 doses in total - total cumulative dose including pre-operative treatment: 250 mg/m^2).



* No doxorubicin in weeks 20 and 26, cumulative dose 250 mg/m^2

Echocardiogram in week 1, if abnormal before each doxorubicin, and at end of treatment

Actinomycin D and doxorubicin should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l. Chemotherapy cycles can be adapted to avoid use of Doxorubicin within 14 days of radiotherapy. Reduce dose of ACT by 1/3 when RT is given within 14 days of this administration. Avoid ACT and doxorubicin from 1 week before until 2 weeks after radiotherapy and then apply full dose.

Note: Patients with local stage III receive flank/abdominal irradiation. Irradiation to metastasis of other sites than lungs is indicated, if not resected or if viable metastasis. Pulmonary irradiation is indicated in case of viable lung metastasis at any point.

4-Drug-Regimen (HR-2)

Groups: C where nodules are viable and incompletely resected or representative resection is not feasible

Total duration of the postoperative treatment is 34 weeks. There are two alternating courses of chemotherapy given at 21-day intervals. The first course starts as soon as the patient has recovered from surgery and clinical condition allows. This should be the case within 21 days after the end of the last preoperative course of chemotherapy. Each cycle commences when absolute neutrophil count is > $1.0x10^9$/l and platelet count >100 x 10^9/l provided rising WBC values.

- **Course 1:** Cyclophosphamide and Doxorubicin in weeks 1, 7, 19 and 31 (4 courses in total)

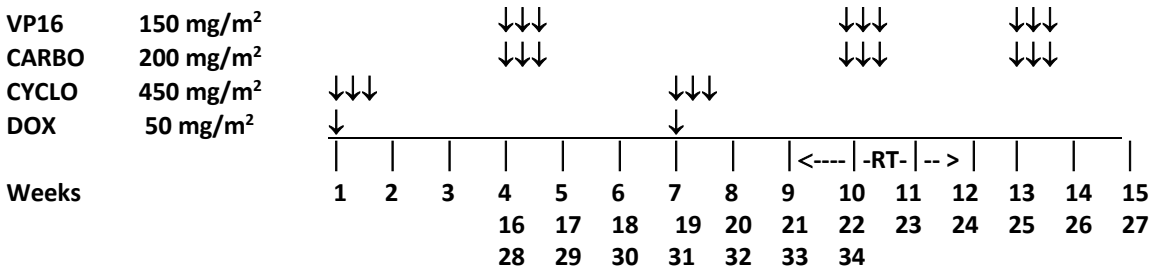
  Cyclophosphamide: 450 mg/m^2 on days 1, 2 and 3; infusion time 1 hour

  Doxorubicin: 50 mg/m^2 on day 1; infusion time 4 - 6 hours
  Cumulative dose of doxorubicin including pre-operative chemotherapy 300 mg/m^2
  Doxorubicin to be started after the first dose of Cyclophosphamide

- **Course 2:** Etoposide and Carboplatin in weeks 4, 10, 13, 16, 22, 25, 28 and 34 (8 courses in total)

  Etoposide (VP16): 150 mg/m^2 on days 1, 2, 3; infusion time 1 hour

  Carboplatin: 200 mg/m^2 on days 1, 2, 3; infusion time 1 hour, Consider dose reduction for carboplatin to 150 mg/m^2 in case of hematotoxicity after previous course.



Echocardiogram before first doxorubicin in week 1, before week 19, and at the end of treatment.

Radiotherapy for local stage III is postponed to week 10 (= assessment of persisting nodules) in order to combine with pulmonary RT if required. If viable metastases were confirmed at time of nephrectomy, RT to this organ is indicated. If at week 10, complete metastatic clearance has been observed, omit the last dose of doxorubicin in order to limit the cumulative cardiotoxicity of RT and doxorubicin.

Treatment should be delayed if the absolute neutrophil count is <1.0 x10^9/l or platelet count <100 x 10^9/l. G-CSF can be given if delays of treatment or grade 4 neutropenia occurs. Use of Cotrimoxazole is recommended for this regimen as PCP prophylaxis.

Note: All stage III tumours do need local radiotherapy.

4.3.7. Recommended Treatment adjustments during treatment

Actinomycin D, Doxorubicin, Cyclophosphamide, Etoposide and Carboplatin should be delayed if:

- The absolute neutrophil count is <1,0 x10^9/l and not-rising tendency or
- Platelet count <100 x 10^9/l

Actinomycin D should be delayed if:

- Bilirubine > 1.5 x ULN
- ALAT > 5 x ULN
- Clinical signs of VOD

Doxorubicin should be delayed if:

- Bilirubine > 2 x ULN
- ALAT > 5 x ULN
- Grade I mucositis

If a next course is delayed for > 1 week: consider dose reduction of 33% for the next course excluding vincristine. Consider giving G-CSF in case of HR treatment.

4.3.8. Radiotherapy

Please note recommendation to delay flank irradiation to be given together with pulmonary irradiation where possible (not advised in diffuse anaplastic cases, stage III).
Doxorubicin should be avoided from 1 week until 2 weeks after radiotherapy. In that case the chemotherapy cycles can be adjusted in order to receive the planned cumulative dosing.
Avoid actinomycin D from 1 week until 2 weeks after radiotherapy (without substitution).

4.3.9. Treatment Recommendation Overview

The following table gives an overview of most clinical situations with Stage IV nephroblastoma. This table does not substitute the more detailed information in the respective chapters.

Metastasis surgery	Wilms tumour histology	Treatment
Complete remission or very good partial remission Surgical resection if required/feasible	LR or IR & lung nodules 3–5mm	AVD150, CT at week 10: no lung RT unless resection of viable metastasis, then lung RT
	LR or IR & nodules >5mm	AVD250, CT at week 10: no lung/ metastatic RT unless resection of viable metastasis, then pulmonary RT
	LR or IR & no evidence of metastasis	Treatment as localized

Metastasis surgery	Wilms tumour histology	Treatment
Partial response or stable disease Representative nodule resection feasible	LR but viable metastasis confirmed	AVD250, lung/metastatic RT; CT at week 10: if remaining nodules then surgery recommended to achieve CR if feasible
	LR & completely necrotic metastasis	AVD250, CT at week 10: if remaining nodules then surgery recommended to achieve CR if feasible
	LR or IR & no evidence of viable tumour	Contact principal investigator, potentially treatment as localized or AVD250; CT at week 10: if remaining nodules then surgery recommended to achieve CR if feasible, no RT to metastases
	IR & viable metastasis confirmed	CDCV, lung/metastatic RT; CT at week 10: if remaining nodules then surgery recommended to achieve CR if feasible
	IR & completely necrotic metastasis	AVD250 regimen, CT at week 10: if remaining nodules then surgery recommended to achieve CR if feasible
Resection not feasible	LR	AVD250, CT at week 10: reconsider resection and discuss lung/metastatic RT
	IR	CDCV, CT at week 10: if remaining nodules lung/metastatic RT is indicated
All	HR	Ask principal investigator for advice
Mixed Surgery metastasis indicated	Confirm metastatic disease by histology	If metastases present then treat according to worst histology and worst response

Abbreviations: LR: Low risk histology; IR: Intermediate risk histology; HR: High risk histology; RT: Radiotherapy; CT: Computerized Tomography

4.4. Management of bilateral disease (stage V) and bilaterally-predisposed unilateral Wilms Tumour

The aim of these recommendations is to consider all bilateral diseases since the goal is to spare as much renal function as possible by preserving as much normal renal tissue as possible. This guideline deals with bilateral WT, bilateral nephroblastomatosis (NB), unilateral WT with NB on the other side, bilateral NB and WT in a single kidney or in a horseshoe kidney. In addition, patients with an unilateral WT and a congenital syndrome or condition that is associated with bilateral tumour development will be managed according to this guideline. Previously syndromes and constitutional chromosomal abnormalities associated with WT into 3 risk groups. At least those patients included in the high or moderate risk group should follow this guideline. Most important will be the question for nephron sparing surgery in this patient group.

Table 1 Conditions with an increased risk of Wilms tumour

High risk (>20%)
- *WT1* deletions (including WAGR syndrome)
- Truncating and pathogenic missense *WT1* mutations (including Denys-Drash syndrome)
- Familial Wilms tumour
- Perlman syndrome
- Mosaic variegated aneuploidy
- Fanconi anaemia D1/Biallelic *BRCA2* mutations

Moderate risk (5–20%)
- *WT1* intron 9 splice mutations (Frasier syndrome)
- Beckwith-Wiedemann syndrome caused by 11p15 uniparental disomy, isolated *H19* hypermethylation, or of unknown cause
- Simpson-Golabi-Behmel syndrome caused by *GPC3* mutations/deletions

Low risk (<5%)
- Isolated hemihypertrophy*
- Bloom syndrome
- Li-Fraumeni syndrome/Li-Fraumeni-like syndrome
- Hereditary hyperparathyroidism-jaw tumour syndrome
- Mulibrey nanism
- Trisomy 18
- Trisomy 13
- 2q37 deletions

*Individuals with hemihypertrophy caused by 11p15 uniparental disomy or isolated H19 hypermethylation are at moderate risk of Wilms tumour.
WAGR, Wilms-aniridia-genitourinary-mental.

Syndromes and constitutional chromosomal abnormalities associated with WT according to Scott RH et al. (2006)

4.4.1 Background

Synchronous bilateral WT (BWT- Stage V) is reported to account for 5% of all nephroblastoma patients. A major challenge in BWT is to achieve high cure rates while preserving as much functional renal tissue as possible for preserving a renal function sufficient for normal growth and development.

The outcome of children with BWT has improved with therapeutic advances in SIOP and COG protocols. In 1989, Coppes et al. reported a 10-year overall survival of 69% for patients with

synchronous BWT treated with neoadjuvant chemotherapy and surgery. More recently, different studies reported a long-term OS about 80 %. The most significant risk factor for overall survival (OS) and event free survival (EFS) is local stage with stage III tumours doing worse than stage I and II. The excellent outcome is the result of a strong cooperation between different specialists in international studies and individual treatment approaches according to the tumour response. The most significant morbidity is the risk of end-stage renal disease (ESRD) in this sub-group of patients with an incidence of 9% to 12%. The risk of ESRD increases in patients with greater than 50% loss of renal tissue. Aronson et al. have observed that functional renal outcome is significantly improved after bilateral nephron sparing surgery (NSS) compared to other types of surgery. Independently of the type of treatment, children with WAGR, Denys-Drash or other syndromes associated with WT1 gene mutations, are at higher risk of ESRD. Therefore avoiding total nephrectomy at initial surgery is advised.
In order to facilitate this goal SIOP and COG have recommended the same strategy over the past two decades:

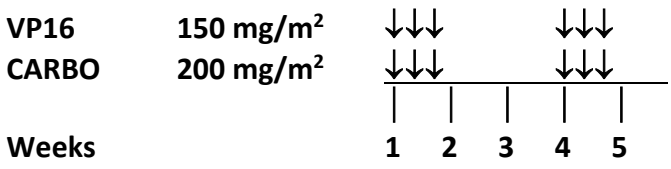
- Front-line chemotherapy to decrease tumour volume as much as possible
- Nephron-sparing surgery as often as possible
- Adjuvant chemotherapy adjusted to the highest histological type and local stage of the tumours

4.4.2. Treatment plan

In all of the following treatment plans drugs and doses are according to unilateral WT. Even if NSS is possible after the first assessment, it needs to be discussed during a multidisciplinary meeting if further shrinkage with chemotherapy would be beneficial to spare more normal kidney.

Chemotherapy guidelines

Doses and administration of all drugs are as recommended in the protocol for unilateral tumours.
In case of non-response (SD, PD or NSS is not possible) in the preoperative phase a change of treatment to carboplatin / etoposide is recommended according to the following schedule:



Surgical guidelines

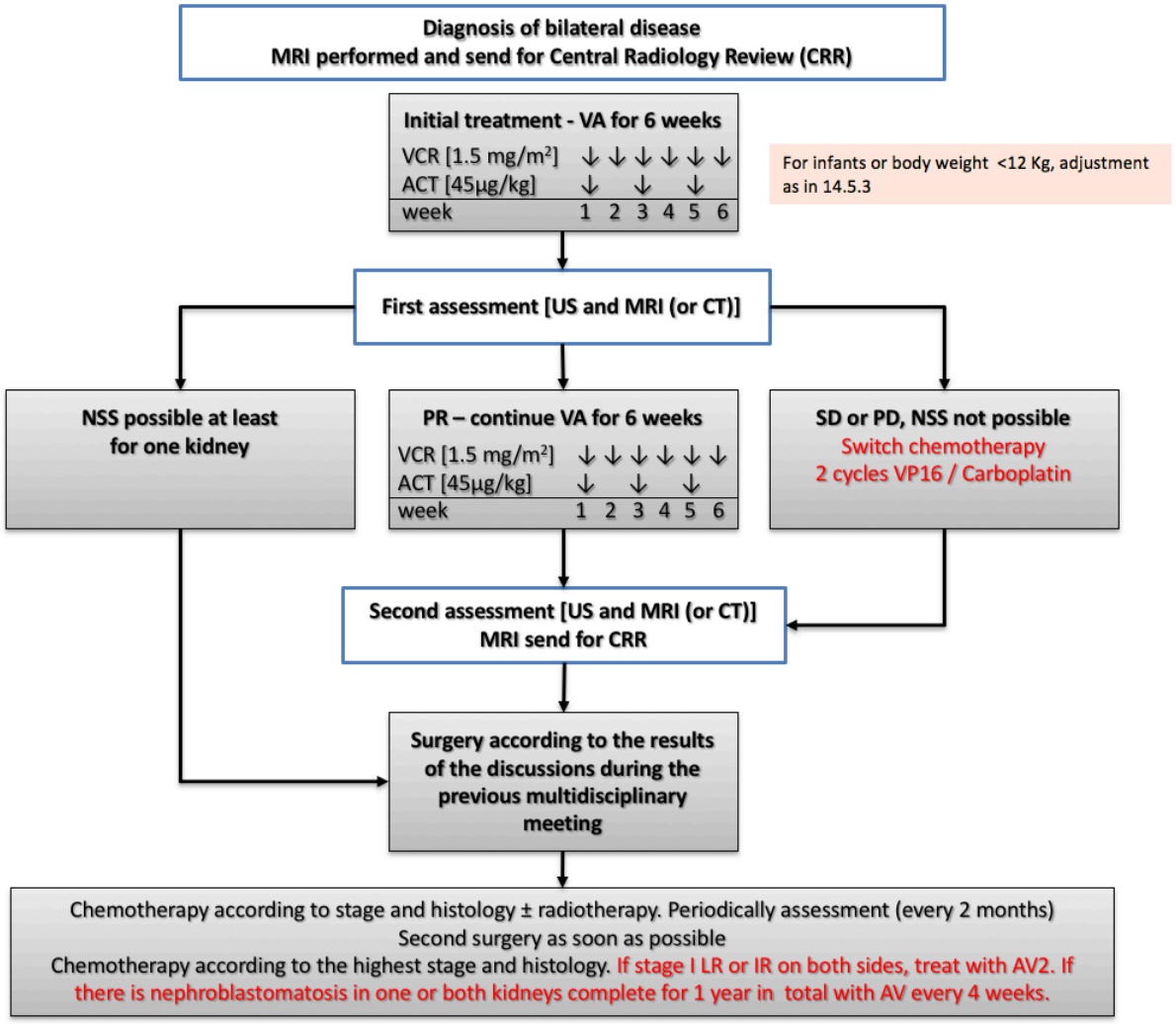
Patients with BWT should benefit from an experienced surgeon in renal parenchyma-sparing procedures. Thus:

- Each patient should be discussed in the context of a national surgical meeting to take decision with the advice of national experts.
- Surgery will be performed only at centres specialized in the treatment of this disease.

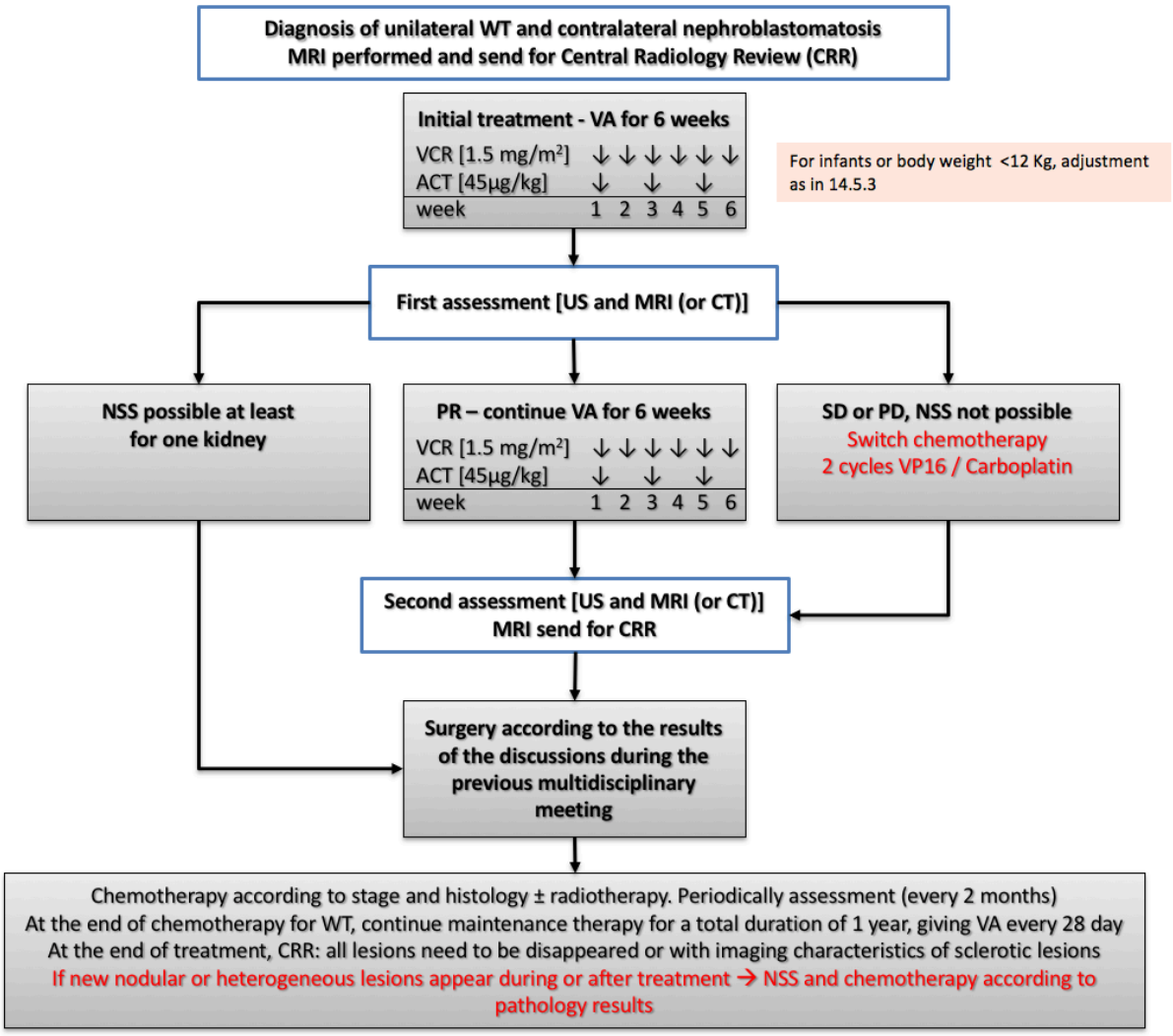
Radiotherapy guidelines:

Recommendations for doses and site are similar to the recommendations for unilateral disease. When indicated, it shall begin concurrent with the initiation of adjuvant chemotherapy.

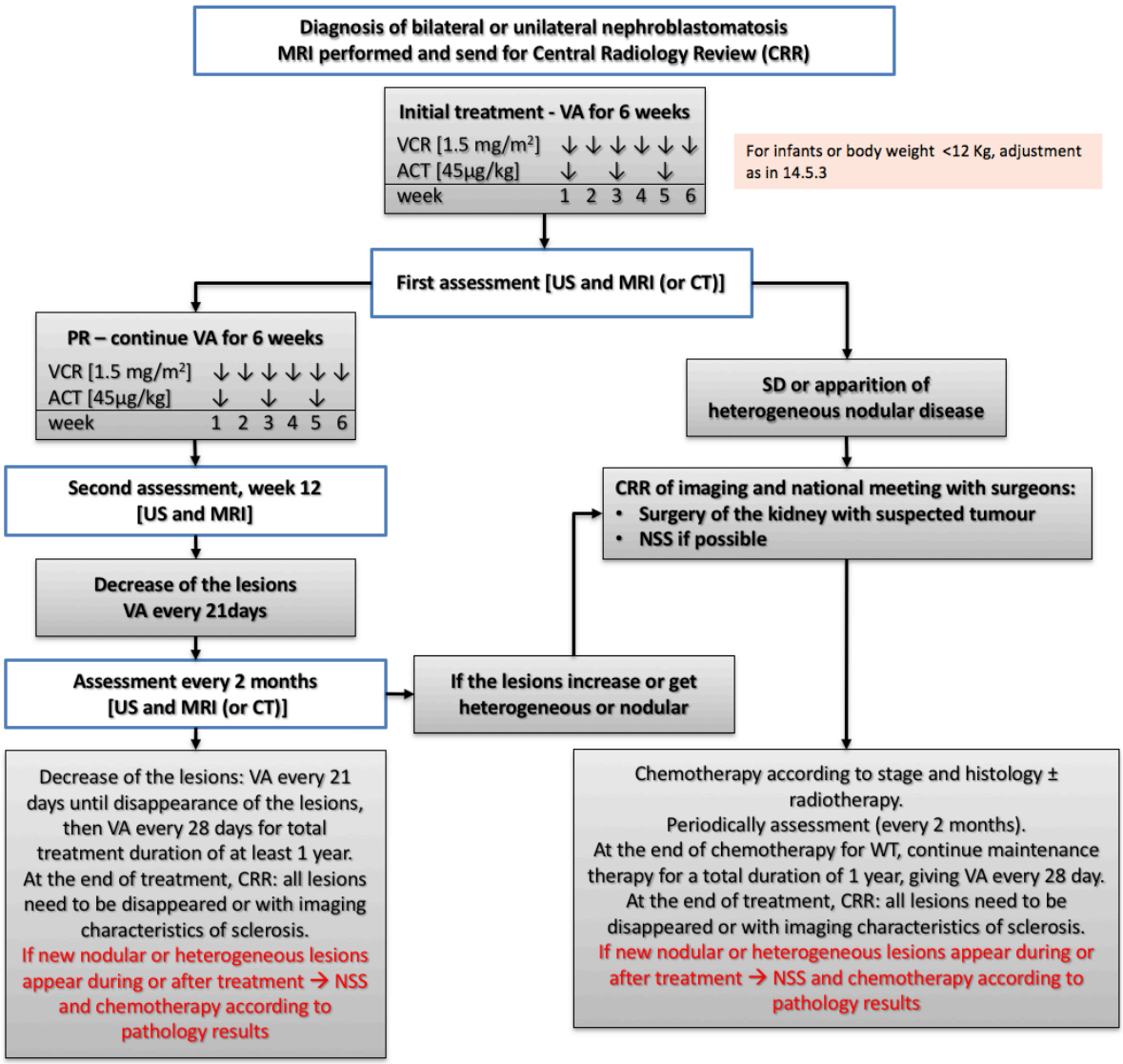
4.4.2.1. Patients with bilateral Wilms Tumour



4.4.2.2. Patients with unilateral Wilms Tumour and contralateral nephroblastomatosis

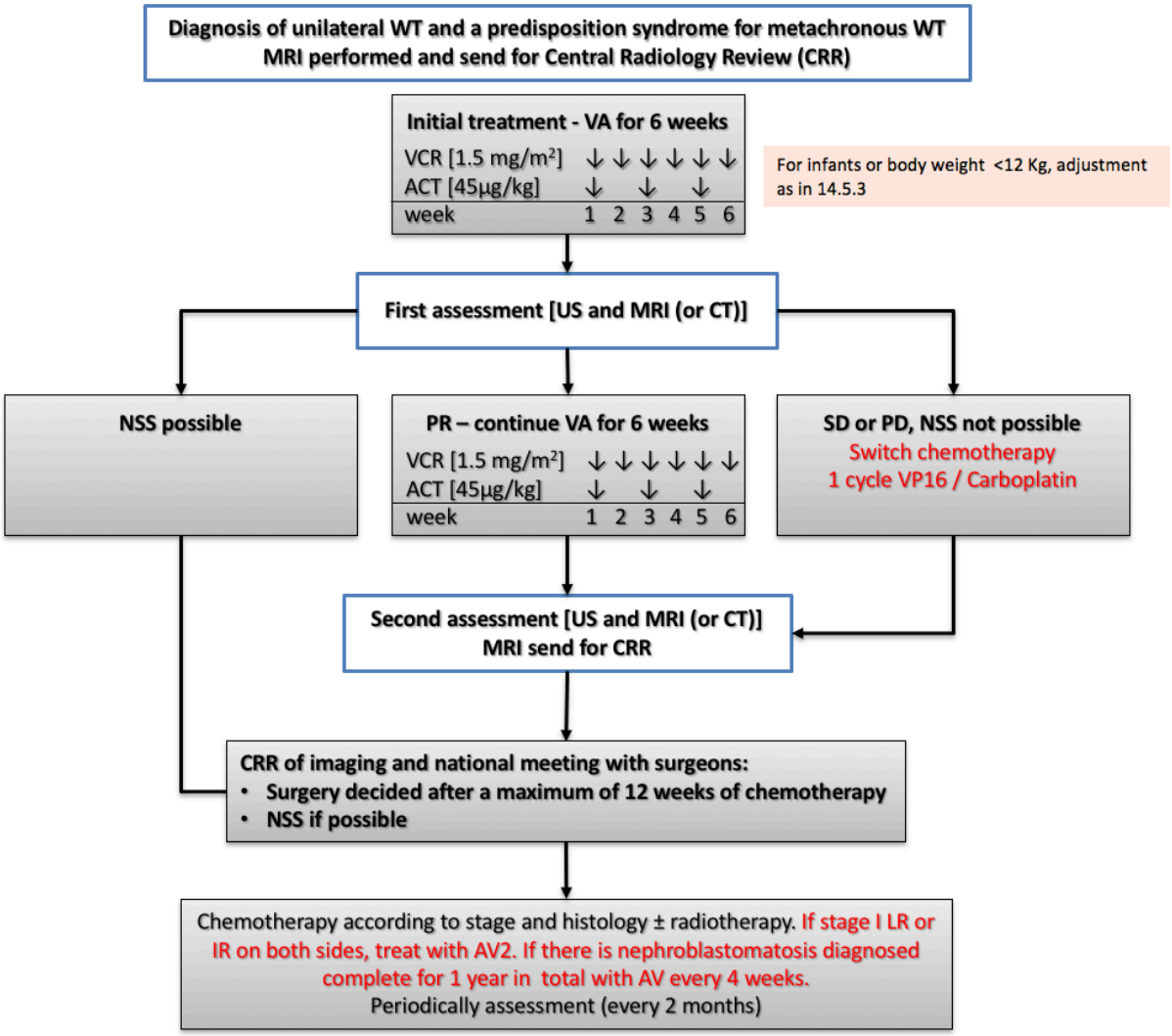


4.4.2.3. Patients with bilateral or unilateral nephroblastomatosis



4.4.2.4. Patients with unilateral tumour and predisposition syndrome as cited previously

These patients are at high risk of metachronous bilateral tumour and need to benefit from a strategy with NSS if possible. Therefore, they are included in treatment options for bilateral disease.



4.4.3. Recommendations based on frequently asked questions

a. **Remaining lesions:** If spherical and/or growing lesions occur under treatment go to surgery to perform NSS. In this situation an anaplastic WT needs to be ruled out. Otherwise continue with AV.

b. **Nephroblastomatosis:** Irrespectively whether nephroblastomatosis has been removed surgically, or is no longer visible on MRI after postoperative chemotherapy continue with maintenance treatment for 1 year.

c. **Duration of maintenance:** Maintenance treatment should continue until a total duration of one year (to include preoperative, postoperative and maintenance treatment).

4.5. Treatment guidelines after primary surgery

The following treatment recommendations are based on the United Kingdom experience in UKW1 & 2 studies. Modifications to the length of therapy, total dose of anthracycline and treatment of focal anaplasia have been made in the light of published data from NWTS 4 and 5 study. Note that the recommended management of infants less than 6 months of age or teenagers above 16 years with a primary intrarenal tumour is immediate nephrectomy.
Risk group assignment in cases treated with immediate nephrectomy is based solely on tumour stage and presence of unfavourable histology (anaplasia). Blastemal predominant type belongs to favourable histology.

4.5.1. Staging

Initial and follow-up diagnostics during treatment is given in section. Definition of tumour stage will be as for tumours receiving pre-operative chemotherapy except that the concept of "regressive changes/necrotic tumour" will not be applicable. It is of particular importance to assign correct local stage. Lymph nodes must be adequately sampled at time of nephrectomy (at least 7).

4.5.2. Histological classification

The SIOP pathological risk group B applies to tumours that have not received pre-operative chemotherapy. Note that the presence of large amounts of viable blastema is of **no prognostic significance** in immediate nephrectomy specimens. Histological classification after immediate nephrectomy is done according to Vujanic et al. (nat rev 2017) and shown here:

Pathological risk group for primary operated cases:

I LOW RISK TUMOURS
- *Mesoblastic nephroma*
- Cystic partially differentiated nephroblastoma

II INTERMEDIATE RISK TUMOURS
- Non-anaplastic nephroblastoma and its variants
- Nephroblastoma - focal anaplasia

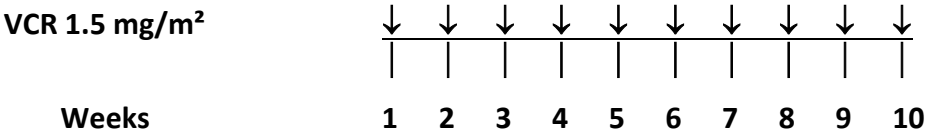
III HIGH RISK TUMOURS
- Nephroblastoma – diffuse anaplasia
- *Clear cell sarcoma of the kidney*
- *Rhabdoid tumour of the kidney*

4.5.3. Post-operative chemotherapy regimens for tumours having primary excision

Patients with low-risk tumours do not receive postoperative chemotherapy even in stage II and III.

Regimen 1 (intensive VCR): Stage I, intermediate risk (excluding focal anaplasia).

- Vincristine: 1.5 mg/m^2 (maximum dose 2 mg) weekly for 10 weeks (10 doses in total). The first dose is to be given once peristalsis is established following surgery.

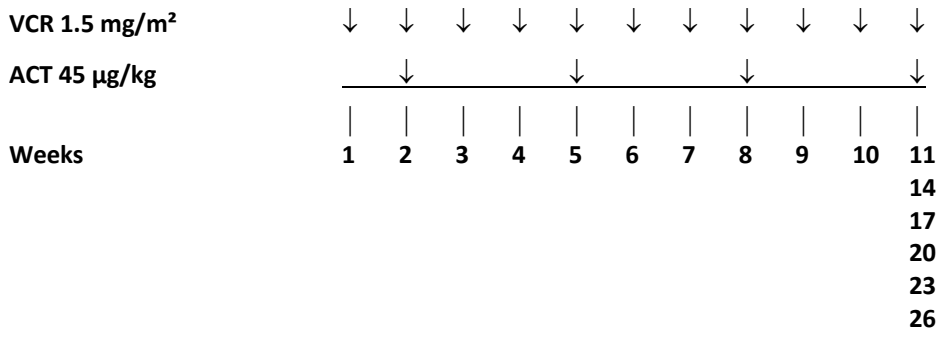


Total duration of therapy: 10 weeks

Note: Infants and children < 12 Kg should be given full dose vincristine when the drug is used alone, unless there are signs of toxicity in which case the subsequent dose should be reduced by 50% followed by cautious increases if tolerated.

Regimen 2 (AV): Stage I, focal anaplasia and Stage II, intermediate risk

- Vincristine: 1.5 mg/m^2 (maximum dose 2 mg) weekly for 11 weeks and then three weekly, at weeks 14, 17, 20, 23 and 26 (16 doses in total)
- Actinomycin D: 45 µg/kg (maximum dose 2 mg) at weeks 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in

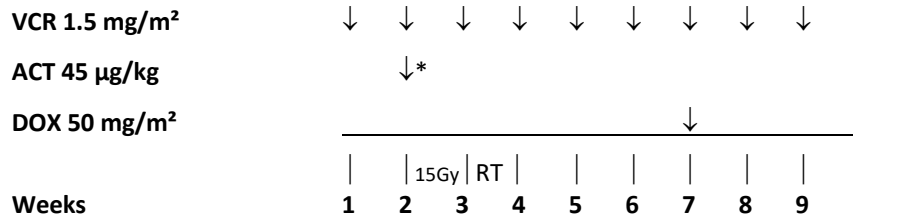


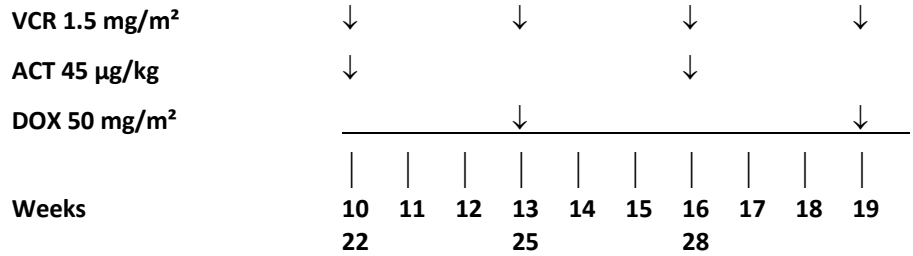
Total duration of therapy: 26 weeks

Note: Infants and children < 12 Kg receive lower doses of both drugs when given in combination

Regimen 3 (sequential AVD): Stage III intermediate risk (includes focal anaplasia)

- Vincristine: 1.5 mg/m^2 (maximum dose 2 mg) weekly for 10 weeks and then three weekly, at weeks 13, 16, 19, 22, 25 and 28 (16 doses in total)
- Actinomycin D: 45 µg/kg (maximum dose 2 mg), 2/3 dose at week 2* then full dose at weeks 10, 16, 22, 28 (5 doses in total).
- Doxorubicin: 50 mg/m^2 at weeks 7, 13, 19, 25 (4 doses (200 mg/m^2) in total). Each dose to be infused over 4-6 hours





*Note: Chemotherapy cycles can be adapted to avoid use of Doxorubicin within 14 days of radiotherapy. Avoid ACT and doxorubicin from 1 week before until 2 weeks after radiotherapy and then apply full dose. Total duration of therapy: 28 weeks.

Note: Infants and children < 12 Kg receive lower doses of both drugs when given in combination

*Abdominal radiotherapy (14.4 Gy) to be given weeks 2 – 4.

4.5.4. Stage IV patients

Stage IV patients having immediate nephrectomy should be few in number and confined to patients presenting as surgical emergencies with unrecognised lung or liver metastases. They should be treated with the three drug "preoperative" chemotherapy for stage IV tumours. Metastatic response should be evaluated at week 6 by chest CT. Subsequent chemotherapy is dictated according to whether or not metastatic complete remission has been achieved by chemotherapy +/- surgery, as per the main protocol recommendations including indications for radiotherapy

Note: Blastemal predominant tumours after immediate surgery are belonging to the intermediate risk group.

4.5.5. Post-operative chemotherapy for high-risk histology tumours having primary excision

WT with Diffuse anaplasia

Stages I - IV - SIOP 'high risk' post operative chemotherapy Abdominal radiotherapy is given to local abdominal stages II and III. Lung radiotherapy is given to all stage IV cases with lung metastases, regardless of metastatic response to chemotherapy/surgery.

MRTK, CCSK and RCC are described in the non WT chapter

Include these patients into the EU-RHAB Protocol.

4.6. Treatment guidelines for relapsed Wilms tumours

4.6.1. Introduction and background

Approximately 15% of patients with intermediate risk WT and 50% of patients with anaplastic or post-chemotherapy blastemal-type WT experience recurrence. Most recurrences occur within two years of diagnosis, although in rare cases relapses have developed later. The general profile of relapse site shows that the lungs and pleura alone account for 50-60%; abdominal recurrences make up to 30% of relapses (isolated abdomen or combined to other sites), while other sites (brain or bone) are involved alone in 10-15% of cases.
A general principle for the treatment of relapsed WT is to use agents not used for primary therapy. Phase 2 trials demonstrated efficacy of ifosfamide (52% objective responses), etoposide (42% responses), and carboplatin (52% responses) either as single agents or as combinations. Investigators at St. Jude Children's Research Hospital documented the activity of topotecan (48% responses in favourable histology WT). The effective use of high-dose therapy with autologous stem cell rescue (ASCR) for the treatment of recurrent WT has been reported by several groups, with survival rates up to 70%.

4.6.2. Diagnostic investigations at relapse

The diagnostic investigations for a child with suspected recurrent WT are detailed below.
Biopsy, to obtain histological diagnosis, is strongly recommended in clinically doubtful situations. These may include:

1. Late recurrence, occurring > 24 months from end of treatment.
2. Isolated single lung or liver nodule.
3. **Important note**: in all the other situations in which the histological confirmation of relapse might be helpful in guiding the clinical approach and judged with a limited risk of morbidity, tumour biopsy is advised, also to implement our biological knowledge on relapsing tumours. Noteworthy to remind, in future new agent clinical trials, it might be important to have a molecular profile of a relapsed tumour before registering patients.

Increased emphasis is placed on the quality and standardisation of imaging. 3D volume measurements of the tumour, both at diagnosis of the relapse and to document response to chemotherapy, are important. MRI or CT scanning are the recommended standard for abdominal imaging. MRI studies with new protocols (ADC mapping) allow assessment of tumour composition, which may be used as a biomarker for response to chemotherapy.
CT thorax scan is recommended to lung and mediastinum re-staging.

All children with a suspected tumour recurrence should have:

- Clinical history and examination
- Measurement of blood pressure and urinary protein
- Abdominal ultrasound
- 3D cross sectional imaging of abdomen (either MRI or CT)
- CT scan chest, with documentation of number and largest size of any visible lung nodule
- Functional imaging of the kidneys (DMSA scan) prior to re-treatment
- Echocardiogram for patients receiving doxorubicin, or receiving pulmonary radiotherapy or doxorubicin already given

4.6.3. Eligibility and risk stratification

Three risk categories for recurrent WT will be identified:

1) **Group AA**: Patients with initial stage I or II low/intermediate risk SIOP-2001 histology WT, with relapse after therapy including only vincristine (V) and/or actinomycin-D (A), and no RT. Also, patients fulfilling the same criterion of not having received previous drugs apart from VA, and receiving up-front nephrectomy will be included (see patients receiving primary surgery).

   This group is expected to have EFS estimates in the 70-80% range, and account for 30% of all recurrences.

2) **Group BB**: Patients treated initially with ≥3 chemotherapy drugs with or without radiation. Patients with second and subsequent relapses may be entered if prior therapy was according to group AA, in the absence of alternative treatment solutions by the responsible treating physician.

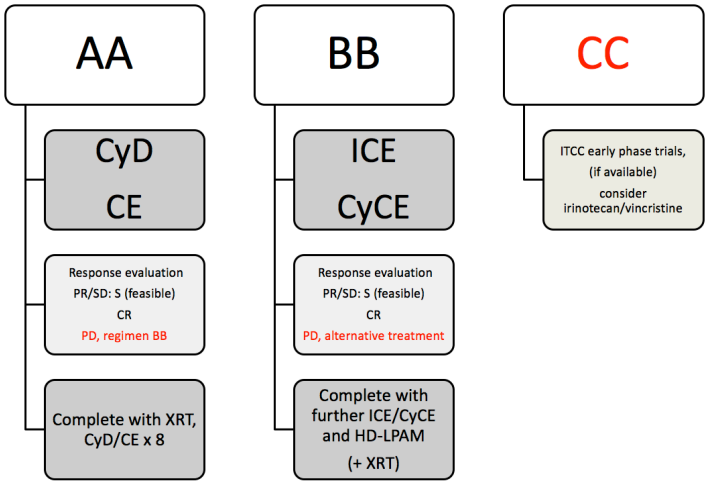
   This group, accounting for 45-50% of the children with WT who relapse, is expected to have survival rates in the 40-50% range

3) **Group CC**: patients with initial stage II to IV diffuse anaplastic or stage II and IV blastemal-type histology after pre-operative chemotherapy The great majority of these patients will have already received doxorubicin, etoposide, carboplatin, ifosfamide or cyclophosphamide (according to their national protocols).

   These patients are expected to have survival rates in the 10% range This group accounts for 10-15% of all WT relapses.

Important note: histology is intended of the initial tumour (not at relapse). If anaplasia, not previously recognised in the primary tumour, turns out at relapse, we advise to discuss the case with the national coordinator.

i. Flow diagram with treatment recommendations



Flow diagram with treatment recommendations according to groups, AA, BB and CC. (CyD: cylophosphamide + doxorubicin; CE: carboplatin +etoposide; I: ifosfamide, S: surgery, CR: complete remission, PR: partial remission, SD: stable disease, PD: progressive disease. ITCC: Innovative Therapies for Children with Cancer: http://www.itcc-consortium.org/)

4.6.4. Therapeutic recommendations

Group AA

Specific assumptions of the recommendations for AA patients will rely on the proven experience with doxorubicin, etoposide, and cyclophosphamide, in terms of toxicity and efficacy, and that the incorporation of carboplatin, whose efficacy is well proven, will likely help to improve the OS rate (since 60-80% of failures are systemic failure).
There are two alternating courses of chemotherapy given at 21-day intervals (total 8). Both combinations consist of two drugs.
Each cycle commences when absolute neutrophil count is ≥ $1.0x10^9$/l and platelet > 75 x 10^9/l and rising.
Use of cotrimoxazole as Pneumocystis Carinii prophylaxis is recommended, as well as use of G-CSF.

Course 1. Cyclophosphamide and doxorubicin (CyD)

Cyclophosphamide: 500 mg/m^2, **every 12 hours** as an infusion over 15 min on days 1 and 2 (total 2 g/m^2/course). Mesna: i.v. bolus of 200 mg/m^2 immediately prior to first dose of Cyclophosphamide followed by continuous Mesna at 1.0 g/m^2/day until 12 hours after last dose of cyclophosphamide.
Doxorubicin: 50 mg/m^2 in 3-hour infusion on day 1.
Weeks: 1, 7, 13 and 19 (total of 4 courses).

Course 2. Carboplatin and etoposide (Carbo/E)

Etoposide: 150 mg/m^2 in 500 ml/m^2 dextrose saline in 2-hour infusion on days 1, 2 and 3.
Carboplatin: 200 mg/m^2 (or AUC = 2.65) in 2-hour infusion on days 1, 2 and 3.
Weeks: 4, 10, 16, and 22 (a total of 4 courses).

Treatment plan

Week											
1	2	3	4	5	6	7	8	9	10	11	12
D			Carbo		Surgery	D		Radiotherapy	Carbo		
Cy			E			Cy			E		
13	14	15	16	17	18	19	20	21	22	23	24
D			Carbo			D			Carbo		
Cy			E			Cy			E		

Single doses: **D**: **50** mg/m^2; **Cy**: **500** mg/m^2 bd x 2 days; **E**: **150** mg/m^2 x 3; **Carbo**: **200** mg/m^2 x 3
Cumulative doses: D: 200 mg/m^2**; Cy: 8** g/m^2**; E: 1.8** g/m^2**, Carbo: 2,4** g/m^2
Reassessment imaging and surgery should be planned for week 6. Note: dose reductions for all drugs if 1. weight 5-12 kg: give dose based on weight/kg (se table page…) 2. weight < 5kg and/or age < 6 months: give dose based on weight/kg with 33% reduction

Treatment scheme for Group AA (D: doxorubicin, Cy: cyclophosphamide, E: etoposide, Carbo: carboplatin)

Group BB

The specific assumption will be that the use of high-dose melphalan and ASCR as consolidation for those children who will have achieved a partial or complete response to induction chemotherapy will improve EFS for children of group BB.

1. Induction chemotherapy

There are four sequential courses of chemotherapy (alternating ICE and CyCE), administered at 21 day intervals, before HD-melphalan.
Since prolonged thrombocytopenia due to carboplatin is expected, we recommend trying not to delay treatment courses, and followed the recommended cut off of 75 x 10^9/l platelets to start the subsequent course.
Each course commences when absolute neutrophil count is ≥ 1.0x10^9/l and platelet > 75 x 10^9/l and rise.
Use of Cotrimoxazole as Pneumocystis Carinii prophylaxis is recommended, as well as use of G-CSF.

Induction

Week **1**	**4**	**6**	**7**	**10**	**13**	**15**
I	Cy	**First evaluation PBSC harvest**	I	Cy	**Evaluation and surgery**	HD-melphalan
Carbo	Carbo		Carbo	Carbo		
E	E		E	E		

Drug	Route of administration	Dose		Day(s)
Ifosfamide (I)	i.v. over 2 hours	66.7 mg/kg/day for infants < 12 months 2,000 mg/m² for children ≥ 12 months		1-3
Cyclophosphamide (Cy)	i.v. over 15 min	440mg/m^2 (total 2.2 g/m^2/course)		1-5
Carboplatin (Carbo)	i.v. over 1 hour	**GFR**	**Dose**	1
		> 150 ml/min/1.73m^2	560 mg/m^2 (18.7 mg/kg for infants)	
		100-150 ml/min/1.73m^2	500 mg/m^2 (16.6 mg/kg for infants)	
		75-99 ml/min/1.73m^2	370 mg/m^2 (12.3 mg/kg for infants)	
		50-74 ml/min/1.73m^2	290 mg/m^2 (9.7 mg/kg for infants)	
		30-49 ml/min/1.73m^2	200 mg/m^2 (6.7 mg/kg for infants)	
		< 30 ml/min/1.73m^2	Hold carboplatin	
Etoposide (E) during ICE	i.v. over 1 hour	3.3 mg/kg/day for infants < 12 months 100 mg/m^2 for children ≥ 12 months		1-3
Etoposide (E) during CCE	i.v. over 1 hour	3.3 mg/kg/day for infants < 12 months 100 mg/m^2 for children ≥ 12 months		1-5
GCSF		5 µg/kg/day subcutaneously from day 4 through ANC > 3,000/µl		
Mesna	with ifosfamide	i.v. infusion over 3 hours during the administration of ifosfamide, at an equivalent ifosfamide dose (2,000 mg/m^2/d for children > 12 months). An additional Mesna 1,000 mg/m^2/d dose is required in a parallel liquid infusion over 24 hours, during all the 3 days of ICE. Reduced dose for children < 12 months		
	with cyclophos-phamide	i.v. bolus of 200 mg/m^2 immediately prior to first dose of Cyclophosphamide followed by continuous Mesna at 1.0 gr/m^2/day until 12 hours after last dose of cyclophosphamide. Reduced dose for children < 12 months		

2. High dose chemotherapy and autologous hematopoietic stem cell rescue

All patients with proven responding tumour will proceed to high-dose chemotherapy with autologous PBSC rescue. Patients must have sufficient stem cells available (defined as PBSC ≥ 3 x 10^6 CD34 cells/kg). Hematopoietic progenitor cells-apheresis will be done approximately at week 6 after CyCE chemotherapy for patients demonstrating responding tumour at first evaluation. Patient will receive GCSF at 10 µg/kg/day starting 48-72 hours following the completion of chemotherapy. Apheresis will be performed according to each institutional standard guideline. If the targeted $CD34^+$ cells cannot be collected after a maximum of two procedures, the flexible nature of the proposed guidelines allows the treating physicians to decide to use alternative factors for stimulation, or to give a further cycle of ICE chemotherapy before a next attempt to collect sufficient $CD34^+$ cells, or to decide to continue induction chemotherapy without high-dose melphalan consolidation.

To start high dose chemotherapy the following needs to be fulfilled:

- Proven partial or complete response to induction chemotherapy
- Sufficient stem cells available (defined as ≥ 3 x 10^6 CD34 cells/kg)

- GFR > 70 ml/min/1.73 m^2 using the Schwartz formula or 24-hour creatinine clearance or radioisotope GFR > 40 ml/min/m^2 or > 70 ml/min/1.73 m^2
- Cardiac function should be assessed as adequate
- Consider fertility preservation

Stem cell infusion

A minimum of 3 x 10^6 CD34 cells/kg (optimum 5 x 10^6 CD 34 cells/kg) PBSC should be used. Stem cells will be infused intravenously on day 0, 48 hours after chemotherapy is completed, immediately following thawing.

High-Dose Chemotherapy followed by Autologous Stem Cell Transplant:

Day	
-2	Melphalan
-1	
0	Autologous Stem Cell reinfusion

Drug doses during consolidation:	
Melphalan	200 mg/ m² total dose over 1 hour
DAY 0: 48 hours following chemotherapy completion - infusion procedure will be by institutional standard. GCSF infusion (5 µg/kg/day begins from day +4 after stem cell infusion and continues daily until ANC is greater for 2,000/µl for 3 consecutive days). Bactrim starts only after neutrophil recovery.	

Group CC

One of the goals of a wider international cooperation on recurrent WT will be to systematically channel WT patients into a limited number of active and emerging experimental studies. This is particularly true for group CC tumours and subsequent (following first one) failures of group BB relapses.

As a priority these children should be referred to centres that are conducting research trials on novel agents in the treatment of children with solid tumours (see: http://www.itcc-consortium.org/ for up-to-date news).

In the absence of available early phase clinical trials for entering WT patients, we suggest adopting the vincristine/irinotecan (VI) regimen as investigated in the recently closed COG AREN0321 protocol.

In case of complete or very good partial remission after the VI regimen, consolidation with HD-melphalan and PBSC rescue might be considered.

Suggested relapse treatment allocation according to initial stage and histology

Stage Histology	I	II	III	IV	V
LR	AA (or AV(D))	AA	AA	BB	According to 'highest' risk of the individual tumours
IR	AA	AA	BB	BB	
IR >500 ml	AA	BB	BB	BB	
HR-blastemal	BB (CC)	CC	CC	CC	
HR-anaplasia	BB (CC)	CC	CC	CC	

4.6.5. Surgical guidelines for relapse

The following statements for surgery in relapsed patients need to be taken into consideration:

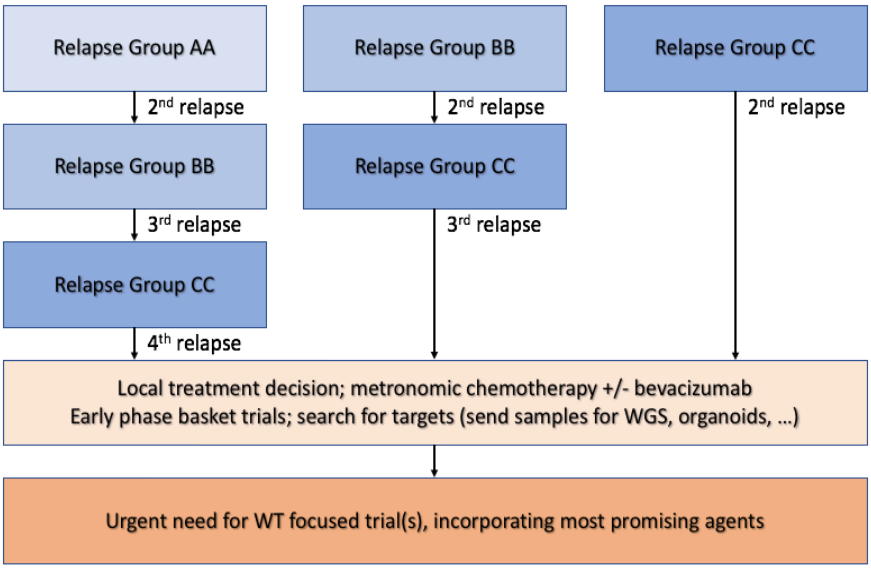
1. The first treatment is second line chemotherapy. Exceptions are late solitary lung metastasis. The CNS metastasis may be a surgical emergency.
2. The goal of surgery should aim for clear resection margins. The tumour bed and any suspicious residual disease should be clearly described to provide detailed information for radiotherapy targeting this site.
3. It is **not** recommended to operate on metastases that have progressed under chemotherapy unless it is a single metastasis.
4. If the relapse occurs in the field of radiotherapy, surgery likely represents the most efficacious local treatment, and all possible efforts should be undertaken to perform a complete resection.
5. For contralateral kidney recurrence (metachronous Wilms), surgical intervention requires an experienced team. Surgery is planned after tumour reduction with chemotherapy also in these patients.

4.6.6. Radiotherapy guidelines for relapse

Radiotherapy guidelines for relapse are given in detail in the radiotherapy section

4.6.7. Flowchart for subsequent relapses

In case of a subsequent relapse please contact your National PI for up-to-date information.
As a suggested overview please see the following schema.



5. Surgical guidelines

General recommendations for unilateral nephrectomy, metastectomy, nephron sparing surgery (NSS) and laparoscopic surgery (minimal invasive surgery (MIS)) are included. In addition, specific guidelines for WTs stage I-III, WTs stage IV, bilateral WTs, relapsed WTs and non-WTs are presented.

5.1. General surgical guidelines

5.1.1. Nephrectomy

Access: the long transverse abdominal incision is the preferred option. The thoraco-abdominal approach may be useful in huge masses located high in the abdomen, preventing the rise in the rate of tumour rupture and other complications. Whatever the incision, lymph nodes sampling must be done.

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. Every lesion should be excised (if resectable) or biopsied (if unresectable) and its position marked. Excised material must be sent to the pathologist in a separate container and its origin clearly indicated.

Thorough inspection of the opposite retroperitoneal space is obligatory **only** if pre-operative imaging (MRI is the preferred option) is unclear or indicates bilateral localisation of the tumour. In such cases intraoperative ultrasound may be useful to localise the lesion. Unequivocal stage V cases will be treated following 'Stage V treatment guidance'.

The procedure

The goal of the procedure is to perform a radical nephro-ureterectomy outside of the Gerota's fascia, including perirenal fat in mono-bloc resection. The colon should be mobilized to expose the retroperitoneal structures. In left sided tumours, the spleen may also be mobilized. On the right side, Kocher's maneuver is helpful in exposing the inferior vena cava and renal vein.

The renal artery and vein should be identified and controlled. The artery should be ligated first to avoid venous congestion and possible tumour rupture. In very large or infiltrating tumours, primary ligation of the renal vessels may be difficult or risky. In such situations, the tumour can be dissected from surrounding structures first, and the vessels ligated when possible.

The tumour should be removed together with its adipose capsule and Gerota's fascia, and if possible with all invaded surrounding structures. Very extensive and mutilating resections (e.g. pancreatectomy) however are not recommended, as these tumours are sensitive both to chemotherapy and radiotherapy. The ureter should be ligated and divided as low as possible in the pelvis.

The tumour bed could be marked with titanium clips to guide future radiotherapy if required.

Tumour thrombus in the renal vein and inferior vena cava

Preoperative evaluation, by MRI, CT or ultrasound scan, should state the patency of the renal veins and inferior vena cava (IVC). Although intravascular extension of the tumour is usually apparent on the pre-operative imaging, a careful examination of both renal vein and inferior vena cava is required during the operation. The classification of venous thrombus is linked to the surgical procedure needed to remove it entirely:

1. A short thrombus in the renal vein may be resected together with the vein.

2. A sub-hepatic thrombus (extending to the infra-hepatic vena cava but below the hepatic veins) should be removed through a vena cavotomy, after controlling the contralateral renal vein and vena cava above and below the thrombus.
3. Cardiopulmonary by-pass will be required in the case of intra-atrial thrombus. It may also be very useful in case of a longer thrombus, extending to or above the level of the hepatic veins.
4. In cases with very extensive infiltration of the vena cava wall, the risks and benefits of surgery should be reconsidered. Even with extensive vascular surgery it may be impossible to achieve complete excision and radiotherapy may be a better option as shown in SIOP 9.

Adrenal gland

The adrenal gland should be left in-situ if a safe resection margin between the tumour and the gland can be guaranteed. In tumours originating from the upper part of the kidney, adrenal preservation should not be attempted unless clear margins had been identified on preoperative images, or unless there is a clear plane at operation.

Lymph nodes

Sampling and histological examination of lymph nodes (LN) is imperative for accurate staging and subsequent treatment. This includes hilar LNs if not included in the radical nephrectomy specimen, and inter-aorto-caval LNs below the level of the renal pedicle even if not suspicious. It is useful to note that inter-aorto-caval LN normally belong to the right sided tumours as the anatomical border between left and right is the aorta and not the midline of the vertebral bodies but should be also accessed for left-sided tumours. Suspicious LNs at the aortic bifurcation, ipsilateral iliac axis, origin of the celiac trunk and superior mesenteric artery should also be sampled. It is recommended that at least 7 nodes are sampled and preferably not ruptured including the LNs sampled together with the specimen. They must be carefully labelled and sent to the pathologist separately with an accurate description of their position and character. Radical LN dissection does not enhance survival and therefore is not part of the surgical therapy.

Tumour rupture

In case of a tumour rupture the anatomical site and potential spread within the operational field should be documented. Infiltrations into adjacent tissue, affected LNs, macroscopic residues and macroscopic tumour ruptures should be described in detail.

5.1.2. Nephron sparing surgery (NSS) in unilateral cases

Unilateral cases may also benefit from NSS, but the nephrologic advantages and risk of recurrence have to be precisely evaluated for each individual case. Contra-lateral urological and nephrological disorders and genetic syndromes of an increased risk of WT rather than a risk of hyperperfusion nephropathy in the remaining kidney are important criteria when this option is considered.

NSS is acceptable in cases of unilateral non-syndromatic WT provided the following criteria are met:

1. Tumour restricted to one pole of kidney or peripheral at mid-kidney

2. Volume < 300 ml at diagnosis (the risk of positive LNs approx. 2 % only in small tumours)
3. No preoperative rupture (The imaging criteria for rupture: retroperitoneal peritumoural effusion/hemorrhage, peritoneal hemorrhage or nodules, spontaneously or by open biopsy and no intraoperative rupture)
4. No intraluminal tumour on preoperative imaging in renal pelvis
5. No invasion of surrounding organs
6. No thrombus in the renal vein or vena cava
7. No multifocal tumour
8. Excision can be performed with oncological safe margin
9. Kidney remnant is expected to show remaining function
10. At least 66% of renal tissue should be spared after the tumour resection with a margin of healthy tissue, to give any worthwhile protection against hyper perfusion. If this is in doubt pre-operative DMSA may be able to define expected post-operative function.

In case of visceral metastasis, NSS should not be systematically ruled out but considered carefully.
In all possible cases of NSS a reference surgical opinion is mandatory also stating if this patient should be referred for NSS to an experienced centre.

Remarks

A significant volume reduction after preoperative chemotherapy suggests a better chance of successful NSS but is not mandatory as some tumours have radiological modifications suggesting necrotic transformation without decreasing in size.
Functional imaging of the kidneys should be considered prior to surgery.
Resection must be performed with margins of healthy renal tissue. Enucleation is not adequate local treatment. In case of microscopically incomplete resection, further local treatment depends on a number of factors and should be discussed with the multidisciplinary team. In unfavourable subtypes of renal tumours, however, complete nephrectomy seems necessary.
Positive LNs at pathology after NSS indicate radiotherapy but NOT necessarily a completion nephrectomy.
Intraoperative ultrasound scanning can be useful in defining the intrarenal tumour extent.
Following NSS, the remaining kidney should be carefully followed up in short and long term: Doppler sonography two days after surgery. The contribution of spared renal tissue in the total urinary excretion should be assessed 6 months later with scintigraphy (DMSA). Creatinine clearance, hypertension and indicators of renal failure should be looked for/assessed every 3 months during the 2 first years, every 6 months for the next 3 years, then every year. This is important to understand the potential benefits or otherwise on long term renal function of NSS.
All members of the multidisciplinary team should take the decision for NSS together. The surgeon confirms the final feasibility during the operation.
Nephroblastomatosis in the renal parenchyma of the NSS specimen may give rise to metachronous nephroblastoma in the residual kidney. These patients should be followed very carefully.

Classification of nephron sparing surgery (NSS)

A classification for NSS has been developed by Audry et al. and approved by the panel of surgeons as follows:

1) SURGICAL TECHNIQUE
   - *NSS (A)* = Partial Nephrectomy
     = Resection of tumour with a rim of normal renal parenchyma
   - *NSS (B)* = Enucleation
     = Resection of tumour without a rim of normal renal parenchyma

2) SURGICAL RESECTION MARGIN (SRM)
   - Intact pseudo capsule *= (0)*
   - Doubt *= (1)*
   - Tumour breach *= (2)*

3) PATHOLOGICAL RESECTION MARGIN (PRM)
   - Safe rim of renal parenchyma on resection margin, except nephroblastomatosis *= (0)*
   - Intact pseudo-capsule along the resection margin *= (1)*
   - Tumour breach *= (2)*

4) REMAINING RENAL PARENCHYMA (RRP)

A subjective evaluation is done by the surgeon of the percentage of renal parenchyma remaining on the operated kidney
= (n %)

For example, a polar nephrectomy usually corresponds to a RRP of 70%.

A classification for each case would be reported as follows: *"NSS(X)-SRM(n)-PRM(n)-RRP(n%)"*.

5.1.3. Laparoscopic nephron-ureterectomy

Although the classical open approach to renal tumours of childhood is recommended, laparoscopic or laparoscopic assisted total nephrectomy is acceptable in WTs provided the following criteria are met:

1. Resection must adhere to oncological principles and include lymph node sampling.
2. Small, central tumours with rim of "normal" renal tissue.
3. The extraction of the specimen in a bag, without morcellation, through an adequate abdominal wall incision, is mandatory, not only to control the risk of dissemination, but also to ensure adequate histopathological staging.
4. If a NSS is feasible, it should be preferred even if an open approach is needed.

Contraindications for laparoscopic nephrectomy:

1. Tumour infiltrating extra renal structures or extended beyond the ipsilateral border of spinal column
2. Thrombus in the renal vein or vena cava
3. Peripheral location if NSS is not deemed feasible
4. Tumour without any response to chemotherapy due to the risk of tumour rupture
5. Little or no experience in laparoscopic nephrectomy (consider transfer to another unit or obtain more experienced help)

In all possible cases of laparoscopic total nephrectomy, a reference surgical opinion is mandatory also stating if this patient should be referred for laparoscopic surgery to an experienced centre.

5.1.4. Comments regarding pathology specimens

All suspicious structures should be biopsied or resected, marked, described precisely and sent to the pathologist in separate containers, either at initial diagnosis or at relapse. The intact surgical specimen should be delivered fresh (not fixed in formalin) to the pathologist without being opened by the surgeon. Please leave sutures on the ureter, renal vein and artery so that the pathologist is able to find them easily for histological examination. For relapse, the specimen needs to be orientated and suspicious areas should be clearly marked.

5.2. Surgical guidelines Wilms Tumour

5.2.1. Wilms Tumour Stage I-III

See general surgical guidelines above.

5.2.2. Wilms Tumour Stage IV

Lungs

Metastasectomy for lung metastasis should not be a primary intervention. Response under preoperative chemotherapy needs to be assessed. The timing of lung surgery depends on the response to chemotherapy and the treatment protocol. Metastasectomy can be performed either as a single stage approach together with the nephrectomy or preferably as delayed surgery after one or two courses of post-operative chemotherapy if metastasis are still present after preoperative chemotherapy. If a complete remission can be achieved by surgery after preoperative chemotherapy. Otherwise, timing of lung surgery is recommended as detailed in the stage IV-section

A thoracotomy approach is recommended in case of one-sided operable nodules. Bilateral resectable lung metastases should be excised either via two lateral thoracotomies, median-sternotomy or a bilateral anterior thoracotomy (clamshell approach) depending on surgical choice and anatomy. Size and location of metastases should allow for complete removal of all the lesions with limited extension of resections. A safety margin is recommended for any kind of metastasectomy if possible. Wedge resections can frequently be the best approach. If wedge resection will not achieve complete excision, then segmentectomy or lobectomy is acceptable. Pneumonectomy is not justified.

Peripheral nodules located sub-pleurally may be amenable to a thoracoscopic approach.

All excised lung lesions should be labelled with highest anatomical accuracy in order to correlate with radiological imaging and relate in case of pulmonary relapses whether the relapse occurred at a previously resected site or not.

Liver

For isolated liver metastases a wedge resection is appropriate after neoadjuvant chemotherapy. Extensive and potentially mutilating resections are not recommended before the possibility of further chemotherapy is explored.

Other sites

Metastases outside lung or liver should be excised completely if the operation can be done without mutilation, or loss of vital organs.

Complete excision of metastases where reasonably possible is strongly recommended. Further local and systemic treatment can depend on it and its histologic finding. Furthermore,

it possibly reduces the risk for local relapse. It is not recommended to operate on metastases that have progressed under pre-operative chemotherapy, as complete excision is rarely successful in such circumstances. Alternative chemotherapy and/or radiotherapy should be explored first.

5.2.3. Bilateral Wilms Tumours (Stage V)

Bilateral cases should be treated individually. The main surgical aim is to preserve as much functional renal tissue as possible. Due to the small numbers of such cases, it is recommended that a team experienced in the care of such patients is involved. Surgical intervention requires an experienced team and consideration should be given to centralising such cases to few centres. Thus:

- Each patient should be discussed in the context of a surgical national meeting to take decision with the advice of national experts.
- Surgery will be performed only at centres specialized in the treatment of this disease.

Surgery is planned after tumour response to chemotherapy, by either decreased size or radiological changes in favour of necrosis. If there is no tumour reduction under chemotherapy, tumours might be of stromal subtype where surgical resection of the tumour needs to be considered before intensifying chemotherapy. Chemotherapy for longer than 12 weeks rarely brings further response prior to surgery and therefore it is not recommended. Surgical resections can be multiple for one kidney.

The abiding principle is to achieve bilateral nephron sparing resections either in a single stage approach or in two separate operations performed not more than two post-operative courses apart. Biopsy of surgical margins to assess the complete resection of the tumour should be performed if not harmful for the remaining kidney. The less involved kidney should be operated on first. Complete nephrectomy on one side with NSS on the opposite side is acceptable providing enough functional renal tissue can be preserved.

If in spite of favourable appearances on imaging, the tumours appear unresectable at surgery, the tumours could be biopsied, preferably with the Tru-cut needle, and the patient treated with further chemotherapy. However, in rare cases bilateral complete nephrectomy may be the only surgical option. The options for radiotherapy as local treatment are limited after NSS but there are examples from the SIOP 9 study indicating that low dose radiotherapy (10Gy) and chemotherapy may result in long-term remission even after incomplete excision without any alteration of the renal function. This possibility should be taken into account in patients for whom bilateral nephrectomy would be the only means to achieve complete excision, or in patients with Denys-Drash syndrome with a lifethreatening blood pressure not responding to conservative treatment. If bilateral nephrectomy is performed, vascular access for dialysis (Permcath) should be inserted at the time of the second nephrectomy. Peritoneal dialysis may also be possible, although not usually in the immediate post-operative period. Transplantation should be planned provided there is no recurrent or residual disease, and preferably after 2 years of disease free survival.

When bilateral tumours are diagnosed accidently, during operation in a previously untreated patient, NSS, if possible, is the preferred option. But if NSS is not possible open or retroperitoneal US guided Tru-cut biopsy and/or primary closure of the abdomen and upfront chemotherapy as described above needs to be balanced.

5.2.4. Relapsed Wilms Tumour

First relapses, whether metastatic or local, are curable in a significant proportion of patients. Treatment should therefore be conducted with the intention of cure. A detailed imaging of the sites of relapse should be obtained before any surgical decisions. General considerations regarding surgery as described above do apply for relapses as well. The following paragraphs provide further statements for surgery in relapsed patients.

The first treatment is second line chemotherapy. Exceptions are late (> 2 years) solitary lung metastasis. The nature of such lung lesions appearing a long time after the treatment for Wilms' tumour may not be clear until histological examination. The CNS metastasis may be a surgical emergency.

In the remaining cases, surgical resection should be undertaken after a response to chemotherapy is apparent and when all persisting sites of disease are amenable to complete excision. The goal of surgery should aim for clear resection margins. The tumour bed and any suspicious residual disease should be clearly described to provide detailed information for radiotherapy targeting this site.

It is **not** recommended to operate on metastases that have progressed under chemotherapy, as complete excision is rarely successful in such circumstances. Alternative chemotherapy and/or radiotherapy should be explored first.

Surgical excision of liver or lung nodules should be reserved for small numbers of operable metastases, after chemotherapy and only in patients with stable disease or partial response. The indication needs to be done together with surgeons, radiotherapists and oncologist.

If the relapse occurs in the field of radiotherapy, all possible efforts should be undertaken to perform a complete resection. Local relapse and lung or liver metastases are frequently resectable. Lymph node relapse, especially if in a previously irradiated field is a very difficult problem. Even radical para-aortic lymphadenectomy may bring no benefit to the patient as the lymph node invasion frequently continues into the mediastinum.

For contralateral kidney recurrence (metachronous WT), surgical intervention requires an experienced team. Surgery is planned after tumour reduction with chemotherapy also in these patients.

5.3. Surgical guidelines for non-Wilms Tumours

5.3.1. Clear cell Sarcoma of the Kidney (CCSK)

Use surgical guidelines as described for Wilms tumours

5.3.2. Renal Cell Carcinoma (RCC)

Complete Surgical Tumour Resection (R0) is the mainstay of cure in paediatric RCC. The standard recommended surgical procedure is radical nephrectomy (RN). We recommend being cautious to consider partial nephrectomy in children. The EORTC led a prospective randomized clinical trial (RCT), comparing radical nephrectomy with partial nephrectomy in solitary T1-T2 N0M0 renal tumour < 5 cm with normal contralateral kidney function and WHO performance status of 0-2. At 9.3 years survival follow-up, 198 patients (72.5%) were alive after radical nephrectomy and 173 (64.4%) after NSS. Local recurrence occurred in one patient in the nephrectomy group and in six in the NSS group. Indications to NSS are increasing for adult patients: it is now considered in cases of small tumours (i.e. < 4 cm [up to $\leq$ 7cm?] diameter, possibly all T1-T2 RCC) and – if technically feasible - in all cases with reduced renal function or/and renal malformation and in all cases with estimated higher risk of metachronic secondary RCC or secondary renal function deterioration such as especially RCC as part of a

syndrome (Tuberous Sclerosis, VHL, others), RCC after chemotherapy or as second malignancy, RCC or renal failure in the family. We need to remind that in children, still the differentiation between RCC and WT is not possible by imaging studies, even in the adolescence group, and WT remains the most frequent renal tumour type. However, we believe that any case of small renal neoplasm in children > 10 years should be regarded as a potential RCC, and consequently be discussed with the reference surgeons, with the aim of considering NSS procedures in selected cases. In addition, it is difficult to extrapolate the tumour dimension criteria from adulthood experience, since the kidney dimensions in children are different. NSS is advised in such cases only after extensive discussion with the SIOP surgical panel [34, 35]. The standard indications for adult NSS in RCC according to the European Association of Urology guidelines [36] are divided into the following categories:

1. absolute (anatomic or functional solitary kidney),
2. relative (functioning opposite kidney that is affected by a condition that might impair renal function in the future), and
3. elective (localized unilateral RCC with a healthy contralateral kidney).

Relative indications also include patients with hereditary forms of RCC who are at high risk of developing a tumour in the contralateral kidney in the future [36]. During the last decade, NSS has become the gold standard for the treatment of T1a tumours (< 4 cm) in adult patients with a normal contralateral kidney and – when performed in carefully selected patients in specialized centres - NSS can be safely applied in patients with larger renal tumours. In adult patients several studies showed equivalence of NSS and RN in oncological outcome in localized RCC at least in T1RCC.

Data for NSS in paediatric RCC are very limited. However, no difference exist between NSS and RN concerning the oncological outcome. Nevertheless, before performing NSS in a child, we recommend to discuss the indication with the surgical board of SIOP-RTSG in all cases, similar to what is recommended in all other pediatric renal tumours.

General surgical principles in RCC:

- The completeness of surgical resection is of prognostic importance
- Low stage disease has a better prognosis than later disease stages
- NSS might have a role in low-volume localised cancer in carefully selected patients.
- Expert's opinions are strongly recommended in case of partial nephrectomy and regional lymphadenectomy as these still need to be determined.

Regional lymph node positive RCC (stage T1-4, N1-2, M0)

Most children with RCC will be diagnosed after initial WT treatment preoperatively. Therefore, the role of regional LN re-dissection in cases that were suspected of WT and had LN sampling only, is still under debate in paediatric patients with RCC. Paediatric patients with RCC and positive LNs seem to have a relatively more favourable outcome than adults. In case the diagnosis of RCC is known at the time of surgery, total regional lymphadenectomy needs to be done whenever feasible without significant surgical morbidity. In an Italian study of 16 paediatric RCC patients with local LN involvement, the survival rate in patients with extended retroperitoneal LN dissection (RLND) was markedly better than in cases with a more limited LN resection (8 of 9 with RLND alive and disease free vs. 1 of 7 without RLND).

Distant metastatic RCC (stage T1-4, N0-2, M1)

In case of metastatic RCC complete renal tumour resection with negative surgical margins as described above is strongly advised together with retroperitoneal LN sampling.

After a medical treatment approach (recommendations see below) for response evaluation, surgical resection of all metastases should be attempted as completely as possible.

5.3.3. Malignant rhabdoid tumour of the kidney (MRTK)

In most patients the diagnosis of MRTK is unknown before surgery. Therefore, the general guidelines for surgery of paediatric kidney tumours as described above need to be adhered. Total resection of MRTK is significantly correlated with increased relapse free survival, as advanced stage has a significantly negative impact on survival. Van den Heuvel-Eibrink and colleagues reported 19% for stage III compared to 50% for stage I EFS after 5 years. Tomlinson compared stage I&II with stage III, IV and V resulting in 41% OS compared to 19% OS.

Delayed surgery in non-completely resectable MRTK is preferred, instead of delaying treatment. MRTK usually shrinks on anthracycline containing treatment, and intensive treatment is often providing a setting in which a complete resection becomes possible. It is encouraged not to delay surgery too long, as the biology of the disease tends to give rise to early progression.

Due to the aggressive nature of MRTK a NSS cannot be recommended. Tumournephrectomy is thus the surgical approach of choice.

5.3.4. Congenital mesoblastic nephroma (CMN)

Complete nephrectomy is the treatment of choice in localized disease and should be done according to the general surgical guidelines provided above. The perirenal fat needs to be removed always, as CMN tends to infiltrate in the surrounding tissue. Re-resection should be performed in case of incomplete tumour resection or incomplete removal of the perirenal fat. Metastectomy is advised in exceptional cases with solitary metastasis.

6. Radiotherapeutic guidelines

Depending on tumour stage, histology, chemotherapy response and resection status, in about 15 % of the children with nephroblastoma radiotherapy (RT) still plays an important role in curative treatment concepts.
In addition, palliative RT may contribute to the treatment options in cases with no curative intent.
In general, the indications and treatment strategies for RT in the SIOP– 2001 – protocol have been adequate and successful, so not many changes in the context of RT had to be implemented in the new protocol.
Some important changes, which are described in detail later in this chapter, have been made:

- No boost irradiation to the lymph nodes in stage III with initially positive lymph nodes and complete resection.
- The dose of whole lung RT has been reduced to 12 Gy in intermediate risk histology cases.
- Whole lung RT is indicated in the case of intermediate risk histology with complete resection but histological residual disease.
- In cases of recurrent disease with lung metastases without prior lung irradiation during first line treatment whole lung RT should be performed in all histology- and remission types.
- New irradiation techniques like IMRT and IGRT may be used as long as they contribute to a dose reduction in normal tissue at risk (e.g. liver, heart), include the target volume as recommended and avoid substantial dose scattering to non-involved areas in a larger volume.

6.1. Radiation therapy treatment of local abdominal disease

6.1.1. Indications for post-operative local or flank RT:

- Intermediate risk, stage III (lymph nodes positive N+, residual disease left after surgery, tumour rupture); (In adults also stage II)
- High risk, stage II (except blastemal subtype[1])
- High risk, stage III (all histological subtypes)
- Stage V according to local stage

6.1.2. Indications for post-operative whole abdominal RT:

Whole abdominal RT is indicated for diffuse intra-abdominal tumour spread or gross preoperative or intraoperative “major rupture”.

6.1.3. Start of RT

Abdominal/flank RT will start as soon as possible within 2 – 4 weeks after abdominal surgery. If there is an expectation for an additional RT for lung metastases, the abdominal RT will be postponed and starts after lung surgery. It is ideal to give lung- and flank RT in one field together.
In cases with a high risk of local recurrence in the flank after surgery, mainly in cases with diffuse anaplasia, flank irradiation should not be delayed and can be delivered separately from whole lung RT.

[1] Since the poor prognosis of blastemal subtype is caused by the occurrence of metastases and not by increased local recurrence unlike in other high risk tumours there is no necessity for a local radiation in stage II

Age related dose reduction

Total dose is dependent on pathology. The daily fraction dose to ICRU prescription points is conditioned by the age of the child (younger children <2 years and >2 years) and the volume (e.g. whole lung or abdomen) encompassed.

Dose per fraction may be reduced in children <2 years of age to 1.5 Gy/fraction (flank irradiation) or 1.25 Gy/fraction (whole abdominal irradiation).

The dose per fraction will be decided by the treating radiation oncologist and will depend upon the age of the child and the volume encompassed. One fraction per day should be treated daily, five days per week.

In general a national RT reference institution should be contacted in these rare cases.

6.2. Local flank radiotherapy - dose and fractionation

6.2.1. Intermediate risk histology – local flank RT

- Stage III based on positive lymph nodes or microscopic residual disease: 14.4 Gy in 8 fractions (1.8 Gy per fraction) to the involved flank or pre-operative tumour region
- Boost to the macroscopic residual abdominal disease after surgery: 10.8 Gy boost in 6 fractions on macroscopic residual tumour (leading to a total dose of 25.2 Gy)
- No boost on the lymph node area is needed, if no macroscopic residuals are detectable in this area.

6.2.2. High risk histology – local flank RT

General Indication on Stage II and III (except blastemal type in stage II):

Diffuse anaplastic type:

Stage II and III:

- 25.2 Gy in 14 fractions (1.8 Gy per fraction) to the involved flank.
- Boost to macroscopic residual disease after surgery with 10.8 Gy to a total dose of 36 Gy.

Blastemal type:

Stage III:

- 25.2 Gy in 14 fractions (1.8 Gy per fraction) to the involved flank.
- Boost to macroscopic residual disease after surgery with 10.8 Gy to a total dose of 36 Gy.
-

For Rhabdoid tumour and CCSK see corresponding chapters

6.3. Whole abdomen radiotherapy – dose and fractionation

Stage III based on spillage/rupture:

- Whole abdomen with 15.0 Gy (IR) or 19.5 Gy (HR) in 10 or 13 fractions (1.5 Gy per fraction).
- Consider reduction of the total dose in children younger than 2 years to 12.0 Gy.
- Dose per fraction may be lowered to 1.25 Gy in case of toxicity and very young children (< 2 years).

Stage III based on macroscopic peritoneal deposits (IR and HR):

- Whole abdomen with 19.5 Gy in 13 fractions of 1.5 Gy.
- Consider a boost to a limited area if necessary up to 25.2 Gy (IR) or 36 Gy (HR) for macroscopic remnants.

- Reduction of the total dose in children younger than 2 years to 12 Gy.
- Dose per fraction may be lowered to 1.25 Gy in case of toxicity and very young children (< 2 years).

6.4. Summary recommendation of radiation therapy treatment of abdominal disease

	Stage II	Stage III (except major rupture)	Stage III (major rupture)
Intermediate Risk	no indication	14.4 Gy in 8 fractions, +/- 10.8 Gy boost	Whole abdomen 15.0 Gy in 10 fractions +/- 10.8 Gy boost
High risk **Diffuse anaplasia**	25.2 Gy in 14 fractions +/- 10.8 Gy boost	25.2 Gy in 14 fractions +/- 10.8 Gy boost	Whole abdomen 19.5 Gy in 13 fractions +/- 10.8 Gy boost
High Risk **Blastemal type**	no indication	25.2Gy in 14 fractions +/- 10.8 Gy boost	Whole Abdomen 19.5 Gy in 13 fractions +/- 10.8 Gy boost

6.5. Dose reduction of chemotherapy

Avoid ACT and doxorubicin from 1 week before until 2 weeks after radiotherapy and then apply full dose.

6.6. Radiation therapy treatment of stage V (Bilateral Wilms Tumour)

Management of bilateral WT is constantly evolving and still stands as a therapeutic challenge. Patients receive postoperative therapy according to histology and to the highest assigned risk for either kidney.

Local RT is indicated after nephrectomy according to the guidelines for unilateral disease. Furthermore RT may be adequate to prevent local recurrence in case of positive surgical margins (stage III) as part of nephron sparing surgery (enucleation, partial nephrectomy). A national radiotherapy reference institution should be contacted in these cases.

6.6.1. Indications for postoperative local radiotherapy

Bilateral Nephroblastoma (Stage V) with complete resection of all gross tumours - according to local stage

- Intermediate risk histology, stage III (nodes positive N+, positive margins, residual disease left after surgery, tumour rupture)
- High risk histology, stage II (except blastemal type) and stage III (all high risk histologies)

6.6.2. Radiation therapy treatment after nephron sparing surgery - dose and fractionation

In case of irradiating a remaining kidney after nephron sparing surgery the dose to the whole kidney should not exceed 10-12 Gy (12 Gy maximum dose), even if there is high risk histology.

Boost irradiation focussed to areas at risk (surgical margin) is difficult to perform because of small target size and target movement; nevertheless, it may be taken into account if the technical preconditions make a proper dose distribution reliable. (Brachytherapy in selected cases).

In general a radiotherapy reference institution should be contacted in these cases.

Stage II:

In cases of high-risk histology except blastemal type the area at risk (surgical margin) or the whole kidney should be irradiated to a total dose of 10.8-12 Gy in 1.5 – 1.8 Gy per fraction.

No indication for radiotherapy to cases with intermediate risk histology.

Stage III:

In patients with positive margins (local stage III), any histologically type should be irradiated to the area at risk (surgical margin) or the whole kidney to a total dose of 10.8-12 Gy in daily fractions of 1.5-1.8 Gy.

In patients with stage III because of lymph node involvement and local stages I or II (intermediate risk) or stage I (high risk) only the para-aortic lymph node area should be irradiated with 14.4 Gy (intermediate risk) or 25.2 Gy (high risk), 1.8 Gy per fraction.

In patients with local stage III (intermediate risk) or local stages II and III (high risk) and lymph node involvement, a flank irradiation should be performed; the target volume has to be reduced after 12 Gy maximum dose to the remaining kidney using a shrinking field to the lymph node area.

6.7. Radiation therapy treatment of metastatic sites

6.7.1. Indications for pulmonary radiotherapy (primary treatment)

Low Risk Histology:

Indication of RT in LR tumours should be discussed with national PI, since it is usually **not** indicated or it is per definition not a LR tumour.

Intermediate risk histology:

- No complete remission of the lung metastases after chemotherapy (week 10 of postoperative chemotherapy) and/or surgery in chest computed tomography.
- Histological viable tumour in resected metastases after chemotherapy and surgery.

Pulmonary Radiotherapy should not be given:

- If a CR is achieved in computed tomography latest at week 10 of postoperative chemotherapy
- If representative resection of nodules at time of nephrectomy all showed no viable metastasis
- If a CR of all metastases is achieved surgically based on the finding from the Chest-CT Scan at time of nephrectomy and no viable metastasis was found.

High risk histology:

- All cases of primary lung metastases regardless of the response to chemotherapy or surgical treatment.

Dose and fractionation

- The total dose is 12 Gy (intermediate risk) and 15 Gy (high risk) for both lungs.
- The dose per fraction is 1.5 Gy (with homogeneity correction), delivered within 8-10 fractions.

A boost of 10-13 Gy (intermediate risk histology) and 15-20 Gy (high risk histology) should be considered for areas of macroscopic residual disease after surgery using highly conformal radiation techniques (SBRT), if possible and normal tissue dose constraints can be respected.

Timing of pulmonary radiotherapy

In case of abdominal RT with pulmonary RT it is recommended to treat the chest and the abdomen simultaneously in one planning procedure (resp. in one field) in order to avoid any gap or overlap of both fields (cardiotoxicity).

In case of resected abdominal stage III disease with a high probability of local recurrence such as cases with diffuse anaplasia histology, abdominal RT may be applied after surgery and pulmonary radiotherapy may be given later in a separate field.

6.7.2. Indications for hepatic radiotherapy

Liver metastases which do not respond completely to chemotherapy and which cannot be completely resected with negative margins should be irradiated either with total liver irradiation or partial liver irradiation depending on the number and the distribution of the metastases.

In principle, a similar approach as for lung metastases may be used.

Dose and fractionation

A total dose of 14.4 Gy for intermediate risk and 19.8 Gy for high risk histology should be given to the whole liver; unresected residual metastases after chemotherapy or the area of incomplete resection of metastases may be boosted up to 25.2 (IR) or 36.0 Gy (HR); a simultaneous integrated boost (SIB) technique or stereotactic RT may be used. Dose per fraction is 1.5-1.8Gy.

The total dose to the whole liver should not exceed 20 Gy.

6.7.3. Indications for radiotherapy to other metastatic sites

Metastatic disease to other organs than lung or liver is a rare event in nephroblastoma; therefore the treating radiotherapist should discuss in such cases the radiation therapy options with panel radiotherapists.

Patients with haematogenous metastases to the brain and/or bone metastases at diagnosis should be treated with the appropriate RT fields regardless of response to chemotherapy.

Brain: The whole brain is treated to a dose of 15.0 Gy for intermediate risk and 25.2 Gy for high-risk histology (1.8 Gy per fraction). A boost of 10.8 Gy may be given to a total of 25.2 Gy (IR) resp. 36 Gy (HR). A simultaneous integrated boost (SIB) technique may be used.

Bone: Bone metastases may be treated with a dose of 30 or 30.6 Gy. Dose per fraction is 1.8-3 Gy (individual decision by performance status, prognosis, localisation of the metastases and individual palliative situation).

6.8. Summary recommendations of radiation therapy treatment of metastatic sites

	Metastatic Site			
	Lung	**Liver (incomplete resection)**	**Brain**	**Bone**
Intermediate Risk histology	Whole lung 12.0 Gy in 8 fractions	Whole liver/ local 14.4 Gy in 8 fractions (boost 10.8 Gy)	Whole brain 15.0 Gy in 10 fractions +/- 10.5 Gy boost	Local 30.6 Gy in 17 fractions or 30 Gy in 10 fractions
High Risk histology	Whole lung 15.0 Gy in 10 fractions	Whole liver/ local 20-25.2 Gy in 11 fractions (boost 16.2 Gy)	Whole brain 25.2 Gy in 14 fractions +/- 10.5 Gy boost	Local 30.6 Gy in 17 fractions or 30 Gy in 10 fractions

6.9. Radiation therapy treatment of recurrent disease

6.9.1. Radiation treatment of local relapses in the abdomen

1. Recurrent local tumour in abdomen/flank without previous radiotherapy

Radiotherapy according to histologically type and chemotherapy response; the same procedure as in the first line treatment (see chapter: “Radiotherapy of local abdominal disease”)

2. Recurrent local tumour in abdomen/flank after a previous radiotherapy

All cases receive radiotherapy according to the localisation and the dose and volume of the first line RT. Because of many different situations it is impossible to develop standard recommendations. Nevertheless in many cases a re-irradiation should be possible because of the low doses necessary. New techniques like IMRT should be taken into account as they may contribute to a reduction of dose in normal tissues such as small bowel or liver.
The treating radiotherapist should discuss the radiation therapy options with panel radiotherapists.

6.9.2. Radiation treatment of relapses in the lung

1. No lung irradiation in the first line treatment:

Whole lung RT is **always** indicated in cases of lung metastases as a recurrent disease and no prior lung irradiation for patients with intermediate as well as high risk histology.
Target volume and doses see chapter: “Radiotherapy treatment of metastatic sites, pulmonary RT”
RT should take place after chemotherapy and surgery (if performed).

2. Lung irradiation in the first line treatment:

In this case, no further whole lung RT can be performed. In case of residual disease small volume RT (stereotactic body radiotherapy (SBRT)) should be considered, according to the histological type. The treating radiotherapist should discuss the radiation therapy options with panel radiotherapists.

6.10. Interruptions and breaks

Breaks must be kept to an absolute minimum. Interruptions due to treatment machine service and public holidays must be avoided unless absolute necessary. Both breaks and interruptions should be compensated if longer than 2 days.

Interruptions for myelotoxicity:

- RT should be interrupted if the neutrophil count falls below $0,5x10^9$/l and should not be resumed until the count is at least $1,0x10^9$/l.
- RT should be interrupted if the platelet count falls below $25x10^9$/l and should not be resumed until the count is at least $50x10^9$/l.
- The haemoglobin level should be maintained at a minimum of 10 g/dl during RT with correction by transfusion if necessary.
- GCSF may be used in the case of the neutrophil count falling below 0,5, and continued until it is greater than 1,0.

6.11. Equipment and treatment technique (Simulation/Treatment performance)

Megavoltage equipment (photons form a modern linear accelerator energy usually 4-6 MV, radiation technique AP/PA opposing fields, 3D conformal or intensity modulated radiotherapy (IMRT)-technique, IGRT techniques should be available.

All patients will undergo a simulation procedure with conventional simulator or preferred a virtual CT-simulator (specially to optimize critical organs sparing (heart, liver, contralateral kidney etc.).

The CT based radiation treatment planning is the standard of care.

All Patients will generally be treated in supine position.

6.12. Target volume definition

Target volumes are defined according to ICRU guidelines (ICRU 50 and 62).

Dose uniformity and Reference Points (ICRU):

Target dose is calculated and reported according to the ICRU criteria.

The reference point is in a central part of the target volume.

The dose variation within the target volume should not exceed ±5% until ±7-10% of the prescribed dose. CT based computed dose have to follow the same rules for target dose specification.

Margins for PTV will be influenced by individual departmental policy (availability of 4D-CT scan radiation treatment planning and IGRT, individual IGRT-frequency).

In general the margins that will be applied will be as follows:

6.13. Target volumes

Localisation of primary tumour and kidney for flank/abdominal RT

For RT planning the preoperative tumour extent should be localised according to the **preoperative contrast-enhanced CT and/or preoperative T2-weighted MRI scan**. A preoperative CT or MRI scan is the optimal imaging modality and should be performed to optimize target volume delineation as a standard of care.

The boundaries of tumour residuals during surgery should be marked with **clips**, particularly in the case of areas suspicious of incompletely resected disease.

In addition, important information may be available in the **surgical and histopathological reports.**

For volume-reduced IMRT-techniques a supplemental protocol will be available. These techniques should only be undertaken in centres with extensive IMRT and IGRT experience.
In the case of pre-operative or intra-operative rupture the anatomic location and the intra-abdominal space (intra/retroperitoneal) should be clearly indicated in the surgical note and drawing. Infiltration of the peri-renal fat, diaphragm, involved lymph nodes, macroscopic incomplete resection, microscopic or macroscopic ruptures have to be stated clearly.

6.14. Clinical target volume (CTV) and planning target volume (PTV)

6.14.1. Flank-Radiotherapy

The clinical target volume (CTV) is defined as the preoperative gross tumour volume (GTV)+ 1 cm margin. The CTV may occasionally be adapted or modified in order to spare nearby organs at risk. The internal margin for breathing movements and interfractional movements to PTV is defined as CTV plus 1 cm.
The PTV should extend across the midline to achieve homogeneous irradiation of the full width of the vertebral bodies to prevent a scoliosis. The contralateral kidney should be spared as good as possible.
The radiation field should not be extended into the dome of the diaphragm unless there is tumour extension. If possible do not irradiate major parts of the heart (left sided tumours).
In case of positive lymph nodes (stage III) that have been removed, the entire length of the para-aortic chain of lymph nodes will be included. Lymph node groups that were involved at presentation should be included. Nodal areas will be treated in continuity with the primary tumour area. The cranial field border should be at the thoracic vertebra TH10-/11 level while almost 50% of the celiac axis arises from the aorta at the level of the pedicle of the 12th vertebral body.
Boost volume for residual macroscopic disease:
Extent of residual macroscopic disease at surgery (postoperative MRI/CT scan is necessary) with a 1-2 cm safety margin.

6.14.2. Whole abdominal RT

CTV/PTV: This includes the entire abdominal contents and peritoneum extending from the dome of the diaphragm to the pelvic floor (lower border of obturator foramen).

6.14.3. Pulmonary RT

CTV/PTV: This encompasses both lungs including the apices and costo-diaphragmatic recessus.
If abdominal radiotherapy also is to be given, both fields may be matched and irradiated simultaneously in order to avoid any gap or overlap.

6.14.4. Liver RT

CTV/PTV: This includes the whole liver and as a boost the extent of incompletely resected or residual tumour with margin of 0.5 - 1cm. Margins for PTV depends on the internal target motion and will be influenced by individual departmental policy (availability of 4D-CT scan radiation treatment planning and IGRT). A simultaneous integrated boost technique (SIB) may be used.

6.14.5. RT for brain metastases

CTV/PTV: The whole brain is treated; a boost to single metastases may be performed. A simultaneous integrated boost technique (SIB) may be used.

6.14.6. RT for haematogenous metastases to bone

CTV/PTV: For bone metastases it is not necessary to treat the entire bone. The field include the obvious disease visible on imaging examination, with an appropriate margin depending on the skeletal area involved.

6.15. Normal tissue sparing

Dose in organs at risk is calculated and reported for each organ separately. It is recommended to add the estimated volume of the organ irradiated to the reported dose. Typical organs at risk in nephroblastoma treatment are the vertebral column, lung, iliac bone, contralateral kidney, small bowel, soft tissue of irradiated flank, liver, ovaries, testes, thyroid gland, mammary gland and heart.

6.15.1. Critical organ dose

Kidney: The dose to the remaining kidney should not exceed more than 10 – 12 Gy (V10 < 25-30%).
Liver: The dose to the whole liver should not exceed 20 Gy. A dose exceeding 20 Gy should not be received by more than half of the liver (V20 < 50 %, D_{mean} < 20 Gy).
Lung: The whole lung dose should not be more than 15 Gy in 15 fractions (HR-patients) with correction for inhomogeneity. A dose exceeding 15 Gy should not be received by more than 25% of the lung volume. (V15 < 25%).

6.15.2. Shielding:

Joints: For pulmonary RT the shoulder joints should be shielded.
For whole abdominal RT the hips should be shielded.

6.16. Examples for typical target volumes and radiation portals

(Related to anatomical landmarks)

Stage II high risk, stage III (Fig. 1a-c)
Cranial border:

- Right sided tumours: if feasible 1-2 cm below the dome of the diaphragm (sparing of the liver)
- Left sided tumours: 1-2 cm above the macroscopic tumour (e.g. dome of diaphragm), if possible do not irradiate the heart.

Caudal border: 1-2 cm below the macroscopic tumour e.g. within the iliac fossa often including the iliac crest (Position of the ovaries (homo-/contralateral) is important.
Lateral border: Including der abdominal wall
Medial border: Depending on tumour extension: including the vertebral bodies and shield the contralateral kidney.
Boost volume only for macroscopic residual disease after surgery with 1-2 cm margin (Fig. 1b, c, 2b)

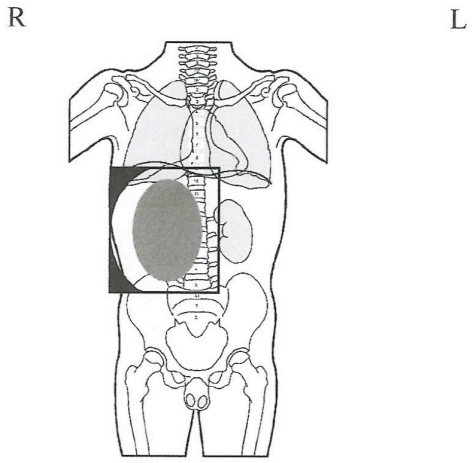


Fig. 1a: Right-sided tumour with stage III (microscopic residual disease, minor rupture). Radiation portal covering the tumour region including the vertebral column, the iliac crest and major parts of the right liver. The same type of radiation portal would apply for a nephroblastoma stage II, high grade.

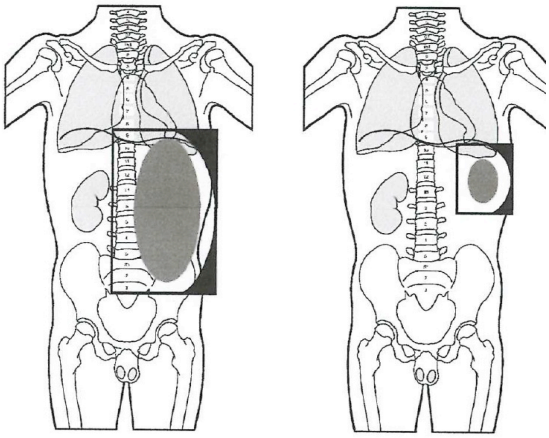


Fig. 1b: Extensive left-sided tumour from the dome of the diaphragm to the fossa iliaca with macroscopic residual disease at the splenic hilus (Stage III). Radiation portal including the major part of the left hemi-abdomen with the vertebral column; boost portal including the left upper abdomen without the vertebral column.

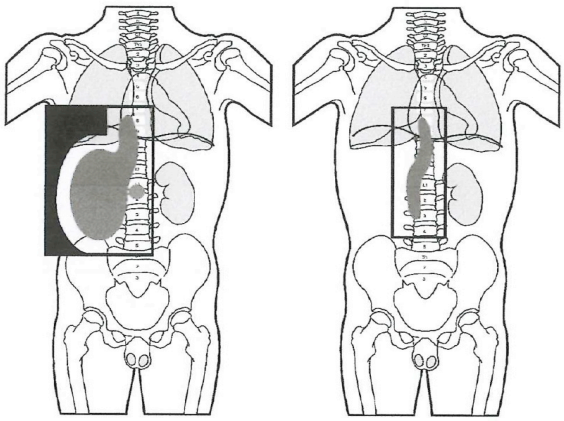


Fig. 1c: Right-sided tumour with paraaortic lymphnode metastases infiltrating the vena cava inferior up to the diaphragm and tumour thrombus up to the right atrium (Stage III): lymph nodes and tumour thrombus could not be completely removed macroscopically by surgery. Radiation portal encompassing the tumour region, the paraaortic lymphnode chain, and the vena cava inferior including part of the right atrium. Boost portals covering the area of the macroscopic residual disease: paraaortic lymphnode chain, vena cava inferior, and the part of the right atrium.

Stage III intermediate and high risk (Fig. 2a, b)
(if lymph node involvement under the level of the renal artery)

Target volume encompasses the whole para-aortic lymph node chain including the homo-lateral pararenal lymph nodes and the macroscopic tumour extends at surgery + 1-2 cm safety margin. The safety margin may not be feasible towards the contra-lateral kidney and to large volumes of the liver.

Examples for typical Target Volumes and Radiation Portals:

Cranial border: Right sided tumours: if feasible 1-2 cm below the dome of the diaphragm (sparing of the liver)

Left sided tumours: 1-2 cm above the macroscopic tumour (e.g. dome of diaphragm), if possible do not irradiate the heart.

Caudal border: 1-2 cm below the macroscopic tumour e.g. within the iliac fossa often including the iliac crest (Position of the ovaries (homo-/contralateral) is important!

Lymph node chain: lower plate of L IV but for preventing inhomogeneous dose to the bone, the border is often the elongation of the caudal border.

Lateral border: including the abdominal wall

Medial border: including the transverse process of the vertebral column.

Boost volume only for macroscopic residual disease in the lymph nodes after surgery

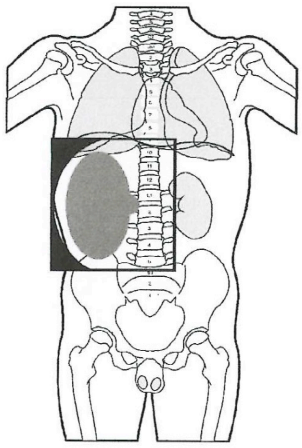


Fig. 2a: Right-sided tumour with one homolateral para-renal lymphnode involved and removed (stage III). Radiation portal covering the tumour region (including the right dome of diaphragm and the iliac crest) and the whole para-aortic chain.

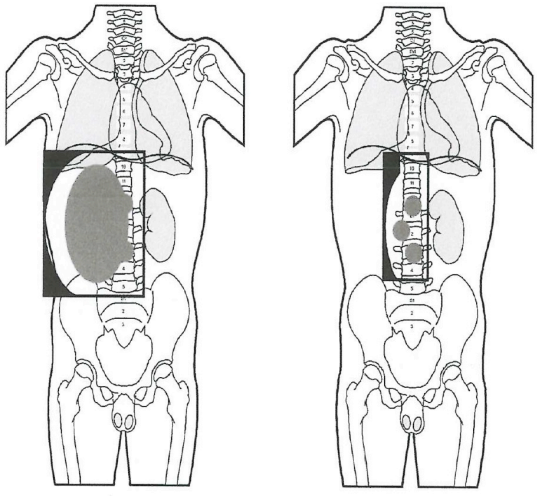


Fig. 2b: Right-sided tumour with several para-aortic lymphnode involved (stage III) and suspicious macroscopic residual disease in the lymphnode chain at surgery (stage III macroscopic residual disease). Radiation portal covering the tumour region and the whole para-aortic lymphnode region. Boost volume in case of macroscopic residual disease refined to the lymphnode chain including the homo-lateral renal hilus.

Stage III (all histologies): major intra-/retroperitoneal rupture

Examples for typical Target Volumes and Radiation Portals:

1) Major intraperitoneal rupture (Fig. 3)

The target volume encompasses the whole intraperitoneal cavity

Cranial border: including both domes of the diaphragm

Caudal border: upper part of the symphysis

Caudal and lateral border: line along the inguinal ligament (sparing the epiphyses of the femoral head).

Lateral border: including abdominal wall. Cave on remaining kidney dose and dose at the testes.

Boost volume only for macroscopic residual disease after surgery with a 1-2 cm safety margin.

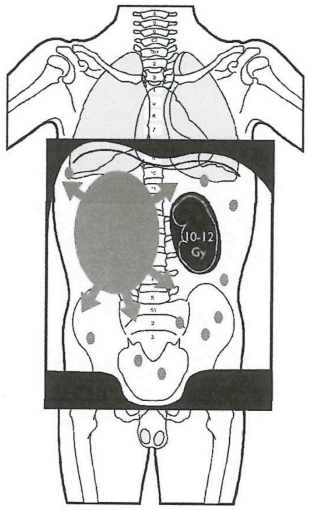


Fig. 3: Massive intraperitoneal rupture during surgery as right-sided tumour broke into many pieces and spread around the intraperitoneal cavity (stage III major rupture). Radiation portal covering the whole intraperitoneal cavity. No boost indicated as no detectable macroscopic residual disease was seen at surgery.

2) Major retroperitoneal rupture (Fig. 4)

Cranial border: including both domes of the diaphragm

Caudal border: upper part of the symphysis

Caudal and lateral border: line along the inguinal ligament (sparing the epiphyses of the femoral head).

Homo-lateral border: including abdominal wall. Cave on remaining kidney dose and dose at the testes.

Contra-lateral border: including the vertebral bodies, line from edge of LV to symphysis (cave contralateral ovary dose and dose at the testes!)

Boost volume only for macroscopic residual disease after surgery with a 1-2 cm safety margin.

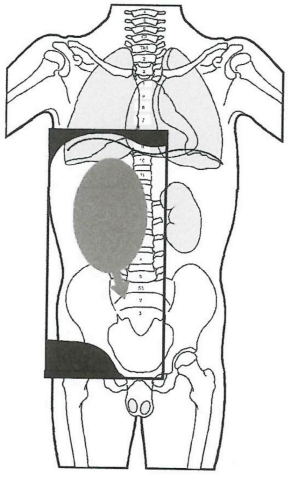


Fig. 4: Extensive retroperitoneal rupture in a huge tumour without contamination of the intraperitoneal cavity (stage III major retroperitoneal rupture). Target volume encompasses the whole homo-lateral retroperitoneal space (right) including the prevertebral space. Boost is indicated if there is macroscopic disease left in the retroperitoneal space during surgery.

Pulmonary radiotherapy (Stage IV)

Examples for typical target volumes and radiation portals: stage IV (lung)

If local abdominal radiotherapy has to be performed, pulmonary and abdominal targets are defined on the same portal imaging. If the targets overlap, a decision has to be taken related to target matching of two adjoining fields or using intensity modulated radiotherapy techniques.

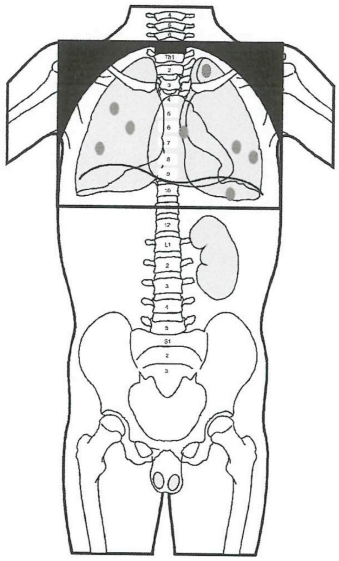
Cranial border: including the top of the lung (some cm above the clavicle)

Caudal and lateral border: including the lung, shielding the shoulder region

Caudal border: including the bottom of the costodiaphragmatic recesses: e.g. 2-4 cm below the radiobiologically visible diaphragm, depending much on the phase of respiration which is to be seen at lateral recesses or on a 4D-CT-planning CT scan (if object the planning tool)

Lateral border: including the thoracic wall

Boost volume (e.g. stereotactic radiotherapy Boost with 10-15 Gy to metastases remnants visible after surgery or chemotherapy at the start of radiotherapy). In very young children, protect as much lung tissue as possible.



Pulmonary metastases at diagnosis (stage IV lung) with residual inoperable disease in the left and central right lung after preoperative chemotherapy. Indication for pulmonary radiotherapy if there is disease after post-operative aggressive chemotherapy (all histologies) or in case of a histological high risk primary tumour, regardless of metastatic response. Radiation portal including both lungs with its recesses.
Remember air-correction when calculating dose. Lateral view needed to calculate dimension of lung tissue.

6.17. General guidelines for radiation therapy for Rhabdoid Tumours of the kidney (RTK)

Indications for postoperative RT to the flank:
Stage I-III RTK (19.8 Gy for children > 1 year, 10.8 Gy for children < 1 year), boost for gross residual tumour after surgery at a total dose of 10.8 Gy.
Indications for the whole abdominal RT:

- 19.5 Gy (1.5 Gy) > 1 year; < 1 year reduce at 10.5 Gy (1.5 Gy)
- Stage III- ascites positive for rhabdoid cells
- Preoperative tumour rupture
- Diffuse operative spill
- Peritoneal seeding

Indication for RT to the lung:
Lung metastases (15 Gy, in 10 fractions) (not in children below three years of age, may be reduced the dose to 10.5 Gy in 7 fractions, boost dose of up to 7.5 Gy (persisting localized lung foci after whole lung irradiation)
Indications for RT to the liver:
Liver metastases, diffusely involved, 19.8 Gy, single dose fraction 1.8 Gy (in infants may be reduced the dose to 15 Gy in 10 fractions. Additional boost irradiation dose of 5.4-10.8 Gy may be administered to limited volumes.
Indications for whole brain RT:
Brain metastases (21.6 Gy) plus boost of 10.6 Gy
Indications for bone metastases RT:
Bone metastases (25.2 Gy)

6.18. Clear Cell Sarcoma of the Kidney (CCSK)

The radiation dose necessary to prevent local recurrence of CCSK is discussed controversial. As most of the children with CCSK are very young it was agreed to lower the dose from 25.2 Gy to 10.8 Gy according to the data presented by the COG.
General guidelines and target delineation as nephroblastoma (see there).

Local stage II-III:

- 10.8 Gy to the flank; in 6 fractions, 5 fractions a week.
- 10.8 Gy boost to macroscopic residual

Metastatic disease:

- Whole lung: 12 Gy in 8 fractions, five fractions a week
- Whole brain: 15 Gy in 10 fractions, 5 fractions a week, optional boost of 10.5 Gy
- Bone metastasis: 30,6 Gy (19,8 Gy for children < 24 month in 11 fractions) in 17 fractions
- Liver: focal as well as diffuse involvement: 19.8 Gy (infants <13 months 10.8 Gy and no boost, patients with residual tumour: optional boost 5-10.8 Gy)
- Lymph node involvement: resected: 10.8 Gy, unresected: boost with 10.8 Gy to suspect areas

6.19. Organs at risk

Bone and soft tissue

It is not clear to what degree a radiation dose of 15 Gy in young children will impair bone and soft tissue growth, which takes place years after radiotherapy. The amount of impairment is dependent on radiation dose, irradiated volume, and age of the child and reveals as kyphoscoliosis, hypoplasia and osteochondroma. The impairment is expected to be smaller after a lower dose of radiotherapy (<15 Gy). It can be assumed that, if there is impairment, this will only be small and without significant clinical relevance. The amount of impairment is certainly larger after radiation dose of 30 Gy.

The whole vertebral column should be included within radiation portal area in order to avoid inhomogeneity, which is known to produce scoliosis. Nevertheless, the radiation portal should not include major parts of the contralateral kidney.

The iliac crest contains the apophysis from which the growth of the iliac bone mainly takes place. In order to avoid asymmetric iliac bone growth radiation dose at this apophyseal line should not be more than 15 Gy.

The epiphyseal lines of the acetabulum cannot be shielded, if the whole intraperitoneal cavity is to be adequately irradiated (“abdominal bath”).

The femoral head should not be included in the treatment volume as it does not belong to the target volume and epiphyseal slipping is a possible consequence after radiotherapy in young children.

The shoulder is not to be included within the treatment volume if pulmonary radiotherapy is indicated.

Reduction of lung volume and dynamic compliance can develop to some degree after radiotherapy to both lungs, more so in young children, because of insufficient growth of the rib–cage.

Liver

Radiation tolerance of the liver depends on total dose and volume irradiated. A radiation dose of 15 to 20 Gy to the whole liver does not by itself produce severe side effects and is indicated in whole abdominal irradiation and may be advisable in some extensive right sided tumours and whole liver irradiation because of metastases. If the boost volume is indicated in the upper right abdomen at least one quarter of the liver should be shielded after 20 Gy. If less than half of the liver is within the treatment volume no special shielding is necessary.

If veno-occlusive disease (VOD) occurred during chemotherapy, the radiation tolerance of the liver might be reduced. Special attention should be paid to further liver shielding.

Gastrointestinal tract

Because of the radiosensitivity of the rapidly proliferating mucosa sparing from irradiation volume is advisable but only possible by adequately tailoring the treatment portal. Side effects like diarrhoea and vomiting may be observed during abdominal radiotherapy in particular if large volumes are treated. Symptomatic treatment for vomiting and for diarrhoea is necessary including intravenous fluids are required. A diet free of lactose and saccharose and with low fat content is recommended for treatment of acute and late radiation enteritis.

Kidney

Dose of the remaining kidney should not exceed 12 Gy (maximum dose). Irradiation of the remaining kidney up to 12 Gy is indicated in total abdominal radiotherapy and in some cases of stage V tumours.
Radiation dose to the contralateral kidney in radiotherapy of the prevertrebral space due to the penumbra at the field margin and scattered radiation usually does not exceed 10-20 % of the radiations dose at the reference point. It may be somewhat higher in medial parts in the remaining kidney lying close to the vertebral column.

Ovary

Ovarian insufficiency induced by irradiation doses of about 15 Gy, if the true pelvis had to be included into the irradiated volume**.**
At least one ovary should not receive a radiation dose of more than 10-15% of the dose at the reference point (15 Gy). As the necessary distance between the field margin and the location of the ovary to achieve this dose can be estimated before treatment performance, much attention should be paid to adequate localization in this regard. If the target dose is 30 Gy the ovarian dose should not exceed 5-10% of the reference dose. Only in total abdominal radiotherapy both ovaries are irradiated to more than 15 Gy.
Nevertheless, little is known about the ovarian tolerance doses in young girls. Hormonal function and fertility can probably be preserved if the ovarian dose can be kept below 2-3 Gy.

Testes

Impairment of spermatogenesis may occur even after scattered radiations dose above 50 to 100 cGy to the testes. Leydig cell function is much less radiosensitive and not influenced by such low scatter radiation dose.
Radiation dose to the testes from scattered radiation should be clearly below 5% of the radiation dose at the reference point (15 Gy). Special attention is necessary in total abdominal radiotherapy because of the close relationship between the caudal border and the position of the testes, particularly in small boys.

Mammary gland/areola

The mammary gland bud is known to be very radiosensitive even in low dose radiotherapy; hypoplasia of the mammary gland may occur after a dose as low as 1-3 Gy in young girls.
Therefore it should be spared from radiotherapy whenever possible. Special attention has to be paid when target volume includes the upper abdomen and the dome of the diaphragm.
In radiotherapy of both lungs some sparing of the mammary gland bud may only be achieved by the build-up-effect in high megavoltage beams.

Cardiac toxicity

Cardiomyopathy in case of pulmonary irradiation, previous treatment with doxorubicin or radiotherapy followed by this drug may increase the chance of this complication. In radiotherapy of both lungs the heart should be spared with new techniques like IMRT whenever possible. Echocardiography should be done at regular intervals to detect early toxicity

7. NON-WILMS TUMOURS OF THE KIDNEY

7.1. Clear Cell Sarcoma

7.1.1. Introduction / background

Clear Cell Sarcoma of the Kidney (CCSK) is an uncommon renal tumour that comprises 3-5% of all primary renal tumours in children. This tumour is observed most often in children between 2 and 4 years of age and is characterized by a highly malignant potential. CCSK represents the second most common paediatric renal tumour after Wilms tumour. In the past, CCSK was considered an unfavourable histology Wilms tumour variant. However, in 1970 it was recognized as a separate clinico-pathologic entity by Kidd. Marsden et al. subsequently called the tumour 'bone metastasizing tumour of the kidney' and Beckwith and Palmer referred to it as 'clear cell sarcoma of the kidney.

Histologically CCSK shows a remarkable morphologic diversity, which renders it sometimes difficult to distinguish this tumour from other renal tumours, such as Wilms tumour, malignant rhabdoid tumour of the kidney and congenital mesoblastic nephroma. In earlier studies, up to 50% of all CCSKs have initially been classified as an entity different from CCSK by local pathologists.

Gene expression profiling studies have reported up-regulation of neural markers and apparent expression of members of the Sonic hedgehog signalling pathway and the Akt cell proliferation pathway (including strong activation of *EGFR*) in CCSK. A cytogenetic marker, which has been consistently identified in CCSK patients is a clonal balanced translocation involving t(10;17)(q22;p13). O'Meara et al. identified that the breakpoints of this translocation involve the genes *NUTM2B/E* (chromosome 10) and *YWHAE* (chromosome 17), and identified the *YWHAE-NUTM2B/E* fusion transcript in 6 of 50 studied CCSK cases. Very recently, recurrent internal tandem duplications (ITD) of the X-linked BCL-6 co-repressor (*BCOR*) gene have been described in CCSK. This *BCOR* ITD and t(10;17)(q22;p13) seem to be mutually exclusive; all reported CCSK patients without t(10;17) harbour the *BCOR* ITD, while cases with t(10;17) do not harbour *BCOR* ITDs. A large scale screening of 159 cases confirmed mutual exclusivity of the duplications that are found in most cases and the rare translocations, but also identified a subset of 12 % of CCSK that lacked both alterations. These may form a novel sub entity of CCSK that may behave differently.

With current intensive treatment schedules, including radiotherapy and multi-agent chemotherapy regimens, outcome has significantly improved (5-year event-free survival ranging from 65% - 85%, 5-year overall survival ranging from 75% - 90%). The current intensive therapy schedule aims to maintain and even improve survival, but also to limit serious late and direct toxicity, such as cardiotoxicity, infertility, metabolic syndrome, obesity and second malignancies by using safe cumulative dosages of anthracyclines, combining ifosfamide and cyclophosphamide use, and reducing radiotherapy dosages. Ongoing biological studies offer the chance to identify molecular targets for more targeted future therapy strategies.

Epidemiology and clinical features

CCSK is extremely rare in the first 6 months of life and in adults, where it has been the subject of only isolated case report. A male predominance has been noted in all large CCSK reports (average male to female ratio of about 2:1). Some studies suggested a predilection for involvement of the right kidney. Most patients present with stage I, II and III disease, and only 6-7% of the patients present with stage IV disease. The most frequent sites of metastases at diagnosis are bone, lung and liver. Unlike nephroblastoma, CCSK is never bilateral.

Relapses occur in about 15% of the cases. CCSK has historically been associated with late recurrences, occurring up to 8 years after initial diagnosis (median time to relapse 17-20 months). Recent reports from the International Society for Pediatric Oncology (SIOP) and the National Wilms Tumour Study Group (NWTSG) have indicated that, following intensified upfront treatment, the pattern of relapses is changing with brain metastases now more common than the classical site of bone metastases in its original description as the 'bone metastasising renal tumour of childhood'. This indicates that the brain might be a sanctuary for cells that are protected from intensive chemotherapy that patients currently receive.

Histology

CCSK tumours have a deceptively bland appearance and many histological patterns. The most common pattern is the classic pattern, with features present at least focally in over 90% of tumours. The classical subtype is characterized by a uniform appearance of a diffuse growth of relatively small cells with normochromatic nuclei, inconspicuous nucleoli, pale staining cytoplasm and ill-defined cell membrane. In only 20% of the cases the tumour cells do have clear cytoplasm. The most characteristic feature is a peculiar vascular pattern consisting of arborizing blood vessels that create an alveolar or trabecular pattern. The classical pattern of CCSK is relatively simple to diagnose, but others including the myxoid, sclerosing, cellular, epithelioid, palisading, spindle cell, storiform and anaplastic pattern can cause problems in reaching the diagnosis. In the differential diagnosis blastemal nephroblastoma, mesoblastic nephroma, PNET and rhabdoid tumour must be considered.
The histogenesis of CCSK is uncertain. Recent studies have shown that tumour cells are positive for Cyclin D1 and NGFR, so these two markers should be used in diagnostically challenging cases. Other markers including cytokeratin, factor VIII associated antigen, epithelial membrane antigen, desmin and S100 protein are negative in CCSK.

Genetics and Biology

One of the recurring molecular markers which has been identified in patients with CCSK is a balanced translocation involving t(10;17)(q22;p13). O'Meara et al. identified that the breakpoints of this translocation involve the genes *NUTM2B/E* (chromosome 10) and *YWHAE* (chromosome 17); the YWHAE-NUTM2B/E transcript was detected in 6 of 50 studied CCSK cases. In addition, CCSKs have been shown to reveal a strong immunoreactivity for the EGF-receptor tyrosine kinase; also, EGFR gene amplification and an *EGFR* mutation have been reported in 2 cases. Gene-expression profiling CCSK studies have reported up-regulation of genes known to act within the Sonic hedgehog signalling pathway and the phosphoinositide-3-kinase/Akt cell proliferation pathway. Very recently, recurrent internal tandem duplications (ITDs) of the X-linked BCL6 co-repressor (*BCOR*) gene have been described in CCSK. This *BCOR* ITD and the t(10;17)(q22;p13) seem to be mutually exclusive. CCSK tumours harbouring *BCOR* ITDs exhibit high expression of *BCOR* mutant transcripts and protein. Consistent with possible disruption of the PRC1.1/BCOR complex in CCSKs, transcriptome profiling reveals widespread upregulation of PRC2 targets in these tumours, suggesting disruption of polycomb regulation. This may explain the, by Gooskens *et al* identified hypermethylation and consequent down-regulation of the gene *TCF21* in all CCSKs (n = 17) except for the samples harbouring the 10;17 translocation. However, additional studies to analyse this connection are needed. Furthermore, the absence of both genetic alterations affecting BCOR and NUTM2B/E-YWHAE in 12 % of cases provides clear evidence for additional molecular subclasses present.

In contrast to WT, CCSK does not appear to be associated with genetic predisposition syndromes, and familial CCSK cases have not been reported so far.

Previous data on treatment and outcome of paediatric CCSK and background for the current protocol

Results from the first three National Wilms' Tumour Study Group (NWTS) protocols suggested that the addition of doxorubicin to the combination of vincristine and actinomycin-D improved the 6-year relapse-free survival (RFS) for patients with CCSK from 25% to 63%. The addition of cyclophosphamide to the regimen of the NWTS-3 trial did not improve the 6-year EFS. However, in the most recent NWTS-5 clinical trial, patients diagnosed with CCSK irrespective of stage were treated with a radical nephrectomy followed by treatment with vincristine, doxorubicin and cyclophosphamide, alternating with cyclophosphamide and etoposide for 24 weeks, and postoperative radiotherapy (10.8 Gy). Five-year EFS and 5-year OS for CCSK patients treated on NWTS-5 were 79% and 89%, respectively. Only one of the recurrences was in the tumour bed and two in the abdomen, indicating that local control achieved after radiological treatment with 10.8 Gy was sufficient. Stage was found to be highly predictive of outcome; 5-year EFS rates for stage I, II, III and IV on NWTS- 5 were 100%, 87%, 74% and 36%, respectively. Current treatment according to the Children's Oncology Group (COG) consists of surgery of resectable tumours followed by vincristine, cyclophosphamide, doxorubicin and etoposide for stage I-III disease. Stage IV patients are treated on an intensified regimen with additional carboplatin. Stage II-III patients receive local radiotherapy (10.8 Gy).

CSSK treatment and outcome according to different treatment regimens

Report	Study	Treatment		EFS	OS
		Chemotherapy	Radiotherapy		
Green 1994	NWTS 1-2	AMD/VCR (8 pt) AMD/VCR/DOX (58 pt)	0 - 37.8 Gy	25% (6y) 63.5% (6y)	25% (6y) 71.9% (6y)
Green 1994	NWTS 3	AMD/VCR/DOX (43 pt) AMD/VCR/DOX/CPM (30 pt)	0 - 37.8 Gy	64.4% (6y) 58.2% (6y)	71.3% (6y) 60.8% (6y)
Seibel 2004	NWTS 4	6m CT (AMD/VCR/DOX) (23 pt) 15m CT (AMD/VCR/DOX) (17 pt)	10.8 Gy	65.2% (5y) 87.8% (5y)	95.5% (5y) 87.5% (5y)
Seibel 2006	NWTS 5	VCR/DOX/CPM/VP-16 (110 pt)	Stage I-IV 10.8 Gy	79% (5y)	89% (5y)
Current COG protocol	AREN0321	VCR/DOX/CPM/VP-16	Stage II/III 10.8 Gy	-	-
Tournade 2001	SIOP 09	AMD/VCR/EPI(DOX)/IFO (16 pt)	Stage II/III 30 Gy	75% (2y)	88% (5y)
Furtwängler 2005	SIOP 93-01 / GPOH	Stage I-IV: DOX/IFO/CAR/VP-16 (53 pt)	Stage II/III 30 Gy	86% (5.9y)	91% (5.9y)
Furtwängler 2013	SIOP 93-01	St I-IV: VP-16/CARBO/IFO/EPI	Stage II/III 25.2 – 30 Gy	78% (5y)	86% (5y)
	SIOP 2001	St I: AMD/VCR/DOX St II-IV: VP-16/CARBO/CPM/DOX			
Mitchell 2000	UKWT2	AMD/VCR/DOX (16 pt)	≥ Stage III 30 Gy	82% (4y)	88% (4y)
Current UK protocol	SIOP 2001	St I-III: VCR/AMD/DOX St IV: VP-16/CARBO/CPM/DOX	Stage II/III 25.2 Gy	-	-
Current AIEOP protocol	AIEOP-TW-2003	St I-IV: AMD/VCR/DOX; AMD/IFO; VP-16/CARBO	Stage I-III 25.2 Gy if < 30m, 34.2 Gy if > 30m	84% (5y)	91% (5y)

Abbreviations: NWTS: National Wilms' Tumor Study Group, JWiTS: Japanese Wilms Tumor Study Group, SIOP: International Society of Pediatric Oncology, GPOH: German Society of Pediatric Oncology and Hematology, UKWT: United Kingdom Wilms Tumour Study Group, AMD: actinomycin-D, VCR: vincristine, DOX: doxorubicin, CPM: cyclophosphamide, VP-16: etoposide, IFO: ifosfamide, CAR: carboplatin, pt: patients, RFS: relapse free survival, OS: overall survival, y: year

Treatment in the United Kingdom Wilms' Tumour Study Group 2 trial (UKWT2) consisted of three chemotherapeutic agents (vincristine, dactinomycin and doxorubicin) administered for 12 months after initial surgery. Only stage III and IV patients received irradiation on the original side of the tumour (30 Gy). Results of the UK-WT-2 study demonstrated a 4-year EFS of 82% and a 4-year OS of 88%. This regimen revealed a high local relapse rate in stage II patients, which urged to include local irradiation in stage II patients in the current CCSK protocol, in order to avoid local recurrence.

SIOP trials include pre-operative treatment with vincristine and dactinomycin for 4 weeks for localized disease, and treatment with vincristine, actinomycin-D and an anthracycline (doxorubicin or epirubicine) for 6 weeks for stage IV patients. Patients registered on the SIOP 93-01 protocol were treated post-operatively with etoposide, carboplatin, ifosfamide and doxorubicin (GPOH patients) or epirubicin (all other patients). Patients registered on the SIOP 2001 protocol were treated post-operatively with actinomycin-D, vincristine and doxorubicin for stage I patients and with ifosfamide, etoposide, carboplatin and doxorubicin for patients with stage II-IV disease. Both SIOP protocols included additional irradiation of the flank (SIOP 93-01 25-30 Gy, SIOP 2001 25.2 Gy) for stage II and III patients. The 5-year EFS of all 191 CCSK patients treated according to SIOP 93-01 and SIOP 2001 was 78% and the 5-year OS was 86%. Stage I patients treated according to the SIOP 93-01 protocol (treated with 4 drugs: etoposide, carboplatin, ifosfamide, doxorubicin) had better 5-year EFS and OS rates (82.6% and 90.1%, respectively) compared to stage I patients treated according to SIOP 2001 (treated with 3 drugs: actinomycin, vincristine, doxorubicin) (5-year EFS 71.5%, 5-year OS 79.6%). In addition treatment of stage I CCSK patients according to current COG protocol (AREN0321): includes also 4 drugs (etoposide, vincristine, cyclophosphamide, doxorubicin). AREN0321 is the first protocol in COG in which stage I CCSK patients are treated without radiotherapy.

Stage IV disease and young age were significant adverse prognostic factors for EFS. Patients with stage I disease had 5-year EFS and OS rates of 79% and 87% respectively, not as excellent as survival rates described in previous studies (Kalapurakal et al 5-year OS 100%, Argani et al 5-year OS 98%).

Five-year EFS and OS rates of patients treated post-operatively with alkylating agents (i.e. ifosfamide, cyclophosphamide) (n = 146) were respectively 83% and 88% versus 67% and 78% for patients treated without alkylating agents (n = 28). Five-year EFS and OS rates of patients treated with ifosfamide (n = 80) were respectively 89% and 94%, and 5-year EFS and OS rates of patients treated with cyclophosphamide (n = 66) were respectively 74% and 78%.

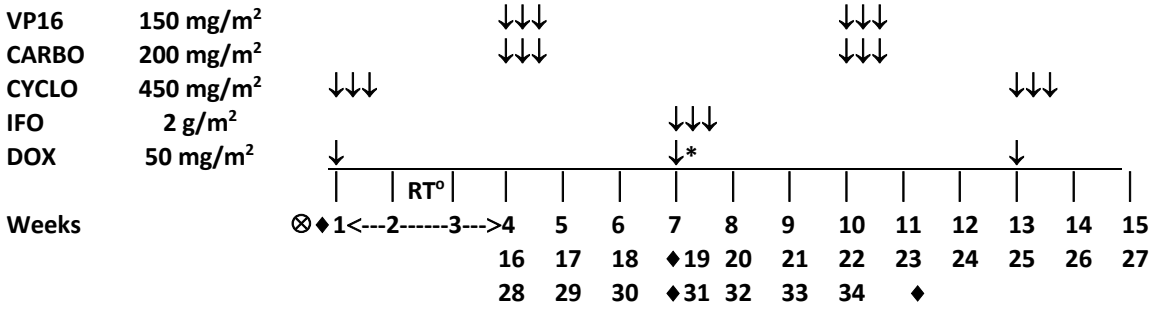
The current SIOP-2016 CCSK guideline aims to include chemotherapy regimens that have been proven to be of value for CCSK patients, in order to maintain excellent survival in localized stage CCSK and further improve survival where possible. It also takes into account that survival is already reasonable for some groups of children, thus intensive therapy may be selectively modified to avoid serious short and long term toxicity. For those purposes, the challenge is to limit the total cumulative dose of doxorubicin to 250 mg/m^2 to avoid cardiotoxicity , to combine cyclophosphamide and ifosfamide in an alternating setting to avoid serious renal toxicity, and reduce the risk of fertility problems, to include chemotherapeutic agents that guarantee CNS penetration, such as ifosfamide and carboplatin, and to limit the dose of abdominal radiotherapy to 10.8 Gy according to the current COG strategy.

For CCSK patients with stage I disease, treatment will be commenced according to SIOP 93-01 (but with alternating ifosfamide and cyclophosphamide), as 5-year EFS and OS rates of stage I CCSK patients treated according to SIOP 2001 (treated with 3 drugs) were inferior to SIOP 93-01 (treated with 4 drugs).

7.1.2. Treatment recommendations

Stage	Pre-operative chemotherapy	Post-operative chemotherapy	Radiotherapy
I	AV	VP16, CARBO, IFO/CYC, DOX	No
II	AV	VP16, CARBO, IFO/CYC, DOX	10.8 Gy
III	AV	VP16, CARBO, IFO/CYC, DOX	10.8 Gy
IV	AVD	VP16, CARBO, IFO/CYC, DOX	10.8 Gy + metastasis in case of in-completeness/impossibility of resection

Detailed descriptions of the chemotherapy treatment schedules are given here:
VP-16 = etoposide = 150 mg/m^2/d in 1 hour i.v.
CARBO = carboplatin = 200 mg/m^2/d in 1 hour i.v.
CYCLO = cyclophosphamide = 450 mg/m^2/d in 1 hour i.v.
IFO = ifosfamide = 2 g/m^2/d in 1 hour i.v.
DOX = doxorubicin = 50 mg/m^2/ in 4-6 hours i.v. , just before the first cyclophosphamide administration (5 courses, omit DOX in week 31)



♦ = Echocardiography: at start of treatment, before week 19, 31 and at end of treatment
*** = no doxorubicin in week 31; maximum cumulative dose of doxorubicin should not exceed 250 mg/m^2 (in case of stage IV: 300 mg/m^2;**
replace DOX with VCR (1.5 mg/m^2, max dose 2 mg/m^2) after 300 mg/m^2)
⊗ = GFR (measure at every third course, or more frequently if there is evidence of renal dysfunction
RT°= Abdominal RT in local stage II and III disease

Dose reductions (see table in section 3.3)

Surgery: See surgical section above
Stage IV: For patients with hematogenous or lymph node metastases outside the abdominal-pelvic region (stage IV) disease still present after treatment with pre-operative chemotherapy (three drugs) or at an extended moment, metastasectomy is advised whenever surgery can be performed without mutilation or loss of vital organs. Otherwise, radiotherapy is strongly recommended.
Radiotherapy: Abdominal RT in local stage II and III. Dose: 10.8 Gy. Postpone DOX during radiotherapy (switch with IFO/CARBO). In case of stage IV irradiation of metastasis is needed.

In case of pulmonary irradiation: Pneumocystis carinii pneumonia prophylaxis with cotrimoxazol is indicated. There is a stopping rule for the reduced radiation dosage implemented.
In case CCSK has been confirmed ***by biopsy*** before start of pre-operative chemotherapy, it is recommended to start with the 5-drug regimen directly (instead of the standard pre-operative chemotherapy regimen). If the standard pre-operative chemotherapy regimen has already been started because of suspicion of Wilms tumour, then switch to the 5-drug regimen. Surgery is advised after 2 cycles and preferably no later than 6 weeks after diagnosis.
Relapsed CCSK: Treatment will be given according to high risk relapses in nephroblastoma.

7.1.3. Recommendations treatment relapsed CCSK

SIOP recently found that consolidation of a second complete remission seems to be a challenge in relapsed CCSK. Intensive treatment, including chemotherapy (ICE) as well as achieving local control by complete surgery (where possible) and/or radiotherapy seems to be of benefit to enhance survival. In addition, high-dose chemotherapy followed by autologous bone marrow transplantation seems to consolidate second complete remission. Possible high-dose chemotherapy drug combinations are*:

- CET: carboplatin, etoposide, thiotepa
- CEM: carboplatin, etoposide, melphalan
- Carboplatin and etoposide
- Carboplatin and thiotepa

*It is recommended contact subcommittee chair

7.2. Renal Cell Carcinoma (RCC)

7.2.1. Introduction / background

Renal cell carcinomas (RCC) in children are rare, accounting for only 2 to 6 % of paediatric malignant renal tumour. Compared with the adult counterpart, the majority of paediatric RCCs show a different histologic subtype, special morphological features and unique genetic abnormalities. Paediatric RCC are predominantly of the translocation type and of the papillary subtype, whereas the clear cell RCC with *von Hippel-Lindau* (*VHL*) gene abnormalities at 3p25-26 dominates in adults. Morphologically, translocation type RCC (20-70% of the paediatric RCC) typically show a distinctive voluminous pale or clear cytoplasm with focal papillary/pseudo-papillary architecture and with psammona bodies. Nevertheless, they also show a considerable morphological overlap with clear cell RCC and papillary RCC. Translocation type RCCs are characterized by specific chromosome translocations involving the transcription factor gene *TFE3* located on Xp11.2 or – rarely - *TFEB* located on 6p2. Both *TFE3* and *TFEB* belong to the microphthalmia transcription factor (MiTF)/TFE family. The various chromosome translocations in paediatric RCC result in gene fusions, most frequently between the *TFE3* gene and the *PRCC* (papillary renal cell carcinoma) gene located on 1q21.2 or the *ASPL* (alveolar soft part sarcoma locus) gene located on 17q25, respectively. Translocations involving the *TFE3* and *TFEB* genes induce an aberrant overexpression of these proteins and can be specifically identified by immunohistochemistry or FISH. Microarray analyses revealed a very different gene expression profile of translocation type RCC compared to other RCC types, reflecting a distinct biological behaviour. In adult clear cell RCCs, the inactivation of the *VHL* gene results in an up-regulation of the VEGF-and PDGF signalling pathway successfully targeting with VEGF – and PDGF- receptor tyrosine kinases (RTK) inhibitors. In contrast, in translocation RCC the MET-RTK has been shown to be the most up-regulated RTK.

Corresponding to the distinct morphological and genetic characteristics, children and adolescents suffering from RCC show particular clinical features and a different course of disease in comparison to adults. Paediatric RCCs occur with equal frequency in girls and boys with a mean age of over 10 years. A significant proportion of paediatric RCC patients suffer from a special underlying disorder such as tuberous sclerosis, chronic renal insufficiency, urogenital malformations or have been previously treated with chemotherapy. Furthermore, a special subgroup of paediatric RCC exists as a second malignancy after neuroblastoma. The most significant difference to adult RCC, is the better outcome of paediatric RCC with regional lymph node metastases without distant metastases with survival rates of over 70% without adjuvant therapy based on retrospective studies (in adults below 30%).

The majority of paediatric RCC are localized diseases, which can be cured with surgical tumour resection alone (survival rate over 90%). The relatively small subgroup of children suffering from a distant metastatic RCC has a poor prognosis, as in adults . Nephron-sparing surgery is established in adult RCC smaller than 4 cm. In small cohorts of paediatric RCC patients no relapses were observed after nephron sparing surgery. Because of an increased risk of metachronic disease in the other kidney in paediatric RCC especially after underlying disorders, the nephron sparing surgery would be desirable if possible.

Currently there are no published prospective study data of an unselected paediatric RCC cohort and their treatment. Therefore, we do not know which adjuvant therapy could improve the outcome of distant metastatic paediatric RCC patients and – possibly – of a subgroup of particular advanced regional lymph node metastatic RCC.

Former small studies and single case reports showed objective responses in paediatric metastatic RCC patients after INFa/IL2 therapy at a comparable rate as in adult RCC. Recently a retrospective analysis of various targeted therapies in translocation RCCs showed a significant objective response rate with the RTK inhibitor Sunitinib (PR in 3 of 3 patients) in comparison with Sorafenib (only SD as best response) and Temsirolimus/Everolimus (1 PR, 6 SD). In a preclinical study, translocation-type RCC cells with ASPL-TFE3-gene fusion responded to *MET* receptor tyrosine kinase inhibitor administration with decreased cell growth.
The objective of a SIOP paediatric RCC study is to obtain new knowledge about RCC in children and adolescents including their biological behaviour and clinical course in a large unselected prospective cohort. This will help to improve treatment in the different subtypes of RCC. The most significant challenges of treatment are the development of an effective adjuvant therapy in advanced paediatric RCC patients (distant metastatic RCC, possibly advanced local lymph node metastatic RCC) and nephron-sparing surgery in selected RCC patients.

Epidemiology

The SEER program reports an age-adjusted incidence of RCC of 0.5 cases per million people under the age of 19 years. A German population-based study of childhood RCC (including children < 16 yrs) showed a median age at diagnosis of 10.6 years, with a male: female ratio of 1 to 1.1.

Clinical Features

The most common symptoms at diagnosis are pain (30-40%), gross haematuria (30-40%), and abdominal mass (20-25%). Non-specific constitutional symptoms such as fever, weight loss, and lethargy are seen in 15-40% of children.

Imaging

Imaging is done according to the guidelines

Pathology

The histology of paediatric RCC is distinct from that of adult RCC. In literature before 1990, many cases of paediatric RCC were described as having clear cells with a papillary pattern. Renshaw described tumours with distinctive voluminous clear cytoplasm, which he proposed were a newly recognized type of RCC involving translocations of Xp11. In 2004, the World Health Organization officially recognized translocation RCC, which is associated with a family of translocations involving the *TFE3* or *TFEB* genes, as a distinct class of RCC. It is now estimated that translocation RCC accounts for 20-50% of paediatric and young adult RCC. Other histologic types of RCC described in children include papillary RCC (about 30%), chromophobe RCC, sarcomatoid RCC, collecting duct carcinoma, RCC arising from Wilms tumour, renal medullary carcinoma, RCC after neuroblastoma, and RCC not otherwise specified. The clear cell (conventional) subtype, by far the most common type of RCC in adults, is uncommonly observed in children. A careful morphological and molecular analysis by Bruder included 6 paediatric patients with the histologic appearance of clear cell RCC. However, none of these cases had LOH at chromosome 3p, the site of the *VHL* gene, or mutations of *VHL*, indicating that the clear cell RCC in children is distinct from adult clear cell RCC.

Paediatric RCC can be classified according to The WHO 2016 classification system of RCC which –beside the adult type RCC- also considers RCC types with predilection for young age groups, such as translocation-RCC and post Neuroblastoma-RCC.

Papillary RCC: paediatric papillary RCC has the classic papillary architecture as described in the WHO classification, comprising 20-50% of all RCC.

Clear cell RCC also can be classified according to the WHO classification.

7.2.2. Staging RCC

Primary Tumour (T)[a]

[a]Reprinted with permission from AJCC: Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.	
TX	Primary tumour cannot be assessed.
T0	No evidence of primary tumour.
T1	Tumour ≤7 cm in greatest dimension, limited to the kidney.
T1a	Tumour ≤4 cm in greatest dimension, limited to the kidney.
T1b	Tumour >4 cm but not >7 cm in greatest dimension, limited to the kidney.
T2	Tumour >7 cm in greatest dimension, limited to the kidney.
T2a	Tumour >7 cm but ≤10 cm in greatest dimension, limited to the kidney.
T2b	Tumour >10 cm, limited to the kidney.
T3	Tumour extends into major veins or perinephric tissues but not into the ipsilateral adrenal gland and not beyond Gerota fascia.
T3a	Tumour grossly extends into the renal vein or its segmental (muscle containing) branches, or tumour invades perirenal and/or renal sinus fat but not beyond Gerota fascia.
T3b	Tumour grossly extends into the vena cava below the diaphragm.
T3c	Tumour grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava.
T4	Tumour invades beyond Gerota fascia (including contiguous extension into the ipsilateral adrenal gland).

Regional Lymph Nodes (N)[a]

[a]Reprinted with permission from AJCC: Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in regional lymph node(s).

Distant Metastasis (M)[a]

[a]*Reprinted with permission from AJCC: Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.*	
M0	No distant metastasis.
M1	Distant metastasis.

Anatomic Stage/Prognostic Groups[a]

[a]*Reprinted with permission from AJCC: Kidney. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 479-89.*			
Stage	**T**	**N**	**M**
I	T1	N0	M0
II	T2	N0	M0
III	T1 or T2	N1	M0
	T3	N0 or N1	M0
IV	T4	Any N	M0
	Any T	Any N	M1

7.2.3. Genetics and Biology

Germline mutations/syndromes

Several genetic syndromes are associated with predisposition to RCC. The best described is von Hippel Lindau (*VHL*) Syndrome, caused by mutations in the *VHL* gene at chromosome 3p25. *VHL* encodes a protein that regulates the level of the hypoxia inducible factor (HIF) family of transcription factors. VHL is a component of a protein complex that promotes the ubiquitin-mediated degradation of HIF, which binds to promoters of genes involved in angiogenesis, erythropoiesis, energy metabolism, iron metabolism, cell proliferation, apoptosis, and other processes that are dysregulated in human cancer. Tuberous sclerosis is caused by mutations in the *TSC1* and *TSC2* genes, which encode the hamartin and tuberin proteins, central regulators of the mammalian target of rapamycin (mTOR) pathway. The most common renal tumour in individuals with tuberous sclerosis is angiomyolipoma, but affected individuals are also susceptible to RCC with clear cell morphology. Hereditary papillary RCC is caused by mutations in the *MET* oncogene, which encodes the hepatocyte growth factor receptor, which signals through the phosphatidylinositol 3-kinase (PI3K) pathway. The Birt-Hogg-Dubé Syndrome is caused by mutations in *FLCN*, which encodes the protein folliculin, which interacts with the mTOR pathway. Individuals with germline mutations of two tricarboxylic acid (Krebs) cycle genes, fumarate hydratase (*FH*) and succinate dehydrogenase (*SDH*), are also susceptible to RCC. *FH* is the gene responsible for hereditary leiomyomatosis and papillary RCC, a cancer predisposition syndrome in which patients develop uterine and cutaneous leiomyomas as well as papillary RCC subtype 2. Germline mutations of the *SDHB*, *SDHC*, and *SDHD* genes are responsible for familial paraganglioma and pheochromocytoma. Individuals with *SDHB* mutations are also at risk for early onset RCC. Mutations of the *FH* and

SDH genes impair progression through the tricarboxylic acid cycle, thereby diminishing oxidative phosphorylation and leading cells to rely on glycolysis for energy metabolism even in normoxic conditions.

Tumour-specific genetics

Translocation RCC is associated with translocations involving genes that encode members of the microophthalmia (MiTF) family of transcription factors. The most involved gene is *TFE3* on chromosome Xp11, which can fuse to several partners including *ASPL* (17q25), *PRCC* (1q21), *PSF* (1p34), *NonO* (Xq12), and *CLTC* (17q23). The TFE3-ASPL translocation is the same translocation seen in alveolar soft part sarcoma. A recent gene expression study has identified several novel genes that are differentially expressed between the Xp11 translocation carcinomas and conventional renal carcinomas. This has shown that Xp11 translocation carcinomas may be more similar to alveolar soft part sarcoma than to conventional renal carcinomas. Additionally, gene expression profiling has identified potential therapeutic targets in the Xp11 translocation RCC. For example, the ASPL-TFE3 fusion protein transactivates the promoter of the MET receptor tyrosine kinase, leading to MET protein overexpression. Inhibition of the MET receptor tyrosine kinase may therefore be a potential avenue of targeted therapy for these RCC. Translocation RCC also express high levels of phosphorylated S6, a measure of mTOR pathway activation, which suggests that mTOR inhibition may be effective in this tumour type. A less common type of translocation RCC involves a fusion of the untranslated *alpha* gene (11q12) to the *TFEB* gene (6p21). Interestingly, 15% of translocation RCC occur in individuals who were previously treated with chemotherapy for a variety of paediatric malignancies and non-malignant conditions .

	Gene (chromosome)	Major clinical manifestations
von Hippel-Lindau	VHL (3p25-26)	Clear-cell renal cell carcinoma; CNS haemangioblastomas; pheochromocytoma; retinal angiomas; pancreatic endocrine tumours; paragangliomas; cystadenoma of broad ligament or epididymis
Hereditary papillary renal carcinoma	C-Met proto-oncogene (7q31-34)	Type 1 papillary renal cell carcinoma
Hereditary leiomyomatosis renal cell carcinoma	Fumarata hydratase (1q42-43)	Type 2 papillary renal cell carcinoma; leiomyomas of skin or uterus; uterine leiomyosarcomas
Birt-Hogg-Dubé	BHD1 (17p11)	Chromophobe renal cell carcinoma; oncocytoma (benign); transitional tumours; cutaneous fibrofolliculomas; lung cysts or pneumothorax
Tuberous sclerosis	TSC1 (9q34) or TSC2 (16p13)	Multiple renal angiomyolipomas; renal cell carcinoma; renal cysts/polycystic kidney disease; cardiac rhabdomyomas; neurological disorders or seizures; multiple skin findings, including angiofibromas, fibromas, and nevi

Possibly related underlying conditions in: preexisting renal cysts, urogenital malformation (horse shoe kidney, cryptorchism), renal failure/post renal transplant (RCC in non-removed own kidney), genetic syndromes/malformation (tuberous sclerosis, Saetre-Chotsen syndrome, XYY syndrome, supernummerous nipple), previous neuroblastoma, coccygeal immature teratoma, angiomatous formation, family history of urogenital tumour and kidney malformations.

7.2.4. Treatment

Background information

Tumour resection is the mainstay of therapy for paediatric RCC. It is important to underline that most children and adolescents with a renal mass are presumed to have Wilms tumour and usually undergo radical nephrectomy and lymph node sampling/resection (after neo-adjuvant chemotherapy) according to Wilms tumour surgical guidelines. Hence, despite we are aware about the increasing indication of conservative surgery, like nephron sparing surgery, it is likely that in most cases the nephrectomy has been already done when the diagnosis of RCC has been made. In cases which are highly suggestive for RCC, it should be discussed pre-operatively if to prefer NSS – if technically applicable- or complete nephrectomy.

The role of radical lymph node dissection remains to be determined. There is no evidence for efficacy of radical lymph node dissection in childhood RCC. Lymph node sampling is recommended.

Many patients with localized disease have fared well without adjuvant therapy. Among adults and children with translocation RCC, age ≥ 25 years, lymph node involvement, high Fuhrman grade, and presence of distant metastatic disease were associated with poor survival. In pure paediatric series, however, local lymph node involvement was not associated with unfavourable outcome, even among patients who did not receive adjuvant therapy. The Children's Oncology Group AREN0321 study is prospectively registering cases of RCC in children and adolescents, and collecting data concerning which adjuvant treatment was applied in metastatic cases.

Children with metastatic RCC have a poor outcome. Although successes with high-dose interleukin-2 have been reported, it is recognized in that non-clear cell renal cell carcinomas do not typically respond well to immunotherapy. Emerging data on translocation RCC suggest that some tumours respond to vascular endothelial growth factor receptor (VEGF)-targeted therapy (sunitinib, sorafenib, ramucirumab). Among the agents reported, sunitinib seems to be most active. In one series, 7 of 14 patients (50%) treated with sunitinib as either first or second-line therapy for translocation RCC had partial or complete response. Seven of 7 patients who had progressive disease on VEGF-directed therapy and switched to mTOR inhibitors showed at least transient disease stabilization, including one with a partial response.

Responses to gemcitabine/doxorubicin alternating with gemcitabine/oxaliplatin have also been observed. Prospective studies to evaluate therapies for metastatic and recurrent childhood RCC are warranted.

Renal medullary carcinoma (RMC) is a renal epithelial neoplasm that has been described as the "7th sickle cell nephropathy. It is an aggressive cancer that occurs in adolescent and young adult patients with sickle cell trait or haemoglobin SC disease. The mean age of presentation is 19 years, with a reported range from 5 to 40 years. There is a male predominance, with a

male to female ratio of 2 to 1. There is no single pathognomonic genetic abnormality seen in RMC, but *BCR-ABL* translocations or *ABL* gene amplification have been described in rare cases, as have *ALK* gene rearrangements. Absence of SMARCB1 (INI1/hSNF5) protein staining by immunohistochemistry has been observed in RMC, suggesting that rhabdoid tumour of the kidney and RMC may have common biological, as well as clinical, features. Both are characterized by an aggressive metastatic pattern and relative chemotherapy resistance.

Patients with RMC almost always present with metastatic disease and have fatal outcomes. Transient responses have been observed after treatment with methotrexate / vinblastine / doxorubicin / cisplatin (MVAC) or platinum / gemcitabine / taxane. A patient with RMC was shown to have a complete tumour response after treatment with the proteosome inhibitor bortezomib.

Until now, the optimal treatment of the different subtypes of paediatric RCCs is widely unclear because of the rarity of RCC in children and the complete lack of results from prospective studies with sufficient patient numbers.

On the other hand there is a huge number of published studies concerning adult RCCs and adequate treatment strategies for them. But because of the significant biological differences and differences in prevalence of the subtypes, between adult and paediatric RCCs, namely the great majority of adult RCC displays the clear cell histology and not the translocation one, applicability to paediatric RCC management is restricted.

7.2.5. Treatment recommendations

In general, complete surgery is the most adequate approach in all children with RCC. In patients with metastasis an adjuvant medical treatment is necessary.

Localized RCC (Stage T1-4, N0M0):

Complete Surgical Tumour Resection (R0) is the mainstay of cure in paediatric RCC. The standard recommended surgical procedure is radical nephrectomy (RN = removal of the tumour-bearing kidney). We recommend to be cautious to consider partial nephrectomy in children. The EORTC led a prospective randomised controlled trial (RCT), comparing radical nephrectomy with partial nephrectomy in solitary T1-2 N0M0 renal tumour < 5cm with normal contralateral kidney function and WHO PS 0-2. At 9.3 years survival follow-up, 198 patients (72.5%) were alive after radical nephrectomy and 173 (64.4%) after NSS. Local recurrence occurred in one patient in the nephrectomy group and in six in the NSS group. Though prospective data are absent, partial nephrectomy is now considered in cases of small tumours, possibly all T1-T2 RCC) and –if technically feasible- in all cases with reduced renal function or/and renal malformation and in all cases with estimated high risk of metachronic secondary RCC or secondary renal function deterioration such as RC as part of a syndrome (Tuberous Sclerosis, VHL, others), RCC after chemotherapy or as second, RCC or renal failure in the family. Indications to partial nephrectomy (PN= nephron-sparing surgery[NSS]) are increasing for adult patients. We need to be reminded that in children, still the differentiation between RCC and Wilms tumour is not possible by imaging studies, even in the adolescence group, and Wilms tumour remains the most frequent renal tumour type. However, we believe that any case of small renal neoplasm in children > 10 years should be regarded as a potential RCC, and consequently be discussed with the reference surgeons, with the aim of considering NSS procedures as well, though only in selected cases. In addition it is difficult to extrapolate the tumour dimension criteria from adulthood experience, since the kidney dimensions in children are very different, and partial nephrectomy is advised in such cases only after extensive

discussion with the SIOP surgical panel. The standard indications for adult NSS in RCC according to the European Association of Urology guidelines are divided into the following categories: (1) absolute (anatomic or functional solitary kidney), (2) relative (functioning opposite kidney that is affected by a condition that might impair renal function in the future), and (3) elective (localized unilateral RCC with a healthy contralateral kidney). Relative indications also include patients with hereditary forms of RCC who are at high risk of developing a tumour in the contralateral kidney in the future. During the last decade, NSS has become the gold standard for the treatment of T1a tumours (<4 cm) in adult patients with a normal contralateral kidney" and – when performed in carefully selected patients in specialized centres - PN can be safely applied in patients with larger renal tumours. In adult patients several studies showed equivalence of PN and RN in oncological outcome in localized RCC at least in T1RCC.

Data for PN in paediatric RCC are very limited, however revealed no difference between PN and RN concerning the oncological outcome.

Therefore, before performing NSS in a child, we recommend this to be discussed with the surgical board of SIOP-RTSG in all cases, similar to what is recommended in all other paediatric renal tumours.

General surgical principles in RCC:

- The completeness of surgical resection is of prognostic importance.
- Early stage disease has a better prognosis than later stage disease stages.
- Partial nephrectomy might have a role in low-volume localised cancer in carefully selected patients.
- Experts opinions are strongly recommended in case of partial nephrectomy and regional lymphadenectomy as these still need to be determined.

Regional Lymph Node Positive RCC (stage T1-4, N1-2, M0)

First it is advised to perform a complete renal tumour (if necessary RE-) resection with negative surgical margins as described in section1).

In addition, in case the diagnosis of RCC is known at time of surgery, total regional lymphadenectomy is recommended at the time of renal tumour resection whenever feasible without significant surgical morbidity, as the fact that the surgical tumour resection seems to be the crucial mainstay of cure among the treatment modalities in paediatric RCC. Apart from a more correct tumour staging, that procedure may improve the outcome. In an Italian study of 16 paediatric RCC patients with local lymph node involvement, the survival rate in patients with extended retroperitoneal lymph node dissection (RLND= on the left; excision of hilar, periaortic, and ipsilateral common iliac nodes; on the right, hilar, interaortocaval, retro-paracaval, and common iliac nodes) was markedly better than in cases with a more limited lymph node resection (8 of 9 with RLND alive and disease free vs. 1 of 7 without RLND.

Most children with RCC will be diagnosed after initial WT treatment preoperatively. Therefore, the role of regional lymph node re-dissection in cases that were suspected of WT and had lymph node sampling only, is still under debate in paediatric RCC's, especially as lymph node positive paediatric RCCs seem to have a relatively more favourable outcome than adult RCC patients.

There is no clear evidence (from paediatric nor adult literature) that, in completely resected, more advanced regional lymph node involvement (i.e. >6 LN RCC+?) an adjuvant therapy is of any value.

Distant Metastatic RCC (stage T1-4, N0-2, M1)

Surgical treatment: complete renal tumour resection with negative surgical margins as described above is strongly advised, and retroperitoneal lymph node sampling (not dissection) is recommended in case of enlarged lymph nodes.

Adult data have shown that an initial reduction of tumour burden in RCC through nephrectomy, i.e. cytoreductive nephrectomy may improve the treatment results after adjuvant therapy with interferon-alpha. In cases of initial unresectable renal tumours a neo-adjuvant use of drug treatment (see below) may be considered, in order to perform surgery after tumour shrinkage.

As a secondary surgical measure, after a medical treatment approach for (6-)12(-18) weeks (recommendations see below) for response evaluation reasons, surgical resection of all metastases should be attempted as completely as possible.

The value of radiotherapy to metastatic disease is limited.

7.2.6. Medical treatment:

Multi targeted tyrosine kinase inhibitor: Sunitinib

We recommend using **Sunitinib** in metastatic paediatric RCC as first-line adjuvant drug. Adult guidelines now recommend Sunitinib, Pazobanib and Bevacizumab + interferon-alpha, though the latter is not well accepted because of its intravenous route. Sunitinib is a multitargeted tyrosine kinase inhibitor (TKI) that acts mainly on the vascular endothelial growth-factor receptor (VEGFR) and platelet-derived growth-factor receptor (PDGFR), which play a role in both tumour angiogenesis and tumour cell proliferation. In addition, Sunitinib inhibits receptor tyrosine kinases (RTK) RET and c-KIT.

Sunitinib significantly improved the progression-free survival (PFS) in metastatic adult clear cell RCC as compared to interferon following its accelerated FDA approval for the treatment of metastatic adult RCC. However, we have underlined that there is lack of comprehensive evidence for Sunitinib in non-clear cell RCC, and only very limited outcome data with Sunitinib in paediatric RCC are available. Prospective data of an unselected paediatric RCC cohort for judgment of the most appropriate adjuvant treatment in metastatic paediatric RCC are completely lacking.

A few case reports have shown objective responses with Sunitinib in metastatic translocation-type RCCs in adults. In 2012 a first case report documented a persistent response during 24 months in a paediatric metastatic translocation RCC patient.

In a retrospective analysis of various targeted therapies in advanced Xp11 translocation type RCCs (mostly confirmed only by TFE3/TFEB immunostaining without genetic analysis) the best objective response rate was found with the RTK inhibitor Sunitinib (PR/CR in 7 of 14 patients) in comparison with Sorafenib (only SD as best response) and Temsirolimus (1 PR, SD), including 5 patients under 18 years (2-16) with one CR for 16 months and one PR for 15 months and one SD for 8 months after Sunitinib. In a retrospective review of 14 metastatic RCCs in children and adolescents from Italy (1973-2010) 2 patients received RTK inhibitors. In both

cases objective responses were noticed: in one case with Sunitinib during 3 months and in one case with Sorafenib for 6 months.

Dosages and schedule Sunitinib:

A phase I study including pharmacokinetic analyses in paediatric patients with refractory solid tumours showed that the clearance of Sunitinib was similar between children and adults but the maximum tolerated dose was only 15 mg/m^2/d in this intensive pre-treated patient population. Other Sunitinib studies performed in paediatric patients showed safe dosing of 20-25 mg/m^2/day. In adults the approved Sunitinib dose is 50 mg/d.

Therefore, in the first course, a dose of 20-25 mg/m^2/d (not higher than 25 mg/d absolute daily dose in patients < 12 yrs for the first dose) for 28 days and 14 days break is recommended. Higher doses can be considered in later courses in case of no relevant (WHO grade 3 or 4) toxicity, on expert advice. In patients > 16 years and/or > 50 kg body weight, adult dosages could be considered from the beginning. Close clinical control of possible toxicity and a monitoring of blood counts, liver transaminases, bilirubin, renal function, hypothyroidism and cardiac function are obligatory.

Tumour response assessment will be documented after every treatment course at least in the first six months using the RECIST criteria (www.recist.com).

Drug treatment duration:

In case of objective response, drug treatment should be administered for at least 1 year, possibly a longer duration for 2 (-3) years –depending on therapy tolerance and toxicity- may improve the outcome. Resection of residual metastases should be done after (8) – 12 – (16) weeks whenever possible.

If residual - unchanged - tumour lesions are existent longer than 3 (-6) months, an alternative drug treatment should be considered. In case of tumour progression or relapse a second-line treatment is recommended.

mTOR inhibitor therapy (evirolimus, temsirolimus)

Temsirolimus and everolimus are inhibitors of the mammalian target of rapamycin (mTOR), a serine-threonine kinase, that regulates cell growth and survival. In adults, mTOR inhibitors are recommended in poor risk metastatic RCC or/and as second-line therapy. Very few cases with Temsirolimus use in translocation RCC and temporary responses have been reported.

Experiences with mTOR inhibitor therapy in paediatric RCC are extremely limited. Everolimus is currently approved for subependymal giant cell astrocytoma (SEGA) treatment in children with tuberous sclerosis, a genetic disorder with a predisposition to RCC. In a currently published case report on a child with tuberous sclerosis, the authors reported that Temsirolimus treatment had led to substantial shrinkage of multifocal RCC tumours assessed as PR.

MET tyrosine kinase inhibitor (TKI) therapy

Aberrant transcriptional up-regulation of MET by TFE3 fusion proteins in translocation-associated RCCs and preclinical evidence of anti-proliferative effect of MET TKI exposition have raised hopes for the therapeutic potential of MET inhibitors in these RCCs. First data of a phase II study with Tivantinib, a selective inhibitor of MET, however, were disappointing with no objective responses in 6 translocation-type RCC. Thus, in our opinion, MET TKI therapy in paediatric RCC should currently not be recommended.

Alternative and second line drug treatment:

Immunotherapy. Several years ago, before the targeted drug era had evolved, immunotherapy was considered the standard treatment of metastatic adult RCC, producing single-agent objective response rates below 20% but with a curative potential in a small subset of patients (especially patients with good-risk features as good performance status and normal organ function, low LDH, normal BC and BSG, according to the prognostic index in adult RCC). In paediatric RCC, where such prognostic profiles are not identified as yet, a very few small studies and retrospective analyses documented objective responses and a survival benefit following interferon-a (IFN-a)–and/or interleukin-2 (IL-2)–based therapy in a small percentage/number of patients comparable with adult experiences.

Combined IFN-a plus bevacizumab and high dose IL-2 therapy are optional and recommended immunotherapy protocols in metastatic adult RCCs.

Following IFN-a/IL-2/capecitabine/13-cis-retinoic acid combination with maintenance immunotherapy for three years in adult metastatic RCC patients, an objective response rate of 54%, a median PFS of 14.7 months and a 2-year survival rate of 52 % were observed, suggesting a possible improvement after a combined version with prolonged immunotherapy. We observed one child with metastatic translocation-type RCC surviving disease-free > 10 years after combined IFN-a/IL-2/capecitabine/13-cis-retinoic acid according to the German DGCIN protocol published by Atzpodien et al.

Allogeneic hematopoietic stem cell transplantation (HSCT)

In case of refractory/relapsed metastatic RCC, HSCT has been considered as a rescue possibility if there is no evidence for a better alternative. So far, no evidence exists that this is of benefit.

A clear graft versus tumour (GVT) effect by allogeneic reduced intensity stem cell transplantation in metastatic RCC has been shown and the rescue potential of HSCT in adult cytokine-refractory RCC has been reported. The use of HSCT in adults was hardly compromised because of a high treatment-related mortality rate. In children a higher HSCT tolerance could be expected. In a recently published case the curative potential of reduced intensity HSCT in a paediatric metastatic RCC patient was demonstrated with a 5.7 year-progression-free survival after the initial HSCT.

Treatment approaches for paediatric RCC:

Disease stage	**Treatment approach**
Localized disease (T1-4M0N0)	- Complete nephrectomy - Nephron sparing surgery only if feasible and always after consultation of the SIOP surgical panel
Regional lymph node metastases (T1-4M0N1-2)	- Complete tumour resection including lymph node sampling
Distant metastases (T1-4M1N0-2)	1. Surgery: Complete radical tumour nephrectomy + lymph node sampling. Surgery of distant metastases only after adjuvant therapy (& response judgment). 2. Adjuvant therapy: best available suggestion: Sunitinib. If non-response: mTOR inhibitor (evirolimus, temsirolimus), TKI (tivantinib) or lastly immunotherapy can be considered.

The role of **radiotherapy** is limited in RCC. For details see radiotherapy section above

7.3. Malignant Rhabdoid Tumour of the Kidney (MRTK)

7.3.1. Introduction / background

Rhabdoid tumours represent a group of highly malignant childhood tumours characterized by common histology and usually the loss of INI1 expression in immunostaining. They can arise in the CNS, the soft tissues, the liver and the kidney. Though arising in different tissues, they usually share biallelic SMARCB1 or SMARCA4 inactivation. This suggests a common genetic development of Rhabdoid tumours. Rhabdoid tumours can arise at different sites in a single patient if the patient suffers from a germline mutation.

Malignant Rhabdoid Tumour of the Kidney (MRTK) shows an early onset with a median age at diagnosis of 10-18 months. 22-38% of MRTK patients have metastasis at diagnosis. Metastatic disease often arises within the first two years of life, in contrast to nephroblastoma where stage IV patients younger than two years are an absolute rarity. Furthermore the number stage III and IV tumours, is high compared to other renal tumours. Their prognosis is still unsatisfactory with many relapses occurring early, often shortly after end of treatment or even during treatment.

Standard high risk renal tumour regimens as well as non-rhabdomyosarcoma regimen (EpSSG) have been unsatisfactory so far, resulting in 20-40% OS. Mainly due to the rarity of the disease, no randomized trials investigating the efficacy of single agents or drug combinations in MRTK have commenced. So far in vitro testing, case reports and small series suggest sensitivity of MRTK to anthracyclins , alkylating agents, such as platinum derivates and oxazophosphorines, and radiation therapy. A positive contribution of high dose treatment with stem cell rescue (HDSCT) has been reported in case series only. Despite multimodal treatment including these agents and treatment modalities OS remains poor. This remains true for cases currently treated according to the ongoing UH1 protocol in the COG high-risk renal tumour studies whereas relevant toxicity causing repeated suspension of the latter protocols is a serious issue (Dome J., personal communication on preliminary results).

Gain of knowledge about response and outcome to a specific treatment is hampered by the rarity of MRTK and lately by several conflicting treatment protocols. Common international treatment guidelines specifically designed for MRTK will significantly accelerate gain of knowledge in this rare disease.

Epidemiology

MRTK accounts for about 1.4 to 2.4% of all childhood renal tumours in. The UK age standardized incidence between 1993 and 2010 was 0.6 per million children. In Germany 32 MRTK had been registered at the national childhood cancer registry over a time span of 16 years resulting in 0.23 per million. A report from the Automated Childhood Cancer Information System Project including 45 MRTK reported an incidence of 0.1 per million for 0-14 years and 1.0 per million for the first year of life presumably underestimating the real incidence.
Median age at diagnosis is 10 - 18 months with 22-38% of patients presenting with metastasis already at a young age. Thus, MRTK is the most frequent metastatic renal tumour in children younger than two years. MRTK usually metastasizes to the lungs. In progressed cases bones, CNS and other tissues have been reported. Synchronous involvement of cerebral, liver and/or soft tissue Rhabdoid tumours are highly suspicious for Rhabdoid Tumour Predisposition Syndrome (RTPS) with a germline mutation in one of the genes involved in the SWI/SNF

complex. The incidence of RTPS is not clear yet. RTPS might be associated with improved survival, as reported in seven cases with AT/RT showing long term survival.
Of all childhood Rhabdoid tumours 45-48% arise in the kidneys, 14 – 18% in the head and neck and 36-38% in the liver and soft tissue. Soft tissue sites are more frequently seen in older children and adults where they account for 60-88% of all Rhabdoid tumours. MRTK show a relatively equal gender distribution.

Biology

Jaclyn Biegel and colleagues in 1989 reported the association of monosomy 22 to AT/RT and later on could narrow down to biallelic inactivation of SMARCB1 on 22q11.2 in most cases. In roughly 15% of cases RTs have maintained SMARCB1 expression, suggesting other SWI/SNF complex inhibiting mutations. Recently Schneppenheim, Hasselblatt and colleagues identified both a germline and a somatic nonsense mutation of SMARCA4/BRG 1 in a RTPS family and a boy as reason for SWI/SNF complex disruption.
The proportion of MRTK patients with germline SWI/SNF complex disruption is not determined yet. In recent studies it was estimated with 15-35%. However since RTPS patients are probably overrepresented in the analysed cohorts the true percentage still needs to be determined in a cross-sectional study irrespective of familial predisposition. Bourdeaut and colleagues found only one germline affected parent out of 21 parent pairs examined suggesting a high rate of de novo germline mutations. Children suffering from germline mutations are significantly younger than the somatic MRTK children.
Various mutations including deletions, duplications, non-sense mutations, premature stop-codons, frameshift-mutations and others have been described for SMARCB1. Interestingly exons hit by a mutation seem to have an association for MRT, AT/RT or MRTK.
In all cases the loss of SMARCB1/INI expression leads to a loss of SWI/SNF chromatin-remodelling complex integrity. Similarly biallelic SMARCA4 inactivation causes the lack of BRG1, another crucial subunit of SWI/SNF complex. Both defects eventually cause a loss of function of SWI/SNF-complex in chromatin compaction. This presumably causes easier access of polymerases to chromosomes and thus a non-specific activation of many downstream pathways involving amongst others sonic hedgehog pathways, Wnt-pathway, aurora-kinase pathway and cell-cycle controls, f.e. cyclin D1, p16 and p14. This is in contrast to the genetic stability of RTs, which harbour only very few mutations as compared to other tumours and show no oncogenic canonical pathway mutations.
EZH2 dependent polycomb repressor complex (PRC2) has been shown to work antagonistic to the SWI/SNF-complex *in vitro*. Thus targeting EZH2 might be another potential future treatment option.

7.3.2. Treatment

In EU-RHAB Consensus Therapy Recommendations are given for MRTK. All patients with a MRTK should be registered in EU-RHAB and treated according to these recommendations that are described in detail in Part II of the European Rhabdoid Registry V4 from 2015 (starting page 129). The protocol of the Multinational Registry for Rhabdoid Tumours of any anatomical site (EU-RHAB) can be requested from the Study centre in Augsburg/Germany (Frühwald M: *European Rhabdoid Registry. A multinational registry for rhabdoid tumours of any anatomical site*. V4, 2015):

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The following section will give a short overview about different treatment options.
Experience reported here is not solely based on experience with renal tumours but including experience with AT/RT and MRT too.

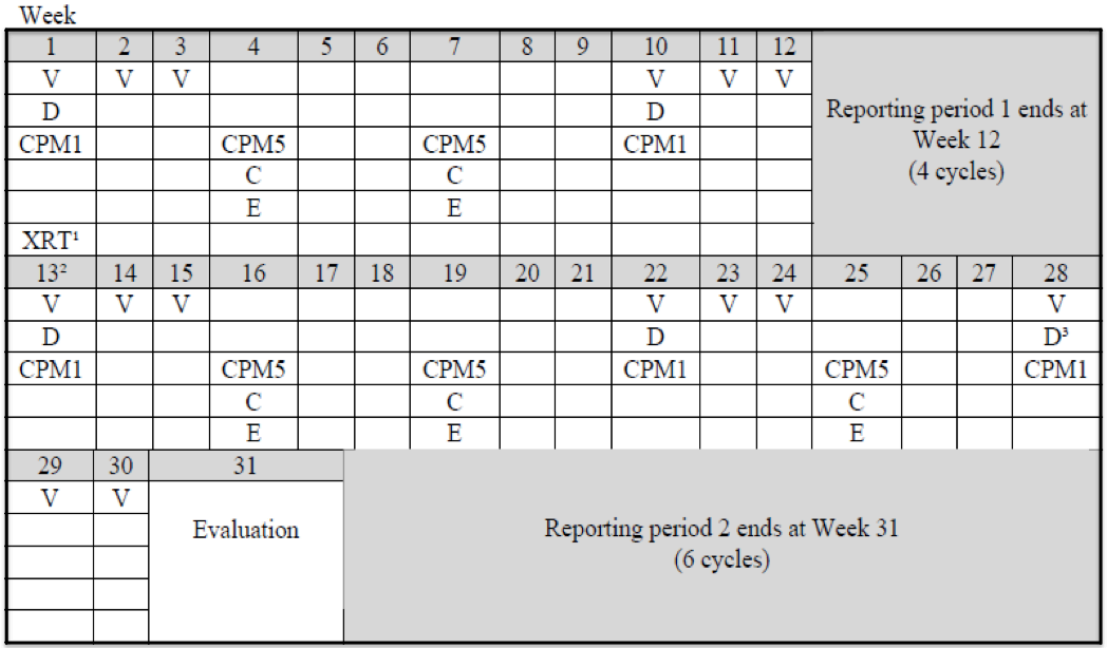
Surgery

Total resection of MRT or AT/RT is significantly correlated with increased relapse free survival, similarly advanced stage in MRTK has a significantly negative impact on survival. Van den Heuvel-Eibrink and colleagues reported 19% for stage III compared to 50% for stage I. Tomlinson compared stage I and II with stage III, IV and V resulting in 41% OS compared to 19% OS. Further discrimination into subgroups was not done by any of the authors.
Preoperative treatment is advisable in non-completely resectable MRTK, instead of delaying systemic treatment due to prolonged postoperative recovery after complicated surgery. MRTK usually significantly shrinks on anthracyclin containing regimens, and intensive treatment is often providing a setting in which a complete resection becomes possible. However delaying surgery should be limited to a few cycles of treatment, as the biology of the disease tends to give rise to early progression.

Chemotherapy

Until now no randomized study comparing regimens has been conducted. However several hints concerning the effect of specific drugs have been published. Waldron, Wagner and colleagues reported, taken together, three stage IV patients successfully treated with combinations of doxorubicin, cyclophosphamide, vincristine, ifosfamide and etoposide. Anthracyclin based treatment showed promising results in AT/RT in a recent report and anthracyclins have shown to induce volume decrease in the preoperative setting of MRTK. However Tomlinson and colleagues did not find a difference in survival based on the use of doxorubicin. The report fails to give details on the different cohorts to rule out a selection bias due to probable accumulation of higher stages in the doxorubicin receiving cohort. Alkylating agents, especially ifosfamide seem to be important in the treatment of extracranial RT. In a series of 13 children from St. Judes, only those receiving ifosfamide survived.
MRTK patients have been treated using different protocols over the last decades. The NWTSG treated their patients after upfront nephrectomy according to their unfavorable histology protocols during NWTS 1 to 4, largely based on vincristine, dactinomycin and doxorubicin with or without cyclophosphamide. In NWTS 1-5 Children having a local stage I or II had 41% OS, while higher stages showed 19.5% OS. Starting with NWTS 5 patients received a separate MRTK-protocol, based on carboplatinum, etoposide and cyclophosphamide, yielding 25.8% OS on 31 patients (AREN0321 High Risk Renal Tumours Trial Protocol). More recently, MRTK patients in North America were treated according to COG high risk protocol UH1 for localised MRTK. Stage IV patients and macroscopic residual stage III received an Irinotecan window treatment, which failed to show increased response (Dome J, preliminary data, personal communication). UH1 had to be closed several times for cardiac failures, VOD and respiratory distress syndromes. As a consequence total cumulative doses of doxorubicin had to be reduced from 375 mg/m^2 to 225 mg/m^2 and cyclophosphamide, etoposide cycles were reduced by 20% (Table 1 – Comparison of cumulative doses, Table 2 –Schedule of UH1). Also, despite significant treatment toxicity no convincing increase in survival was achieved so far. The COG regimens included radiation doses of 10.8 Gy flank for all stages. 22.5 Gy whole abdomen in specific cases.

Drug	Cumulative Doses (mg/m²)	
	UH-1	Revised UH-1
Cyclophosphamide	17,000	14,800
Doxorubicin	375	225
Vincristine	22.5	22.5
Carboplatin	3000	3000
Etoposide	2500	2000
Duration (weeks)	28	28



A similar approach was recently chosen by EpSSG using the same cumulative dosages and schedules. In recent oral presentation, OS for liver and kidney RT was stated to be only 17.5% (B. Brennan, Oral presentation at the Rhabdoid Tumour meeting, Paris 2013). Proposed adjustment of treatment was shortening of intervals to two weeks and introducing ifosfamide. EpSSG recommended irradiating with a dose of 19.8 Gy irrespectively of age and stage, and 19.5 Gy for whole abdomen irradiation. EPSSG tends to perform abdominal surgery late, only after 4 cycles of intensive treatment, as recommend for non-resectable stages such as stage IV.

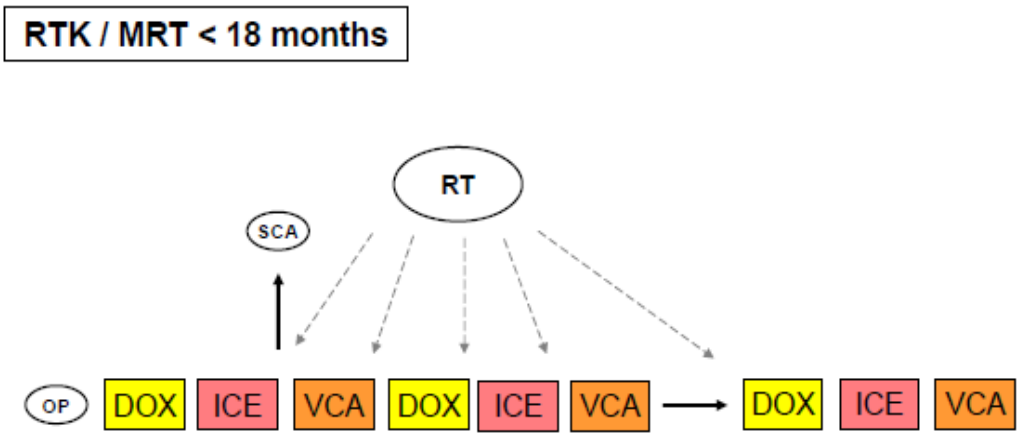
Week

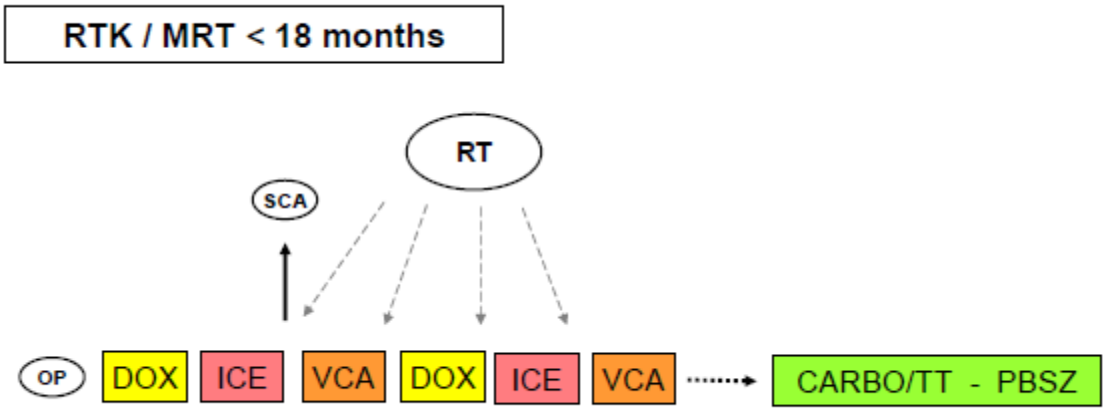
1	2	3	4	5	6	7	8	9	10	11	12				
V	V	V							V	V	V				
D			Cy*			Cy*			D						
Cy			C			C			Cy						
			E			E									
13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
V	V	V							V	V	V				V
D			Cy*			Cy*			D			Cy*			D
Cy			C			C			Cy			C			Cy
			E			E						E			

29	30
V	V

Starting with SIOP 93-01 MRTK was treated with alternating courses of carboplatinum and etoposide and doxorubicin and ifosfamide (SIOP93-01) or cyclophosphamide (SIOP2001). The cumulative dose of doxorubicin was 300mg/m^2 (I-III) and 400mg/m^2 for stage IV. 5y-EFS were 50%, 28%, 19% and 18% for stage I, II, III and IV respectively in 107 patients. The SIOP irradiation dose was: 30 Gy flank and 20 Gy whole abdomen.

The EU-RHAB registry is a common treatment approach to cranial, renal and extra-cranial and extra-renal Rhabdoid tumours. It includes block treatment on a two week schedule with two cycles of alternating blocks of doxorubicin (70mg/48h), ICE (3x2g/m^2 ifosfamide,1 x 500mg/m^2 carboplatinum, 3 x 100mg/m^2 etoposide) and VCA (vincristine 1x1.5mg/m^2, cyclophosphamide 1 x 1.5g/m^2 and dactinomycin 2 x 25µg/kg), followed by optional high dose treatment with carboplatinum and thiotepa or one more cycle of three blocks (Figure 1 – Overview of treatment schedule with or without HDSCT). Irradiation should be given as early as possible. Doses recommended are 19.8 Gy flank irradiation in children >12 months of age and 10.8 Gy for children <12 months of age. **For further details use the EU-RHAB Registry protocol as stated above.**





With evolving knowledge about targeted therapies a variety of small molecules have been tested preclinically on rhabdoid tumour cell lines and/or xenograft models: Arsenic trioxid; Aurora Kinase A radiosensitzing; cyclin D inhibition by f.e. flavopiridol, Alvocidib or Fenretinide and Tamoxifen, HDAC inhibition by romidepsin (effective in AT/RT not in MRTK cell lines) . A few have been tested in phase I and II studies: Aurorakinase A inhibitor Alisertib in a COG phase I and UK phase II study, results pending; HDAC inhibitor Vorinostat partly combined with cis-retionic acid in a phase I including two AT/RT, without objective response. However considering the etiology of MRTK it is unlikely a single agent will yield continuous response.

Radiotherapy

The role of radiotherapy (RT) in MRTK still needs to be determined.

The young age of MRTK patients often encourages physicians to omit flank irradiation or lung irradiation in those patients, thus it remains uncertain whether different tumour biology in infant patients or omitting irradiation accounts for the significant difference in survival repeatedly reported for younger patients.

Looking at AT/RT cohorts, the association of survival and RT is compelling. In 1 series only one out of ten patients, including three infants, receiving RT in first line treatment died and one was alive with disease. In contrast three out of 21 without RT in first line, 19 younger than three years, survived without evidence of disease. Two of them received RT in second line treatment.

In a report about MRTK treated in NWTS1-5, 100 of 142 had received RT. 4y OS was 28.5% in RT patients and 12.2% in non-RT patients (p=0.25). Again, RT was more frequently given to older patients or younger patients with advanced disease, thus rendering interpretation of the data difficult. Interestingly RT-dose of > 25 Gy might be of benefit in older patients.

52 patients having MRTK have been treated in the GPOH from 1993-2013. Patients with a local stage III, receiving RT had 36% OS whereas OS was 19% OS when not RT was not administered (Furtwängler, Rhabdoid Tumour meeting, Paris 2013). Sultan and colleagues, reporting on SEER data, showed a significant impact of RT on survival (HR 1.89; 1.29-2.78 95%CI; p=0.0012) in multivariate analysis adjusted for age and stage, both being of significant influence too. In 229 patients analysed, only 45 had MRTK and the remaining patients AT/RT or MRT.

In summary RT seems to be justified even in infants with MRTKs. Further details are given in the **EU-Rhabdoid Registry**.

7.3.3. Recommendations

a. Diagnostics

i. Imaging

SIOP UMBRELLA - MRTK specific implications: Whole body MRI, cranial MRI

ii. Histology

SIOP UMBRELLA - MRTK specific implications: Recommend tru-cut biopsy in children younger than 24 months suffering from metastasis or familial predisposition (Family history for AT/RT; MRT or MRTK), without delaying the start of treatment.

iii. Genetics

Analysis of tumour tissue, patient's and in case of germline mutation of parents' samples for somatic and germline mutation of SMARCB1 and SMARCA4.

b. Treatment

The aim of this guideline is to facilitate best uniform treatment of all MRTK in the SIOP collaborative centres.

i. Chemotherapy

See the respective section in EU-RHAB Registry for Rhabdoid Tumours of the Kidney

ii. Irradiation

See the respective section in EU-RHAB Registry for Rhabdoid Tumours of the Kidney

iii. Surgery

See the respective section in EU-RHAB Registry for Rhabdoid Tumours of the Kidney

c. Follow up

Refer to SIOP-RTSG UMBRELLA and EU-RHAB – Additional cMRT/Whole body screening in germline mutation patients as a screening

7.4. Congenital Mesoblastic Nephroma (CMN)

7.4.1. Introduction / background

Epidemiology

Congenital mesoblastic nephroma (CMN) is a rare tumour that accounts for about 3% of all paediatric renal tumour. However, it is the most common renal neoplasm in the first 3 months of life. The median age is ≤ 1 month in most published series and CMN is frequently recognized before or at time of birth, illustrating the embryonal origin of the disease.

Clinical features

The most common presentation of CMN is an abdominal mass/distention, followed by hypertension and gross haematuria. Patients are usually asymptomatic and the mass is detected as an incidental finding. In some patients, the tumour is diagnosed on prenatal ultrasound. Other very rare findings are hypercalcaemia and hyperreninaemia. Metastatic disease at time of initial presentation has not been described. Among 101 patients in two of the largest series, there were no cases of lymph node involvement or distant metastatic disease. However, cases of metastasis to the brain and lung have been documented at time of recurrence.

Histology

There are two main histologic subtypes of CMN: classic (or conventional) and cellular. Some CMNs have a mixed pattern with features of both subtypes. Classic CMN tends to present in very young infants and neonates, whereas cellular CMN is seen in older infants.

Genetics

Cellular CMN is morphologically similar to infantile fibrosarcoma (IFS), underscored by the completely similar chromosomal translocation t(12;15)(p13;q25), which results in a fusion of the *ETV6* (*TEL*) gene with the *NTRK3* gene. *ETV6* encodes a transcription factor with a helix-loop-helix protein dimerization domain and *NTRK3* encodes a receptor tyrosine kinase. The chimeric ETV6-NTRK3 protein is postulated to have constitutively active tyrosine kinase growth pathway signalling. A recent gene expression analysis of CMN showed that these tumours have a distinct gene expression profile compared to other paediatric renal tumours. The expression pattern was consistent with receptor tyrosine kinase activation, with evidence of PI3-AKT, SRC, and MAPK activation. Interestingly, 4/14 cellular CMN manifested the gene expression pattern of CMN, but did not have detectable ETV6-NTRK6 transcript, indicating that molecular mechanisms other than the ETV6-NTRK6 fusion are responsible for the development of some cellular CMN. Another aberration commonly described in cellular CMN is trisomy 11. In most cases, trisomy 11 occurs together with t(10;15)(p13;q25). CMN has never been reported with germline trisomy 11 nor other genetic predisposition syndromes. Also, familial CMN cases have not been reported so far.

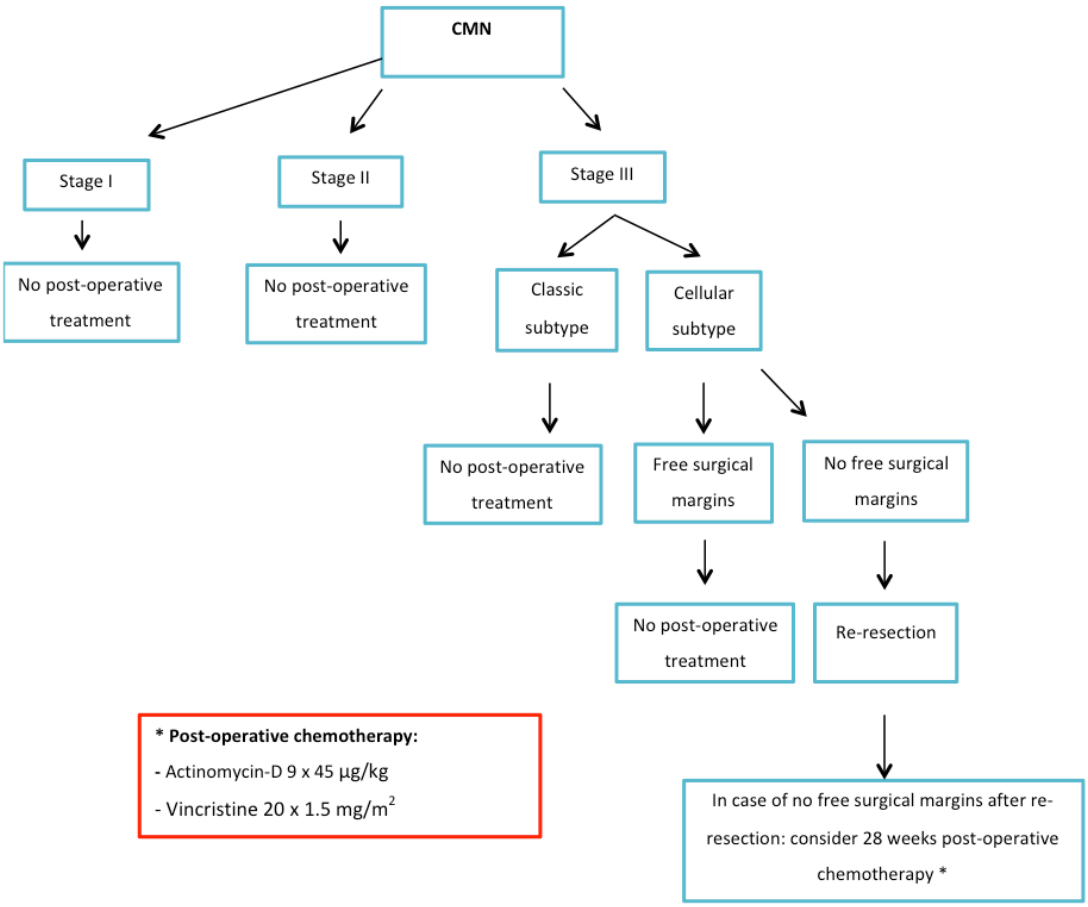
7.4.2. Treatment and outcome

Outcomes for patients with CMN are generally excellent when treated with nephrectomy only, with overall survival rates of about 95%. The few tumours that recur are almost exclusively of the cellular subtype. It remains to be established whether patients with stage III cellular CMN benefit from adjuvant chemotherapy. In a series published by the German Pediatric Oncology Group (GPOH), two of five patients with stage III cellular CMN developed recurrent disease

(no recurrences in four patients with stage III classic CMN), whereas only one of the remaining 45 patients with other disease stages had a recurrence. Three of five patients with cellular stage III CMN were treated with adjuvant chemotherapy at initial diagnosis; these patients remained free of disease after initial treatment. In a report of the United Kingdom Children's Cancer and Leukaemia Group (CCLG) no recurrences occurred in 6 patients with stage III disease (2 cellular, 3 mixed and 1 classic type), only 1 of these 6 patients was treated with adjuvant chemotherapy because of tumour spill.

Report	Study	N	Surgery only	Post-operative chemo-therapy	Radio-therapy	EFS	OS	Cause of death
Howell 1982	NWTS	51	23	28 (ACT, ACT/VCR)	4	98% (1y)	98% (1y)	Sepsis (1)
Sandstedt 1983	SIOP	29 (9 classic, 20 cellular)	24	5 (all cellular)	1	93% (4y)	93% (4y)	Sepsis (2)
Furtwängler 2006	SIOP 93-01 (GPOH)	50 (29 classic, 21 cellular)	41	9 (3 VCR, 3 ACT / VCR, 2 AVD, 1 VP16 / CYC / DOX / CARBO)	1 (extensive abdominal infiltration cellular CMN)	94% (4.2y) (3 recurrences, all cellular, 1 stage I and 2 stage III)	95% (4.2y) (2 dead, all cellular, 1 stage I, 1 stage III)	Tumour
Chaudry 2009	Children's Hospital (Boston), The Hospital of Sick Children (Toronto)	30 (13 classic, 3 mixed, 14 cellular)	NA	NA	NA	93%	NA	NA
England 2011	CCLG	50 (23 classic, 10 mixed, 14 cellular)	46	2 (ACT/VCR, ACT/VCR/CYC) (mixed type stage III)	0	100% (4.4y)	100% (4.4y)	-

Studies of cellular CMN have shown that these tumours respond to regimens containing different combinations of vincristine, dactinomycin, doxorubicin, and cyclophosphamide. This is not unexpected based on the sensitivity of infantile fibrosarcoma to similar sarcoma-directed therapy. Responses to ifosfamide/carboplatin/etoposide (ICE) have also been noted in patients with tumours refractory to the other agents.



* Before starting chemotherapy for 28 weeks discuss with the National PI!

Surgery

Complete nephrectomy is the treatment of choice in localized disease. The perirenal fat should be removed, as CMN tends to infiltrate in the surrounding tissue. Re-resection should be performed in case of incomplete tumour resection or incomplete removal of the perirenal fat. Metastectomy is advised in exceptional cases with solitary metastasis.

Chemotherapy

Pre-operative chemotherapy:

< 6 months: immediate surgery

> 6 months: pre-operative chemotherapy (actinomycin-D and vincristine)

Post-operative chemotherapy

In case of progression under treatment with actinomycin-D and vincristine, second line treatment with ICE (see treatment schedule below) is recommended. Other possible drugs are cyclophosphamide and doxorubicin.

Dosing ICE chemotherapy:

Drugs	Administration		Dosing	Days
Ifosfamide	IV over 2 hours		66.7 mg/kg/day for infants < 12 months 2,000 mg/m^2 for children ≥ 12 months	1-3
Carboplatin	IV over 1 hour	**GFR**	**Dose**	1
		> 150 mL/min/1.73m^2	560 mg/m^2 (18.7 mg/kg for infants)	
		100-150 mL/min/1.73m^2	500 mg/m^2 (16.6 mg/kg for infants)	
		75-99 mL/min/1.73m^2	370 mg/m^2 (12.3 mg/kg for infants)	
		50-74 mL/min/1.73m^2	290 mg/m^2 (9.7 mg/kg for infants)	
		30-49 mL/min/1.73m^2	200 mg/m^2 (6.7 mg/kg for infants)	
		<30 mL/min/1.73m^2	Hold carboplatin	
Etoposide	IV over 1 hour		3.3 mg/kg/day for infants < 12 mo. 100 mg/m^2/day for children ≥ 12 mo.	1-3

7.4.3. Treatment recommendations of relapsed CMN

Local relapse / metastatic relapse:

1. Surgery if possible

2. No complete surgical resection:

- Chemotherapy naïve patients: combination of vincristine, dactinomycin
- Chemotherapy non-naïve patients: ifosfamide, carboplatin, etoposide (ICE) +/- radiotherapy, or treatment with combinations of doxorubicin and cyclophosphamide.
- In aggressive cases with ETV6-NTRK3 gene fusions, targeted inhibitors can be considered

Other Kidney Tumours

Other non-WT kidney tumours include soft tissue sarcomas/PNET, neuroblastoma of the kidney, non-Hodgkin lymphoma (primary site in the kidney), teratoma and angiomyolipoma. Together, they account for less than 2% of all primary renal tumours in children. As these are all very rare renal tumours, it is advised to contact the national coordinator in such rare cases.

8. Treatment recommendations for patients with renal tumours below 6 months of age

Wilms tumours:

a. In children below the age of 6 months (182 days), primary surgery is usually recommended. However, this decision requires a multidisciplinary evaluation of the individual risks related to surgery in infants, weighing the risk of tumour rupture against the exposure to preoperative chemotherapy. This includes the risk of giving chemotherapy to a benign tumour (CMN) or suboptimal treatment of MRTK.
b. Postoperative chemotherapy is recommended for intermediate risk and high risk tumours, with adjustment of the dosage of drugs according to age and body weight. Specific guidelines for patients after primary surgery are described.
c. If radiotherapy is indicated, it should be discussed with the national coordinator and the radiotherapist in order to refine the dose and field due to the increased vulnerability of infants.
d. Stage II high risk WT patients: discuss radiotherapy with the national coordinator.

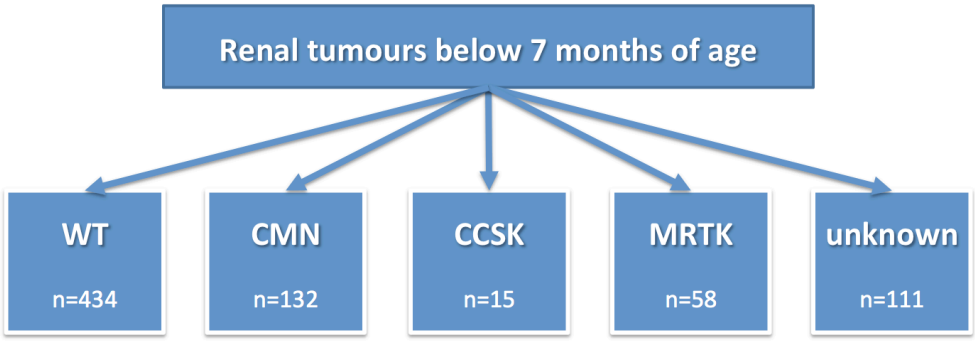
Histological classification of WT into low, intermediate and high risk is different for patients who received preoperative chemotherapy from those who underwent primary surgery. This is important to notice, as most of the children aged below 6 months will be treated with immediate surgery. The histological classification after primary surgery is specified in section.

Non-Wilms Tumours:

Follow guidelines of the UMBRELLA protocol with adjustment of the dosage of drugs according to age and body weight.

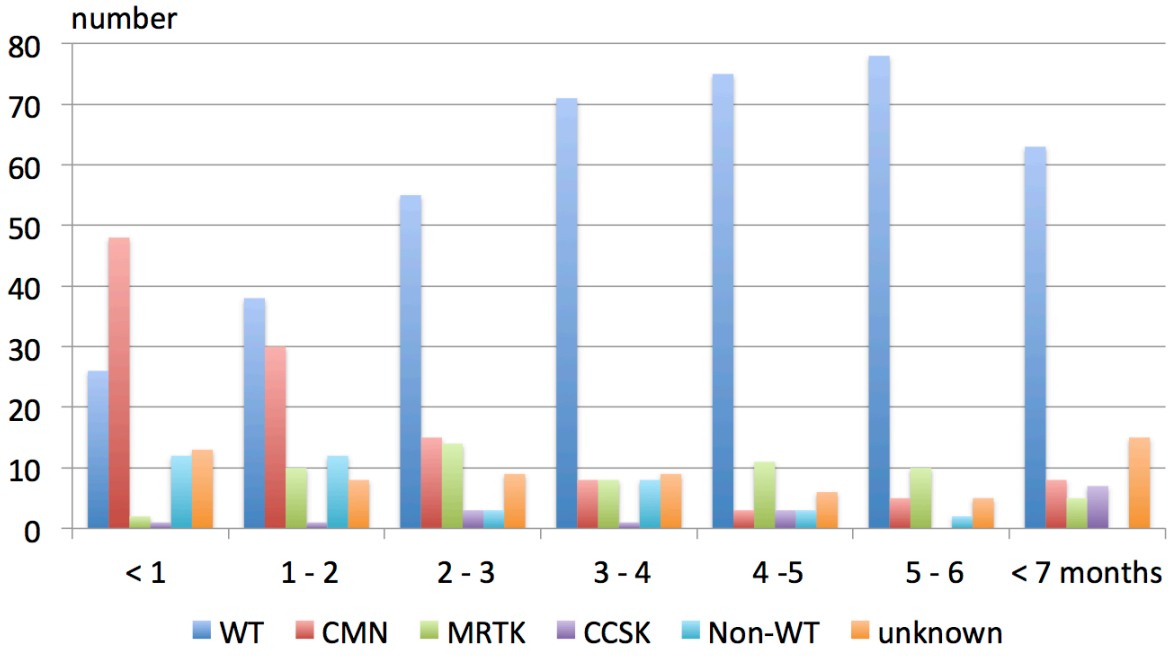
Radiotherapy

If possible radiotherapy should be avoided in these young infants, because of the increased risk of serious long-term toxicity. In case of diffuse anaplasia and/or local stage 3 disease it is advised to discuss the indication, radiation field and dose with the national coordinator before radiotherapy is administered.



Stage I/II	356	98	11	15	17
Stage III	37	17	4	22	7
Stage IV	2	0	0	9	5
Stage V	37	0	0	3	12
Missing	2	17	0	9	70

Distribution of renal tumours in children aged less than 7 months in the retrospective cohort



Correlation between histology and age (months) in infants with kidney tumours < 7 months of age.

9. Patient Follow-Up and late effects

The following table provides a schematic overview of minimal follow-up diagnostics

Relapse detection and toxicity surveillance after discontinuation of therapy						
	1st year	**2nd year**	**3rd year**	**4th year**	**5th year**	**> 5 years**
Physical examination	*Every3rd month*	*Every 3rd month*	*Every 4th month*	*Every 6th month*	*Once a year*	*Optional*
Scans: Wilms' tumours*:						
- *Abdominal ultrasound*	*Every 2-3rd** month*	*Every 3rd month*	*Relapse risk at 3rd year is low for children below 10 years of age. Consider to keep surveillance in year 3-5 for > 10y (14y) For stage V: scans according to e.g., underlying genetics, pre-disposition and renal function.*			
- *Chest x-ray AP or PA and lateral view*	*Every 2-3rd** month*	*Every 3rd month*				
Scans: Non-Wilms' tumours:	*Discuss with national PI due to limited data. Standard would be:*					
- *Abdominal ultrasound*	*Every 3rd month*	*Every 3rd month*	*Every 4th month*	*Every 6th month*	*Once a year*	*None*
- *Chest x-ray AP or PA and lateral view*	*Every 3rd month*	*Every 3rd month*	*Every 4th month*	*Every 6th month*	*Once a year*	*None*
Brain MRI	*Only in case of relapse suspicion CCSK and MRTK or initial brain metastasis*					
Technetium bone scan or whole body MRI	*Only in case of relapse suspicion in CCSK or initial bone metastasis*					
	Patient treated with only sugery (eg congenital mesoblastic nephroma/cystic nephroma) only needs yearly abdominal ultrasound and no chest x-ray					
Urine: protein/creatinine ratio	*Every 3rd month*	*Every 3rd month*	*Every 6th month*	*Every 6th month*	*Once a year*	*Blood pressure + protein/creatinine ratio once a year.* *Contact GP/paediatrician if signs of urinary tract infection.*
Blood: Full blood count, urea, creatinine, cystatin C; Ca^{++}, phosphate, Mg^{++}, albumin, ALAT/ASAT, bilirubin, and blood gas.	*Every 3rd month*	*Every 6th month*	*Every 6th month*	*Every 6th month*	*Once a year*	
Blood pressure	*Every 3rd month*	*Every 3rd month*	*Every 4th month*	*Every 6th month*	*Once a year*	
*Nephrologists****	*Liaise with local paediatric nephrologists at end of treatment.*					
Geneticists	*Patients with underlying pre-disposition, malformations, and/or bilateral disease.*					
ECG/Echocardiography	*Long-term follow-up surveillance advised according to the guidelines from the Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) and local policy. IGHG guidelines are (http://www.ighg.org/), and SIOP supportive care committee.*					
Lung function						
Endocrinology/fertility						
Audiometry						

*: Remember to perform relapse surveillance right after nephrectomy as a significant proportion of the relapses occur during post-operative treatment.
**: High-risk histology (stage III, IV and V) and intermediate-risk histology (stage IV) have a significantly higher risk of relapse the first year after nephrectomy and should have USS/ X-ray every 2nd month.
***Surveillance of kidney function is mandatory and additionally GFR and 24 urine collection can be considered. Referral to a Paediatric nephrologist in case of proteinuria, nephrocalcinosis, hypertonus and decreased kidney function.

Late effects: Despite being associated with fewer late effects compared to most other childhood malignancies, renal tumour survivors still have an increased risk of severe chronic and life-threatening health conditions in adult life when compared to the general population. Most frequently the late sequelae include secondary malignancies, renal, cardiac, pulmonary and gonadal dysfunction, musculoskeletal abnormalities, impaired fertility and hypertension. However, studies on long-term outcomes of WT survivors, as summarised below, are mainly based on patient cohorts treated in the 1980/90s. Since then, overall treatment intensity has been reduced and refined leading to a lower likelihood of long-term sequelae.

Mortality: Comparing observed with expected number of deaths (<2%) 30 years after diagnosis indicates a 4-5 times increased mortality risk, with the main causes being secondary malignancies, and cardiac and pulmonary diseases. Furthermore, approximately 20-25% of survivors are found to have a severe chronic health condition.

Secondary malignancies: The cumulative incidence of secondary malignancies is estimated as 0.5-1% and 2-3%, at 10 and 30 years after diagnosis, respectively. The type of secondary malignancies varies (sarcomas, breast cancer, lymphomas, etc.) but as the majority of these cancers occur within the radiotherapy field, radiotherapy is the main contributing risk factor. Doxorubicin may further potentiate the adverse effects related to radiotherapy due to the drug's radiosensitisation of cells. For surveillance of breast cancer in pulmonary irradiated renal tumour survivors, it is advised to follow the recommendations of the IGHG group.

Cardiotoxicity: Doxorubicin increases the risk of congestive heart failure, with an overall cumulative risk of about 5% at 20 years after treatment. The risk is related to the cumulative dose, and many guidelines recommend that survivors who received ≥ 250 mg/m^2 should undergo long-term cardiac surveillance. Cardiotoxicity risk, as well as the occurrence of heart valve disease, is potentiated by concurrent use of radiotherapy (left flank, whole abdominal or pulmonary RT) and both females and very young patients seem to be more susceptible. For cardiac surveillance it is advised to follow the recommendations of the IGHG group.

Renal function: End stage renal failure is reported in 1% of unilateral WT and about 10% of patients with bilateral disease after 20 years of follow-up. Irradiation to the remaining kidney and the use of high-sk chemotherapy (e.g. ifosfamide and carboplatin) may further increase the risk of end stage renal failure.

Musculoskeletal function: Radiotherapy reduces the growth of normal tissue with severity depending on the dose, radiation field and the patient's age. The younger the patient, the more severe the developmental abnormalities become. Abnormal growth of the spinal column and ribs, breast hypoplasia and impaired muscle development of the torso are the most commonly observed sequelae.

Chronic lung disease: Approximately 5% of WT patients treated with lung RT develop pulmonary disease within 15 years of treatment, with the majority classified as pulmonary fibrosis or unspecified lung disease. Chronic lung disease occurs infrequently in patients not receiving radiotherapy.

Ototoxicity: It is advised to perform audiological screening in children that have been exposed to carboplatin and cisplatin, concomitant co-medication and for the few patients that have received radiotherapy to the head and neck region, after discontinuation of therapy

Gonadal and other endocrine impairment: Gonadal impairment has been documented after whole body irradiation, alkylating agents and high dose chemotherapy. For surveillance of gonadal impairment in female renal tumour survivors, it is advised to follow the recommendations of the IGHG group. The IGHG guideline for male survivors will be launched shortly.

10. References

Chapter 1

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Chapter 7.4

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APPENDIX 1: TECHNICAL DETAILS AND GUIDELINES REGARDING RADIOLOGY

Abdominal ultrasound

Abdominal ultrasound is mandatory. With the right equipment/settings and an experienced operator, it offers valuable non-invasive imaging of the abdomen. Representative images should be appropriately annotated and stored.

Technical Requirements

- curved array probe (≥5 MHz)
    - B-Mode with harmonic imaging
    - Colour-coded duplex sonography
- High frequency linear probe (≥ 10MHz)

Operator Requirements

The operator should be a radiologist or paediatrician with training and experience in paediatric ultrasound and paediatric oncology.

Documentation Requirements (see radiology CRF)

- Each renal lesion size in three dimensions and location within the kidney
- Lesion volume = a x b x c x 0.523
    - In case of multiple lesions each lesion (with a maxiumum of 3) will be measured and the total volume assessed. Response must be assessed for each lesion separately. If the tumour cannot be delineated from the kidney, tumour and kidney should be measured as a whole.
- Relation to remaining kidney, liver, spleen, pancreas, aorta and IVC
- renal veins, vena cava – Duplex and B-mode to exclude thrombus
- Suspicious lymph nodes, hepatic lesions or intraperitoneal implants:
    - Position
    - Size
    - Number
- Abdominal Fluids:
    - Location (intra/retroperitoneal)
    - Haemorrhagic?
- Contralateral kidney: screen for involvement or other abnormalities

Abdominal MRI

In case of renal impairment, abdominal imaging should be done by ultrasound and non-enhanced MRI only.

Initial pre-surgery and follow-up MRI should be carried out according to the following recommendations. Sedation or general anaesthesia is recommended in young children according to local practice.

Operator Requirements

The protocol should be performed by MR-radiographers and radiologists with expertise in paediatric abdominal MRI.

Technical Requirements

- 1.0 Tesla or higher

  Coils: should cover around 1.5 times the area of interest. Surface multi-channel coils are preferred, usually posterior spine coil and anterior body coil. Individual coil elements should be selected as appropriate for the field-of-view of individual pulse sequences.
  The whole peritoneal cavity should be examined, including liver and pelvis.
- Motion artefacts can be minimized with respiratory triggering, echo-navigator, single-slice acquisition sequences, or high-temporal resolution sequences and motion correction such as BLADE (Siemens), Propeller (GE), MultiVane (Philips).
- Recommended spatial resolution is ≤ 4 mm slice thickness, and ≤ 1 x 1 mm^2 in plane resolution (matrix and FOV to be adjusted to the size of the abdomen)
- IV contrast is recommended but not mandatory.

Basic Imaging Protocol Recommendation

Mandatory:

1. Coronal and axial STIR (TE > 70 ms, TI 140-170 ms) or T2 with fat suppression (TE 50-80 ms) with respiratory gating or other compensation for respiratory motion. Cover the whole abdomen and pelvis. Slice thicknesses ≤ 4 mm. In-plane base-resolution, ≤ 1x1 mm.
2. T2-weighted SE non-fat suppressed with respiratory gating or other compensation for respiratory motion covering the entire kidneys/tumour in axial, coronal and sagittal plane. Slice thickness ≤ 4 mm and in-plane base-resolution, approximately 0.9 mm.
3. T1-weighted SE non-fat suppressed of the whole abdomen in axial plane. Slice thickness ≤ 4 mm. In-plane-base-resolution approximately 0.9 mm.

Recommended:

1. If available, a volumetric acquisition with flip-angle optimisation can replace ‘mandatory 2’, e.g. SPACE (Siemens), CUBE (GE), VISTA (Philips). Resolution approximately 1 x 1 x 1 mm^3.
2. Axial diffusion-weighted imaging (may be replaced by the corresponding pulse sequence as outlined in the research section below). Respiratory gating is not mandatory. Cover the entire lesion. EPI readout. Use parallel imaging. TR > 2300 ms; TE as short as possible; slice thickness, 6 mm; in-plane base resolution, approximately 2.7 mm; b values, 0, 50, 200 (250), 400 (500), 800 (1000) s/mm^2. Apply (spectral pre-pulse) fat suppression.
3. If no contraindication for administration of gadolinium chelates:
   Instead of ‘mandatory 3’, Pre-contrast fat-suppressed T1 and contrast-enhanced fat-suppressedT1-W sequences in 2 planes or pre-contrast and porto-venous 3D-spoiled gradient-echo, 3D FLASH or VIBE (Siemens), LAVA (GE), THRIVE (Philips). Breathold is required (depiction of necrotic areas and small lesions within the normally enhancing renal parenchyma).

Research: Optional recommended protocol (Diagnosis and pre-surgery only)

This optional examination is aiming at increasing the knowledge about DWI in nephroblastoma patients. It therefore contains specific recommendations to facilitate comparability of results from different hospitals. It should be used initially and pre-surgery.

- Axial diffusion-weighted imaging (may replace the corresponding pulse sequence in the basic protocol). Respiratory gating is not mandatory. Cover the entire lesion. Single-shot with EPI readout. Use parallel imaging (factor 2). Receiver band-width, 1,500 Hz (12 Hz/pixel) TR, 2800 ms; TE as short as possible (70 - 90 ms); slice thickness, 6 mm; FOV of 350 mm and phase field-of-view of 75% with matrix 128 x 96 gives an in-plane resolution of 2.7 x 2.7 mm^2; b values: 0, 25, 50, 100, 150, 200, 250, 500, 750 and 1,000. Apply (spectral pre-pulse) fat suppression.
- Dynamic contrast-enhanced imaging with T1-weighted spoiled gradient-echo performed during quiet breathing and covering the lesion. Flip angle, 25 degrees. Slice thickness, 6-8 mm; in-plane resolution, 2.5-4 mm. Temporal resolution, 2 s. Temporal resolution has highest priority, and the spatial resolution may need adjustment to achieve high temporal resolution. Consecutive 2-s acquisitions are run for 120 s in total with contrast medium injection 30 s into the run. Gadolinium chelate at 0.1 mmol/kg BW is injected as a bolus using an automated power injector. Please follow MHRA advice and local protocols for administration of gadolinium chelates. This sequence replaces step 3 in the recommended protocol.

Abdominal CT (only if MRI is not available)

A volumetric acquisition should be performed during breath-hold in the porto-venous phase following intravenous administration of iodinated contrast medium (use of an automated power injector is strongly recommended). Cover the abdomen and pelvis. Oral contrast is not mandatory. Unenhanced or delayed images are reserved for specific situations such as renal or tumoural haemorrhage. Appropriate contention should be used according to age to avoid motion artefacts.

Technical Requirements

- Positioning of IV line; IV contrast is mandatory: 2mg/kg iodinated contrast agent (300-370 mg/l iodine concentration), 1.5-2 ml/s flow rate, 35 sec scan delay (porto-venous phase)
- Scan area: from diaphragm to pubic bone
- Tube potential: 80 – 100 kVp
- FOV: adapt appropriately
- Slice thickness: 1-1.5 mm
- Kernel: standard
- Position: supine, arms above head
- Minimum rotation time (≤ 0.5 sec)
- Pitch: 1.0 to 1.3
- Dose reduction options recommended (tube current modulation, iterative reconstruction)
- Tube current adjusted to body weight/age or BMI according to local practice and national DRLs
- Reconstructions in COR and SAG plane.
- NB: parameters are different with dual-source CT

Chest CT

Is not to be performed immediately after a procedure under sedation or general anaesthesia (risk of persisting atelectasis). If in rare situations chest CT is to be performed under GA, controlled ventilation techniques are necessary to reduce the risk of atelectasis.
Appropriate contention should be used according to age to avoid motion artefacts.
Without IV contrast (unless in same session as abdominal CT)

Technical Requirements

- Scan area: All lung parenchyma, from superior thoracic aperture to and including posterior costophrenic angles
- Tube potential: 80 – 100 kVp
- FOV: adapt appropriately
- Slice reconstruction: 1-1.5 mm
- Kernel: lung (B60f 1 mm)
- Position: supine, arms above head
- Minimum Rotation time (≤ 0.5 sec)
- Pitch: 1.0 to 1.3
- Tube current adjusted to body weight/age or BMI according to local practice and national DRLs; the CT dose must provide adequate SNR and CNR to depict small nodules (too noisy images may reduce small lesion depiction)
- Maximum intensity projection (MIP) reconstruction with a thickness of 5-7 mm is recommended to increase detection of lung nodules
- N.B.: Parameters are different when dual-source CT is used)
- N.B.: Lung lesions in patients <2 years at diagnosis are extremely rare in nephroblastoma and therefore suspicious for MRTK.

Chest X-Ray

AP view at diagnosis is mandatory. This could be a chest x-ray made for positioning of the central venous line. During follow-up after end of treatment AP (PA) view will be performed.

Optional diagnostic imaging

- **Selective renal arteriography.** Only in the very rare case of complex anatomy and MR or CT angiography being insufficient
- **MIBG.** If neuroblastoma cannot be ruled out, because:
    - There is no destruction/deformation of calyces or renal pelvis
    - Urine-catecholamine is elevated
    - There is an atypical growth pattern: tumour encasing abdominal vessels
    - There are calcifications
    - There are very large tumours infiltrating the whole kidney
- **MRI of the head.** In case of:
    - MRTK - possible synchronous brain tumour(s)
    - CCSK (optional) - frequent site of metastatic relapse
    - Focal neurology or other clinical signs of cerebral metastasis

Technique:

- ≥ 1.5 Tesla
- Head coil
- Sequences: T1, T2, FLAIR, post-gadolinium T1-W
- At least 2 acquisition planes or 3D sequences

- **Bone Scan:** CCSK – frequent site of primary metastasis (alternatively whole body MRI or PET-scan)

- **Echocardiography**

Fractional shortening, 'ejection fraction' and 'end systolic' wall stress should be documented before the first dose of Doxorubicin in all patients planned to receive doxorubicin, i.e. Stage IV and high risk histology. In patients treated for localised disease, the measurements should be repeated after a total cumulative dose of 150 mg/m2 and again after a total dose of 250 mg/m2, within 3 month of end of treatment. For patients receiving a higher cumulative dose (high risk protocol and stage IV disease), the measurements should be repeated after a total cumulative dose of 150 mg/m2 and 250 mg/m2 and within 3 months of end of treatment.

- **MAG3-Scintigraphy**

Optional to evaluate the side-specific function of remaining renal tissue in specific cases before surgery:

- Genetic predisposition syndromes
- Stage V/Bilateral nephroblastoma
- Bilateral nephroblastomatosis

IMAGING DEFINITIONS

Pulmonary Metastasis:

Chest-CT definition:

Lung nodules with the following characteristics will be recorded

- Non-calcified
- Round shaped
- Sharply marginated

Lung lesions with other characteristics:

- "ground-glass," ill-defined, or diffusely alveolar - they will be considered to be of inflammatory origin
- Linear in shape – they will be considered to be atelectasis
- Calcified - they will be considered to be granulomas
- Triangular or trapezoidal and perifissural or subpleural – they will be considered lymph nodes

The largest nodule will be measured, classified according to diameter and followed-up for response:

- 1 – 2 mm
- ≥3 – 5 mm
- ≥5 – 10 mm
- > 10 mm

The number of lung lesions will be recorded as following:

- 0
- 1 – 4
- ≥5 – 10
- ≥11 – 20
- >20

CUTTING NEEDLE BIOPSY INDICATIONS

According to local protocols cutting needle biopsy can be mandatory or optional. It **should be considered** when:

Unusual clinical presentations:

- Age > 6 years
- Urinary infection or septicaemia
- Psoas infiltration
- Pulmonary and brain metastasis < age of 2 years (suspicious for MRTK)
- Extra-hepatic and extra-pulmonary metastases

Unusual findings by imaging:

- Numerous calcifications
- Voluminous lymphadenopathies
- Renal parenchyma not visible
- Almost totally extra-renal process

Biological findings

- Hypercalcaemia (suspicious for MRTK)
- LDH level > 4N (suspicious for neuroblastoma or malignant haemopathy)

Limitations

Cutting needle biopsies are of limited use in the differentiation of:

- Nephroblastoma vs. nephroblastomatosis
- Diffuse anaplasia vs. focal anaplasia
- Stromal subtype vs. embryonal rhabdomyosarcoma
- Cystic Nephroma, cystic partially differentiated nephroblastoma (CPDN) vs. cystic nephroblastoma

Cutting needle biopsies should not be used in:

- Age 6 months and younger (upfront surgery)
- Completely cystic tumours (consider upfront surgery)

Procedural Recommendations

- Under general anaesthesia
- Ultrasound or CT guidance – make sure to sample solid and viable tumour, avoid sampling of necrotic or cystic areas
- Co-axial technique is mandatory
- Retroperitoneal biopsy tract only (do not use transperitoneal access)
- Use cutting needles with a size of 18 or 16 Gauge to guarantee sufficient tissue for pathologic differentiation.
- No direct fixation of all specimens (part of specimens in culture medium like RPMI or immediate freezing)

APPENDIX 2: DETAILS OF PATHOLOGY

Histological classification

Definitions of Wilms' tumour and its subtypes, and other renal tumours of childhood

Based on the correlation between the histological features and survival, three prognostic groups of typical renal tumours of childhood were discerned in the previous SIOP Trials and Studies: low risk, intermediate risk and high risk tumours.

Mesoblastic nephroma, clear cell sarcoma of the kidney and rhabdoid tumour of the kidney represent separate entities from nephroblastoma but are typical renal tumours of childhood and are included in the SIOP classification and trial/study. Other, less common renal tumours, which may occur at any age including children, should be also registered through the SIOP as they may provide a useful clue in our understanding of renal tumours.

The SIOP (Stockholm) Working Classification of Renal Tumours of Childhood will be followed in this Study.

The SIOP Working Classification of Renal Tumours of Childhood

	Pretreated Cases	**Primary nephrectomy cases**
Low risk	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma* Completely necrotic nephroblastoma	*Mesoblastic nephroma* *Cystic partially differentiated nephroblastoma*
Intermediate risk	Nephroblastoma - epithelial type Nephroblastoma - stromal type Nephroblastoma - mixed type Nephroblastoma - regressive type Nephroblastoma - focal anaplasia	**Non-anaplastic nephroblastoma and its variants** Nephroblastoma - focal anaplasia
High risk	Nephroblastoma - **blastemal type** Nephroblastoma - diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*	Nephroblastoma – diffuse anaplasia *Clear cell sarcoma of the kidney* *Rhabdoid tumour of the kidney*

Please note that nephroblastomas are treated according to their histological type and stage (and only stage I low risk tumours receive no postoperative therapy).

It is important to emphasise that for treatment purposes, in addition to anaplasia, only three major types of nephroblastoma need to be recognised: completely necrotic nephroblastoma (low risk tumours), blastemal (high risk tumour) and others (intermediate risk tumours), but pathologists should assess and record in their reports a percentage of different components (regressive changes, blastemal, epithelial and stromal) as we will be prospectively analysing

these features in order to identify those that might have further prognostic significance. (Cystic partially differentiated nephroblastoma should be diagnosed on imaging studies and treated with surgery only).

Some 5% of Wilms tumours are multifocal (both unilateral and bilateral tumours), and they are more difficult to assess. Currently, treatment of these tumours depends on other parameters such as their histological type and response to preoperative as well, and the best way for a pathologist to manage with them is to adopt two methods of analysis: one method is to assess all nodules together and calculate the percentages of nonviable and viable components as if they represented one nodule; and the other method is to assess them individually (also commenting on their size). The treatment decision should be made at multidisciplinary team meetings and in consultation with national or international lead experts. If blastemal volume is confirmed to be a prognostic factor then the former approach should be adopted. Conversely, if molecular studies show that different nodules developed independently (based on their molecular genetics features), they would be regarded as separate tumours and treated accordingly.

Here follows a short description of the types of tumours that should be entered into this study. More detailed and extensive descriptions are given in the references given for each tumour.

The SIOP histological criteria for Wilms' tumour subtyping are summarised in Table 1.

Table 1. Histological criteria for Wilms' tumour subtyping in SIOP

Tumour type	Histological features **(% of viable tumour)**			
	CIC	Blastema	Epithelium	Stroma
Completely necrotic	100%	0	0	0
Regressive	>66%	0 - 100%	0 - 100%	0 - 100%
Mixed	<66%	0 - 65%	0 - 65%	0 - 65%
	<66%	11 - 65%	0 - 89%	0 - 89%*
Epithelial	<66%	0 - 10%	66 - 100%	0 - 33%
Stromal	<66%	0 - 10%	0 - 33%	66 - 100%
Blastemal	<66%	66 - 100%	0 - 33%	0 - 33%

CIC - chemotherapy-induced changes

* see the criteria for subtyping described in details below

I LOW RISK TUMOURS

MESOBLASTIC NEPHROMA

Mesoblastic nephroma is a renal tumour that usually occurs in the first year of life. The oldest child with confirmed mesoblastic nephroma in the National Wilms' Tumour Study (NWTS) files was diagnosed at the age of 29 months. Cases of 'mesoblastic nephromas' in older children and adults have been shown to be Metanephric Stromal Tumours or some other entities.

There are three histological subtypes of mesoblastic nephroma: the classical, cellular and mixed type. The distinction between the types has no implication for therapy so far. Classical mesoblastic nephroma is a monomorphous tumour composed of spindle cells with large, vesicular nuclei, noticable nucleoli and abundant cytoplasm. The cells are arranged in interlacing bundles and mitotic figures are usually present. The tumour-kidney border is

irregular and long radial extensions (finger-like extensions) of tumour tissue into the adjacent renal tissue are a characteristic finding. Also, within the tumour small rests of connective tissue with entrapped tubules are usually seen. Cellular mesoblastic nephroma has a sharper, pushing tumour-kidney border, increased cellularity and numerous mitoses. Mixed type shows features of both classical and cellular type in any proportion. All types show infiltrative growth and may infiltrate the adjacent perirenal fat (but it is more commonly seen in the classical type) and spread into the renal sinus. Complete, wide surgical resection is the only recommended treatment for localised disease. Local recurrences and metastases have been described in a few cases, especially in children older than six months of age, although some children were < 1 month old at diagnosis. Virtually all relapses occur within 12 months of nephrectomy and in about 70% of relapsed cases the tumour is of the cellular type.
In the differential diagnosis, metanephric stromal tumour, blastemal and stromal nephroblastoma, clear cell sarcoma and rhabdoid tumour of kidney must be considered (*in difficult cases, please consult excellent tables in 4th series of the AFIP Fascicle on 'Tumours of the kidney, bladder, and related urinary structures', 2004*).
Cytogenetic abnormalities of chromosome 11 and a translocation involving chromosome 15 have been reported in cellular mesoblastic nephroma. The finding of ETV6-NTRK3 gene fusions has established a histogenetic link between cellular mesoblastic nephroma and congenital fibrosarcoma and in difficult cases, it is recommended to test for the presence of this translocation (FISH and RT-PCR). It is worth emphasising that only pure cellular mesoblastic nephroma shows the presence of ETV6 rearrangement and ETV6-NTRK3 fusion transcript.

CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA (CPDN)

CPDN is a distinct variant of nephroblastoma that usually occurs in children less than 2 years of age. **The histological criteria for making a diagnosis of CPDN** are as follows:

1. It is composed entirely of cysts and their thin septa;
2. The thin septa are the only 'solid' portion of the tumour;
3. The tumour forms a discrete mass, well demarcated from the non-cystic renal parenchyma;
4. The cysts are lined by flattened, cuboidal or hobnail epithelium; and
5. The septa contain blastemal cells in any amount, with or without other embryonal stromal or epithelial cell types.

Thus, variable differentiated glomeruli, tubules, mesenchyme, striated muscle, cartilage, fibrous tissue, and fat may be admixed with blastemal cells in septa. The presence of well-differentiated tubules only is not enough to make a diagnosis of this tumour and separate it from cystic nephroma. Recent biological studies showed that cystic nephroma and CPDN are not related tumours. However, they are both treated with surgery only and both share the same, excellent prognosis. Intermediate risk nephroblastomas may present with numerous cysts but they also contain solid areas and septa are usually thicker and show chemotherapy-induced changes. Beware that other renal tumours such as clear cell sarcoma and rhabdoid tumour may have a predominantly cystic appearance.

COMPLETELY NECROTIC NEPHROBLASTOMA

Pre-operative chemotherapy given in SIOP results in so-called 'chemotherapy-induced change' in many nephroblastomas. Depending on their initial histological pattern, some nephroblastomas are completely or almost completely necrotic, while others show less marked or minimal/moderate changes. The relationship between the percentage of

chemotherapy-induced changes and prognosis has been shown in other tumours such as osteosarcoma as well as in previous SIOP studies on nephroblastoma in which completely necrotic nephroblastomas had excellent prognosis.

The histological criteria for making a diagnosis of <u>completely necrotic nephroblastoma</u> are:

1. The absence of any viable tumour tissue, especially nests of blastemal, on gross and microscopical examination of multiple blocks taken from different areas of a tumour, according to the recommended protocol (see above); *the presence of scattered mature tubules, stroma and tiny groups of blastemal cells is allowed as they may represent remnants of nephrogenic rests*.
2. The presence of regressive and/or necrotic changes caused by chemotherapy.

Although complete tumour necrosis makes histological diagnosis of any tumour impossible, in many cases 'ghost' tumour structures (mainly blastema, occasionally epithelial elements) can be recognised, and are helpful in distinguishing nephroblastoma from other renal tumours. In addition, the presence of nephrogenic rests, which are virtually never associated with non-Wilms' tumour is a very reliable clue that the tumour has been a nephroblastoma before chemotherapy. Finally, it is well known that regression of other renal tumours such as clear cell sarcoma, rhabdoid tumour or renal cell carcinoma, is minimal to moderate under the actinomycin D - vincristine protocol, and their histological features can be recognised even in treated cases.

The typical histological appearance of treated nephroblastoma is a mixture of necrosis, fibromyxomatous stroma containing lipid- and/or haemosiderin-laden macrophages, and haemorrhage. ***In some cases scattered mature tubules, stroma or tiny groups of blastemal cells may be seen within necrotic areas*** – these may represent remnants of pre-existing nephrogenic rests and should not be regarded as viable tumour tissue. The main pattern of the necrotic area is coagulative-type necrosis of small round cells or tubules, with the majority of 'ghost' structures consisting of large sheets of small, pink, necrotic nuclei, consistent with coagulative necrosis of blastemal cells or tubules. (*If in doubt whether the necrotic tumour is a nephroblastoma, the reticulin staining may help to identify scarce epithelial or mesenchymal 'ghost' structures*). The presence of identical changes in a lymph node is regarded as a proof of its involvement with a tumour and, therefore, it is very important to sample and microscopically examine all lymph nodes removed. Beware of Tamm-Horsfall protein which is sometimes accompanied by discrete tubules in a lymph node – this must not be interpreted as a metastasis (*for other lesions and changes which may mimic lymph node metastases*).

II INTERMEDIATE RISK TUMOURS

Beckwith and Palmer's criteria for histological subtyping of nephroblastomas state that one component has to comprise at least 2/3 (66%) of a tumour mass for the tumour to be subclassified accordingly. However, pre-operative chemotherapy alters the original histological features of nephroblastomas and often results in areas of necrosis and regression. Therefore, the criteria applicable to subclassification of primarily operated tumours have to be modified to take these changes into account. The quantification of regression and viable tumour components is important because they might be of relevance for prognosis for patients. The presence of considerable amount of blastema after pre-operative chemotherapy clearly indicates its non-responsiveness to chemotherapy and has been shown to be associated with poorer outcome. Although the assessment of percentage of

necrosis/regression is subjective, it is very important for subclassification of nephroblastomas, and it should be done on both gross and histological examination.
Histological types of nephroblastoma from this group are described below, but a simple approach is as follows:

1. Assess the percentage of necrosis/regressive changes
2. If they comprise more than 2/3 of a tumour mass – it is a regressive type
3. If they comprise less than 2/3 of a tumour mass – look for a predominant histological component and subclassify a tumour accordingly (blastemal, epithelial or stromal type). If no component is predominant, it is a mixed type.
4. Even if you find focal anaplasia, subclassify the tumour according to its other components.

In the group of intermediate risk tumours, five subtypes of nephroblastoma have been recognised as follows:

NEPHROBLASTOMA - EPITHELIAL TYPE

The histological criteria for making a diagnosis of epithelial type nephroblastoma are as follows:

1. The viable part of a tumour comprises more than 1/3 of a tumour mass;
2. The viable tumour consists of at least 2/3 of epithelial structures;
3. The stromal component may comprise the rest of the viable tumour; and
4. Only up to 10% of blastemal component is present (*if >10% of blastema is present, such tumours should be subclassified as mixed type*).

The epithelial elements are regarded as follows: a) *tubules* – spaces lined by columnar epithelial cells arranged in a fairly regular manner radially around the central space; cell margins are sharp, they have basal, crowded nuclei, and mitotic activity may be marked; tubules are usually back-to-back, with virtually no supporting stroma; b) *rosettes* – circular arranged tumour cells with elongated ovoid nuclei, but no central lumen is present; c) *papillary structures* – finger-like projections of a stroma covered with epithelial cells; d) *glomerular structures* – tuft-like masses of malignant cells surrounded by a well-formed capsule or rather flattened tumour cells. The stromal elements are regarded as follows: undifferentiated stromal cells, myxoid, fibroblastic, smooth muscle, skeletal muscle, adipose cells, cartilage and osteoid formations. The presence of genuine anaplasia classifies the tumour as anaplastic nephroblastoma (focal or diffuse) even if otherwise completely epithelial (see criteria for anaplasia in the chapter for high risk tumours).
Epithelial nephroblastoma usually occurs in younger children (median age 15 months in a SIOP series), and about 80% of cases are in stage I. Beware of 'pure' epithelial nephroblastoma in older children, which may be confused with renal cell carcinoma.

NEPHROBLASTOMA – STROMAL TYPE

Stromal nephroblastoma represents a subtype in which the stromal elements are a predominant component of the tumour. The fetal rhabdomyomatous nephroblastoma, which in the past was regarded as a nephroblastoma with better prognosis, is also included here.

The histological criteria for making a diagnosis of stromal type nephroblastoma are as follows:

1. The viable part of a tumour comprises more than 1/3 of a tumour mass;
2. The viable tumour consists of at least 2/3 of stromal structures;
3. The epithelial component may comprise the rest of the viable tumour; and
4. Only up to 10% of blastemal component is present (*if >10% of blastema is present, such tumours should be subclassified as mixed type*).

The stromal elements are regarded as follows: undifferentiated, myxoid, fibroblastic, smooth muscle, skeletal muscle, adipose cells, cartilage, bone, and osteoid. Stromal differentiation may be induced by preoperative chemotherapy as a stromal type nephroblastoma is far more common in children who have recieved preoperative chemotherapy. It is likely that other tumour components, especially blastema, are destroyed by preoperative chemotherapy while stromal elements are chemotherapy resistant and may even further differentiate and result in prominent skeletal muscle component, for example.

Stromal nephroblastoma usually occurs in younger children and usually shows minimal to moderate chemotherapy induced changes since stromal tissue is usually resistant to chemotherapy.

NEPHROBLASTOMA – MIXED TYPE

The histological criteria for making a diagnosis of mixed type nephroblastoma are as follows:

1. The viable part of a tumour comprises more than 1/3 of a tumour mass;
2. The viable tumour consists of blastemal and/or epithelial and/or stromal elements but none of them comprise more than 2/3 of the viable tumour
3. Tumours which contain >10% of blastema, even if the predominant components are epithelial or stromal components

NEPHROBLASTOMA – REGRESSIVE TYPE

Nephroblastoma – regressive type is a tumour in which chemotherapy-induced changes comprise more than 2/3 of the tumour mass, irrespective of what the viable part of tumour is (except for diffuse anaplasia). Please note that assessment of percentage of necrosis/regression is done on both gross and histological examination, so blocks should be taken not only from viable parts of the tumour mass but also from those that show necrotic/regressive changes.

The histological criteria for making a diagnosis of regressive type nephroblastoma are:

1. More than 2/3 of tumour is non-viable (regressive and/or necrotic changes caused by chemotherapy) on gross and microscopical examination of multiple blocks taken from different areas of a tumour, according to the recommended protocol;
2. The viable tumour elements are histological components of nephroblastoma including blastemal, epithelial and stromal elements.

The typical histological appearance of treated nephroblastoma is a mixture of necrosis, fibro-myxo-sclerotic stroma containing lipid- and/or haemosiderin-laden macrophages, and haemorrhage. The main pattern of the necrotic area is coagulative-type necrosis of small round cells, with the majority of 'ghost' structures consisting of large sheets of small, pink, necrotic nuclei, consistent with coagulative necrosis of blastemal cells.

NEPHROBLASTOMA WITH FOCAL ANAPLASIA

Nephroblastoma - focal anaplasia type is nephroblastoma which contains one or two foci of anaplasia according to the established criteria (see below). Usually, the size of an anaplastic focus should not exceed 15mm. However, it is still important to determine tumour's (underlying) type and if it is blastemal, it should be classified as high risk tumour.

III HIGH RISK TUMOURS

NEPHROBLASTOMA - BLASTEMAL TYPE

This nephroblastoma type belong to high risk tumours but only if diagnosed after pre-operative chemotherapy. In cases diagnosed after primary nephrectomy, blastema predominant nephroblastoma remains in the Intermediate risk tumours.

The histological criteria for making a diagnosis of blastemal type nephroblastoma are as follows:

1. The viable part of a tumour comprises more than 1/3 of the tumour mass;
2. At least 2/3 of the viable tumour consists of blastema;
3. Epithelial and/or stromal components of nephroblastoma may be present in varying proportions.

The blastemal elements are regarded as undifferentiated round or elongated cells, which are usually closely packed and show no evidence of epithelial and/or stromal differentiation. There are several distinctive patterns in which blastemal cells may occur and it is not uncommon to find more than one pattern in the same tumour. They include the diffuse, serpentine, nodular, and basaloid patterns but they are of no prognostic or therapeutic significance. In rare cases it may be difficult to distinguish blastema from early epithelial differentiation – with no reliable immunohistochemical markers to help, the distinction has to be based on histological criteria only.

NEPHROBLASTOMA WITH ANAPLASIA

Anaplasia was recognised as an unfavourable histological feature of nephroblastoma in earlier trials. **The histological criteria for making a diagnosis of anaplasia are as follows:**

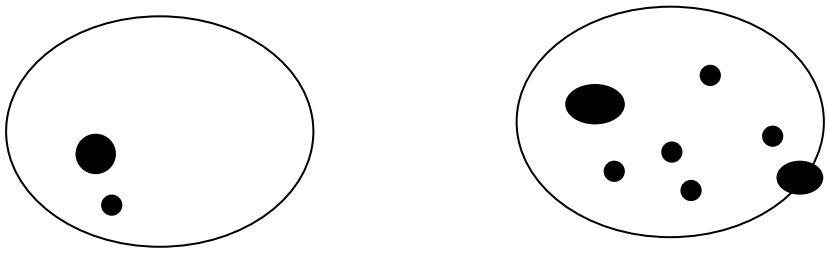
1. The presence of large atypical tri/multipolar mitotic figures;
2. Marked nuclear enlargement, with diameters at least three times those of adjacent cells; and
3. The presence of hyperchromatic tumour cell nuclei.

Please note that all three criteria for anaplasia have to be met in order to make the diagnosis.

Anaplasia may occur in the blastemal, epithelial or stromal component of nephroblastoma and it can be focal or diffuse.

Focal anaplasia is defined as the presence of one or two clearly defined foci, sharply demarcated within a primary intrarenal tumour, without evidence of anaplasia or prominent nuclear atypia in other areas. The size of an anaplastic focus usually does not exceed 15mm.
Diffuse anaplasia is defined if any of the following are present:

1. Non-localised anaplasia, and/or anaplasia beyond the original tumour capsule;
2. Anaplastic cells present in intrarenal or extrarenal vessels, renal sinus, extracapsular invasive sites, or metastatic deposits;
3. Anaplasia is focal, but nuclear atypia approaching the criteria for anaplasia (so-called 'unrest nuclear change') is present elsewhere in the tumour;
4. Anaplasia that is not clearly demarcated from non-anaplastic tumour; and
5. Anaplasia is present in a biopsy or other incomplete tumour sample.



Focal anaplasia **Diffuse anaplasia**

This topographic definition of focal anaplasia makes it mandatory that pathologists carefully document the exact site from which every section is obtained (e.g. on a diagram, specimen photocopy, and/or photograph of the gross specimen). Please use a pre-prepared diagram in the SIOP Institutional Pathology Form F4 or a photograph.
Anaplasia occurs in about 5-8% of patients with nephroblastoma. Preoperative chemotherapy does not obliterate or produce anaplasia but it makes its recognition easier since non-anaplastic areas are destroyed by chemotherapy whereas anaplastic foci remain unchanged. This provides further support to the hypothesis that anaplasia represents more resistant rather than a more aggressive cell line. Diffuse anaplasia excludes the diagnosis of any other type of intermediate or high risk (blastemal type) nephroblastoma (for example, it may occur in excessively regressive WT). The age distribution of anaplastic nephroblastoma differs from non-anaplastic nephroblastoma: anaplasia never occurs in the first six months of life, it is very rare between 6-12 months (1-2%), median age at diagnosis is 61 months and >50% of children are over five years of age (for non-anaplastic nephroblastoma median age is 45 months, and 25% of children are over five years of age).
Although the criteria for anaplasia have been well established, it still represents a diagnostic problem resulting in either missed or 'overdiagnosed' cases, while only in rare instances it is confused with other renal tumours. It is important to bear in mind that all three criteria for the diagnosis of anaplasia have to be met and that some histological changes may mimic anaplasia including calcification, fused or smudged masses of nuclear chromatin due to technical artefact, stain precipitate, circulating megakaryocytes, overlapping cells in thick sections, and bizarre nuclei resulting from chemotherapy with the formation of hyperchromatic multinucleated and bizarre macronucleated skeletal muscle cells in response

to injury. However, the diagnosis of anaplasia in the skeletal muscle must be made if atypical mitoses and other histological criteria are present.

CLEAR CELL SARCOMA OF THE KIDNEY

This distinctive tumour comprises 5% of primary renal tumours of childhood. It is extremely rare in the first six months of life and in young adults, and the majority of patients are between 2 and 3 years of age. There is a male predominance, but no association with chromosomal defects, genetic abnormalities or specific malformations and syndromes has been reported. Unlike nephroblastoma, CCSK is always unilateral and unicentric.

Histologically, this tumour has a deceptively bland appearance and many histological subtypes. The classical pattern has a uniform appearance of a diffuse growth of relatively small cells with normochromatic nuclei, inconspicuous nucleoli, pale staining cytoplasm, and ill-defined cell membrane. In only 20% of the cases do the tumour cells have clear cytoplasm. The most characteristic feature is a peculiar vascular pattern consisting of arborising blood vessels that create an alveolar or trabecular pattern (best seen with the reticulin stain or CD34 marker).

The classical pattern of CCSK is relatively simple to diagnose, but others including the myxoid, sclerosing, cellular, epithelioid, palisading, spindle cell, storiform, and anaplastic pattern can cause problems in reaching the diagnosis. In some CCSKs, there can be extensive hyalinisation and these tumours may be confused with cases of nephroblastoma with sclerosis due to pre-operative treatment, or rhabdoid tumours. In differential diagnosis blastemal nephroblastoma, mesoblastic nephroma, PNET and rhabdoid tumour must be considered (in difficult cases, please consult excellent tables in the 4th series of AFIP Fascicle on 'Tumours of the kidney, bladder, and related urinary structures' the paper by Argani et al. and papers by Gooskens et al. and Furtwängler et al. The histogenesis of the tumour is uncertain. The tumour cells are positive for vimentin and recent studies showed that NGFR and Cyclin D1 markers are strongly positive in CCSK and are very helpful in distinguishing them from other renal tumours. CCSK is generally negative for cytokeratin, factor VIII associated antigen, epithelial membrane antigen, desmin, and S100 protein.

RHABDOID TUMOUR OF THE KIDNEY

Rhabdoid tumour of kidney (RTK) is rare, constituting 2% of paediatric renal tumours. It typically occurs in early childhood, with about 80% of patients younger than 2 years, whereas it is extremely rare after 5 years of age. Two characteristic associations of RTK are hypercalcaemia and the development of synchronous or metachronous primary brain tumours. On the other hand, it is never associated with conditions predisposing to nephroblastoma or with nephrogenic rests.

Histological criteria for diagnosis of rhabdoid tumour include the finding of its characteristic histological features and unique immunohistochemical profile. Typical histological features comprise non-cohesive sheets of cells with abundant eosinophilic cytoplasm and *large eccentric nuclei with prominent eosinophilic central nucleoli* - these are regarded as the most characteristic feature of the tumour and they are always present at least in some areas of the tumour. Another characteristic feature is the presence of *large oval intracytoplasmic hyaline inclusions* composed of whorled masses of intermediate filaments. Both of these features may only be focal, and should be specifically looked for in any undifferentiated renal tumour of childhood. In addition to the classical pattern of rhabdoid tumour, many other patterns have

been described including sclerosing, clear cell sarcoma-like, epithelioid, spindled, lymphomatoid, vascular, pseudopapillary and cystic patterns.
The diagnostic immunohistochemical marker for RTK is *INI1*, which is lost in tumour cells. Molecular studies showed that genetic abnormalities of the *hSNF5/INI1* tumour suppressor gene on chromosome 22 are characteristic for both renal and extra-renal rhabdoid tumours. The presence of an *hSNF5/INI1* mutation results in a marked reduction in nuclear expression of the gene product, detectable immunohistochemically. There is now no need to do other immunohistochemical markers in order to confirm the diagnosis (but one should bear in mind that some other tumours, such as renal medullary carcinoma and epitheliod sarcoma are also negative for INI1).

Nephrogenic Rests

Nephrogenic rests are foci of embryonal cells which persist after 36 weeks of gestation and they are considered as potential precursors of nephroblastoma. They have been found in 35-40% of patients with nephroblastoma and very rarely in routinely examined perinatal postmortem kidneys. They have not been described in association with other typical renal tumours of childhood and their finding in problematic cases is a clue that the tumour is nephroblastoma. Two main types of nephrogenic rests have been recognised: perilobar and intralobar rests. They can be further subclassified as dormant, sclerosing, or hyperplastic, and all these appearances may be present in an individual case. The rests may regress to fibrous tissue or progress to nephroblastoma. Hyperplastic rests may be difficult to distinguish from a small nephroblastoma. Perilobar nephrogenic rests occur in hemihypertrophy and Beckwith-Wiedemann syndrome while intralobar rests are associated with WAGR and Denys-Drash syndromes.
Nephroblastomatosis (NBL) is the term used to describe the presence of multiple or diffuse NRs. NBL is classified as **perilobar** NBL, **intralobar** NBL, **combined** (PLNR and ILNR) NBL, and **universal** (or panlobar, where there are no discrete rests, but entire renal parenchyma is involved). **Diffuse hyperplastic perilobar nephroblastomatosis** is another term that is used to describe universal or panlobar NBL.

Differential diagnosis of renal tumours of childhood

The results of the SIOP Trials and Studies showed that there are significant discrepancies in diagnosis and staging of renal tumours between the institutional pathologists and central pathology review panels. For this reason, rapid central pathology review is now being introduced and all centres participating in the study should submit their cases urgently.
Here are some clinical, macroscopical and histological features of renal tumours of childhood, which might be a useful for reaching a correct diagnosis.
Age at diagnosis is a rather reliable criterion. Anaplastic nephroblastoma has never been described in the first six months and is extremely rare in the first year of life, but after 5 years of age it comprises 10% of nephroblastomas. Clear cell sarcoma of kidney hardly occurs in the first 6 months of life, while mesoblastic nephroma and rhabdoid tumour of kidney are extremely rare in children over 3 years of age.
Grossly, many renal tumours may show areas with **cysts** but only CPDN and cystic nephroma are entirely cystic neoplasms, with no solid areas.
There are some unique features of nephroblastoma, which are very useful in distinguishing it from other renal tumours including:

1. Nephroblastoma is the only typical renal tumour of childhood which may be **bilateral** (in 5% of cases) or **multifocal** (cases of bilateral renal cell carcinoma have been exceptionally reported)
2. **Nephrogenic rests** are commonly present in nephroblastoma but not in other tumours (there is only one report of nephrogenic rests associated with mesoblastic nephroma and CCSK, respectively)
3. **Skeletal muscle, adipose tissue** and genuine **neoplastic tubules** are only seen in nephroblastoma
4. Nephroblastoma and nephroblastomatosis are the only tumour lesions that occurs in **syndromes known to be predisposing to nephroblastoma** (WAGR, Beckwith-Wiedemann, Denys-Drash syndrome)

Immunohistochemical and molecular markers may be helpful in diagnosing renal tumours of childhood.

Other tumours included in the study:

In addition to more common renal tumours of childhood discussed above, there are numerous other tumours, which may occur at any age. All these tumours should be registered and submitted for central pathology review as they may provide important information in our understanding of renal tumours in general. These include:

1. Metanephric tumours (metanephric stromal tumour, metanephric adenofibroma, metanephric adenoma)
2. Adenomas (all other types)
3. Cystic nephroma
4. Renal cell carcinoma (all variants)
5. Transitional cell carcinoma
6. Neuroepithelial tumours (renal neuroblastoma, renal Ewing sarcoma/PNET, renal carcinoid)
7. Miscellaneous sarcomas (without evidence of blastemic cells and/or epithelial component in five different blocks)
8. Renal lymphoma
9. Angiomyolipoma
10. Other tumours (adrenal tumours, teratoma) and lesions (xanthogranulomatous pyelonephritis, etc.), if preoperative chemotherapy for nephroblastoma has been given
11. Metastases from other sites

Histological staging

SIOP WT staging criteria for renal tumours of childhood apart from RC

Stage I

a) The tumour is limited to the kidney.
b) Tumour is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule may be infiltrated by viable tumour which does not reach the outer surface.
c) Tumour may show botryoid / protruding growth into the renal pelvis or the ureter, but does not infiltrate their walls.
d) The vessels or the soft tissues of the renal sinus are not involved by tumour.
e) Intrarenal vessel involvement may be present.

Notes:

- *Be aware of mature tubules within the sinus or hilar region which usually represent nephrogenic rests. Genuine infiltration of the sinus/hilar structures is usually seen as blastemal foci closely related to nerves.*
- *Fine needle aspiration or percutaneous cutting needle ('tru-cut') biopsy does not upstage the tumour.*
- *The presence of necrotic tumour or chemotherapy-induced change in the renal sinus, renal veins and/or within the perirenal fat should not be regarded as a reason for upstaging the tumour.*
- *Viable tumour infiltration of fat between the kidney and the adrenal gland, or of the adrenal gland itself, does not upstage the tumour, if the tumour is contained within the (pseudo)capsule.*
- *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 II (if completely resected) or stage III (if incompletely resected).*

Stage II

a) Viable tumour is present in the perirenal fat and is *not covered* by a (pseudo)capsule, but is completely resected (resection margins 'clear').
b) Viable tumour infiltrates the soft tissues of the renal sinus.
c) Viable tumour infiltrates blood and/or lymphatic vessels of the renal sinus or of the perirenal tissue, but it is completely resected.
d) Viable tumour infiltrates the wall of the renal pelvis or of the ureter.
e) Viable tumour infiltrates the vena cava or adjacent organs (except the adrenal gland, *see above*) but is completely resected.

Stage III

a) Viable tumour present at a resection margin. Non-viable tumour or chemotherapy-induced changes present at a resection margin is not regarded as stage III.
b) Abdominal lymph nodes involvement by either viable or non-viable tumour.
c) Pre- or intra-operative tumour rupture, if confirmed by microscopic examination (= viable tumour at the surface of the specimen in the area of the rupture).
d) Viable or non-viable tumour thrombus is present at resection margins of ureter, renal vein or vena cava inferior (always discuss resection margins with the surgeon).
e) Viable or non-viable tumour thrombus which is attached to the IVC wall is removed piecemeal by surgeon.
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

Notes:

- *Renal vein retraction issue: If tumour thrombus is bulging out at the renal vein resection margin, it may be due to retraction of the vein wall after resection and fixation. Therefore, it should not be automatically regarded as incomplete resection but it has to be discussed with surgeon who needs to clarify whether thrombus was at resection margin before cutting off the vein.*

- *Non-viable tumour in a lymph node should appear to be replacing normal lymph node structures. Groups of macrophages (including haemosiderin-laden) in the lymph node sinus should not regarded as previous tumour infiltration.*
- *Mature tubules can be found in lymph nodes often associated with Tamm-Horsfall protein deposits, but also without it. This should not be regarded as lymph node metastasis.*
- ***The presence of rupture on imaging or at surgery should only be considered as pathological stage III if microscopically confirmed. If not, tumour should be staged on the basis of other criteria seen, and the final treatment stage should be decided after discussion at multidisciplinary team/tumour board meeting.***

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.

Staging in cases of Nephron Sparing Surgery

On the local pathology request form, it should be stated that nephron sparing surgery (NSS) was done. In such cases it is important to investigate the resection margins very carefully. Often the tumour nodules are resected with a small rim of renal parenchyma, especially in cases with multiple nodules within one kidney. Surgeons have agreed to use the following surgical classification for operation:

- *NSS (A) =* Partial Nephrectomy (resection of tumour with a rim of normal renal parenchyma)
- *NSS (B) =* Enucleation (resection of tumour without a rim of normal renal parenchyma)

Histopathological examination should include evaluation of the complete circumference of the lesion. In small lesions, they should be embedded completely. The minimal distance to the resection line/margin has to be measured. A ‘safe rim‘ should not be less than 1mm. The finding of nephrogenic rests at the resection margin is not regarded as positive resection margins, and it should not be considered for staging purposes.

Histopathological assessment should clearly state one of the following findings:

- Safe rim of renal parenchyma on resection margin, except nephroblastomatosis (0)
- Intact pseudo-capsule along the resection margin (1)
- Tumour breach (2)