Supplementary tables 1-4 and supplementary references

Supplementary table 1. COG and SIOP staging systems. Abbreviations: COG, Children's Oncology Group; SIOP, International Society of Paediatric Oncology.

STAGE	COG[1]	SIOP[2]
I	• Tumour limited to kidney, completely resected. • The renal capsule is intact. • The tumour was not ruptured or biopsied prior to removal. • The vessels of the renal sinus are not involved. • There is no evidence of tumour at or beyond the margins of resection. Notes: by definition, extrarenal tumours cannot be stage I - defined as stage II if completely resected with negative margins or stage III if microscopic or gross residual disease.	• Tumour is limited to the kidney. • Tumour is present in the perirenal fat but is surrounded by a fibrous (pseudo)capsule. The (pseudo)capsule might be infiltrated by viable tumour, which does not reach the outer surface. • Tumour might show protruding (botryoid) growth into the renal pelvis or the ureter but does not infiltrate their walls. • The vessels or the soft tissues of the renal sinus are not involved by tumour. Intrarenal vessel involvement might be present.
II	• The tumour is completely resected and there is no evidence of tumour at or beyond the margins of resection. • The tumour extends beyond kidney, as is evidenced by any one of the following criteria: a. there is regional extension of the tumour (i.e. penetration of the renal capsule, or extensive invasion of the soft tissue of the renal sinus); b. blood vessels within the nephrectomy specimen outside the renal parenchyma, including those of the renal sinus, contain tumour.	• Viable tumour is present in the perirenal fat and is not covered by a (pseudo)capsule, but is completely resected (resection margins are clear). • Viable tumour infiltrates the soft tissues of the renal sinus. • Viable tumour infiltrates blood and/or lymphatic vessels of the renal sinus or of the perirenal tissue, but it is completely resected. • Viable tumour infiltrates the wall of the renal pelvis or of the ureter. • Viable tumour infiltrates the vena cava or adjacent organs (except the adrenal gland) but is completely resected.
III	• Residual nonhaematogenous tumour present following surgery, and confined to abdomen. Anyone of the following may occur: a. lymph nodes within the abdomen or pelvis are involved by tumour (note: lymph node involvement in the thorax, or other extra-abdominal sites is a criterion for stage IV); b. the tumour has penetrated through the peritoneal surface; c. tumour implants are found on the peritoneal surface; d. gross or microscopic tumour remains postoperatively (e.g., tumour cells are found at the margin of surgical resection on microscopic examination); e. the tumour is not completely resectable because of local infiltration into vital structures; f. tumour spillage occurring either before or during surgery; g. the tumour is treated with preoperative chemotherapy (with or without a biopsy regardless of type- tru-cut, open or fine needle aspiration) before removal; h. tumour is removed in greater than one piece (e.g. tumour cells are found in a separately excised adrenal gland; a tumour thrombus within the renal vein is removed separately from the nephrectomy specimen). Extension of the primary tumour within vena cava into thoracic vena cava and heart is considered stage III, rather than stage IV even though outside the abdomen.	• Viable tumour is present at a resection margin. Nonviable tumour or chemotherapy induced changes present at a resection margin are not regarded as stage III. • Abdominal lymph node involvement is present by either viable or nonviable tumour. • Preoperative or intraoperative tumour rupture, if confirmed by microscopic examination (viable tumour at the surface of the specimen at the area of the rupture). • Viable or nonviable tumour thrombus is present at resection margins of ureter, renal vein, or vena cava inferior (always discuss resection margins with the surgeon). • Viable or nonviable tumour thrombus, which is attached to the inferior vena cava wall, is removed piecemeal by a surgeon. • Wedge or open tumour biopsy before preoperative chemotherapy or surgery. • Tumour implants (viable or nonviable) are found anywhere in the abdomen. • Tumour (viable or nonviable) has penetrated through the peritoneal surface.
IV	Haematogenous metastases (lung, liver, bone, brain, etc.), or lymph node metastases outside the abdominopelvic region are present. (The presence of tumour within the adrenal gland is not interpreted as metastasis and staging depends on all other staging parameters present).	Haematogenous metastases (for example, lung, liver, bone and brain) or lymph node metastases outside the abdominopelvic region.
V	Bilateral tumours at diagnosis; each side should be substaged according to the above criteria.	Bilateral renal tumours at diagnosis. Each side should be substaged according to the above criteria.

Supplementary table 2. General principles of therapeutic approaches among COG Renal Tumor Committee and SIOP Renal Tumour Study Group. This table is a general overview for patients with Wilms tumour. Please refer to published protocols for details of risk classification, therapeutic regimens, surgical approach and timing, and radiotherapy as these are highly patient specific[2–5].

Shared consensus on indications to neoadjuvant chemotherapy worldwide

- Bilateral WT, bilateral nephroblastomatosis or unilateral WT with contralateral nephroblastomatosis
- Inoperable tumour, or generally in cases which may be at high risk of surgical morbidity
- Intravascular extension into inferior vena cava above hepatic veins
- Tumour in solitary kidney
- Patients suffering from chronic kidney disease
- Patients with WT-predisposing syndromes
- Patients in low- and middle-income countries with large volume tumour and/or in poor clinical condition due to malnutrition or infection

Specific indications to preoperative chemotherapy according to cooperative groups

COG GUIDELINES[3,6–14]	**SIOP GUIDELINES**[5,15–18]
COG recommends primary nephrectomy, when feasible, with regional lymph node sampling as the initial therapy before chemotherapy to ascertain local stage, histology and biomarker status. Biopsy is recommended if primary nephrectomy is not feasible, except in patients with bilateral WT, a solitary kidney, or unilateral WT with a high risk for metachronous tumour (predisposition syndrome, multicentric WT, or children < 1 year of age with contralateral nephrogenic rests). In these latter patients, neoadjuvant chemotherapy should be given without biopsy. Specific indications for neoadjuvant chemotherapy: • Unresectable WT • Patient with a solitary kidney • Unilateral WT with high risk for metachronous tumour (predisposition syndrome, multicentric WT, or children < 1 year of age with contralateral nephrogenic rests). • Synchronous bilateral WT • Tumour thrombus in the inferior vena cava extending above the level of the hepatic veins • Cardiovascular compromise secondary to extensive pulmonary or hepatic metastases • Tumour involves contiguous structures whereby the only means of removing the kidney tumour requires removal of the other structure (e.g. spleen, pancreas, colon but excluding the adrenal gland and diaphragm). Note: it is the surgeons' judgment that nephrectomy would result in significant or unnecessary morbidity/mortality, significant tumour spill, or residual tumour	SIOP recommends preoperative chemotherapy for all patients with a presumptive diagnosis of WT, with the below exception where core needle diagnostic biopsy may be first indicated: • Patients >7 years of age • Presence of urinary tract infection • Psoas infiltration • Lung metastases in patients <2 years of age • Extra hepatic and extra pulmonary metastases • Atypical radiologic or biochemical findings (such as numerous intratumoural calcifications; large lymph node; renal parenchyma not visible; hypercalcemia; lactate dehdrogenase level >4N) • <6 months of age (this is not an absolute contraindication to pre-operative chemotherapy)
Recommended neoadjuvant chemotherapy regimens for those not undergoing immediate nephrectomy (see selected indications): • Unresectable unilateral WT: vincristine and actinomycin D alternating with doxorubicin (regimen DD4A). Reassess at 6 weeks for possible definitive nephrectomy. If not feasible continue until 12 weeks and reassess • Bilateral WT or WT in a solitary kidney: vincristine and concurrent actinomycin D-doxorubicin (regimen VAD) for 6 weeks. Reassess at 6 weeks for possible partial nephrectomy. If not feasible continue chemotherapy until 12 weeks and reassess • Unilateral WT with high risk for metachronous tumour: vincristine and actinomycin D (regimen EE4A) if localized or vincristine/doxorubicin/actinomycin D if metastatic disease • Diffuse hyperplastic perilobar nephroblastomatosis: vincristine and actinomycin D (regimen EE4A)	Recommended neoadjuvant chemotherapy regimens according to different situations • Unilateral localized tumour: 4-week pretreatment with vincristine (weekly) and actinomycin D (biweekly) • Bilateral tumours: vincristine and actinomycin D for no longer than 6–12 weeks is recommended before surgical assessment (carboplatin-etoposide regimen may be added if unsatisfactory response) • For patients with metastasis, six-week of weekly vincristine, biweekly actinomycin D (on week 1-3-5) and doxorubicin (on weeks 1 and 5) is given

Indications to postoperative chemotherapy

COG	**SIOP**
The COG recommends postoperative chemotherapy routinely used in all patients with WT except those classified as Very Low Risk WT, defined as: age <2 years at diagnosis, with stage I favourable histology WT weighing <550 g, confirmed negative lymph nodes and no predisposition syndrome.	The SIOP recommends postoperative chemotherapy in all patients with WT except those with stage I low-risk tumour. The standard agents for chemotherapy for **localized** WT commonly are:

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The agents for chemotherapy for favourable histology WT commonly are:

- Actinomycin D and vincristine (regimen EE4A) with doxorubicin added (regimen DD4A) for higher stage III and IV favourable-histology WT;
- Patients with combined loss of heterozygosity at chromosomes 1p and 16q are treated with regimen DD4A if stage I or II favourable-histology WT, and regimen M (DD4A with cyclophosphamide and etoposide) for stages III and IV favourable-histology WT;
- Revised regimen UH2 (doxorubicin, vincristine, cyclophosphamide, carboplatin, etoposide, irinotecan) is considered to be standard in patients identified to have diffuse anaplastic histology
- Note that for patients with bilateral WT or unilateral WT with high risk for metachronous tumour, chemotherapy following a definitive surgical procedure at week 6 or 12 is determined by post-chemotherapy histology as well as local and overall stage.

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- Low-risk and intermediate-risk tumours: actinomycin D and vincristine, with doxorubicin added only for selected intermediate-risk histologic types (i.e. non-stromal and non-epithelial) with tumour volume remaining >500 ml after pre-nephrectomy chemotherapy
- High-risk tumours: actinomycin D, vincristine and doxorubicin are used for stage I tumours; an intensified regimen containing doxorubicin-cyclophosphamide and etoposide-carboplatin is used for patients with stage II to III tumours.

In patients with **metastases** (stage IV WT):

- An approach with inclusion of doxorubicin at different cumulative dose ranges or with additional drugs (carboplatin, etoposide, cyclophosphamide) is applied depending on well-defined risk factors
- These stratification factors include: speed and quality of response of the metastases to neo-adjuvant chemotherapy, size of lung metastases, surgical outcome after surgical resection of metastases (if done), and histologic risk of primary and metastatic (if resected) tumour
- In high-risk stage IV tumours, given the unsatisfactory dismal prognosis, SIOP researchers are investigating intensification of treatment including additional drugs, like irinotecan and melphalan at myeloablative doses.

In patients with **bilateral** disease (stage V):

- The choice of post-operative chemotherapeutic agents is generally dictated by tumour histologic risk and stage (considering the higher stage), as in unilateral tumours

Abbreviations: COG, Children's Oncology Group; SIOP, International Society of Paediatric Oncology; WT, Wilms tumour; LOH, loss of heterozygosity.

Supplementary table 3. COG standard therapy based on results of first generation of NWTS and COG studies[3,6–10]		
Regimen	**Regimen description**	**Patient features**
Observation	After primary nephrectomy	• VLR, defined as: stage I FHWT, <550 g, age <2 years, negative lymph nodes, no predisposition syndrome; especially in the absence of LOH 11p15 or LOI 11p15
EE-4A	Vincristine, actinomycin D × 19 weeks. After primary nephrectomy	• Stage I not meeting VLR criteria • Stage II FHWT without LOH 1p/16q • DHPLN • Non-metastatic unilateral WT with radiological contralateral nephrogenic rests or predisposition syndrome (unbiopsied)
DD-4A	Vincristine, actinomycin D, doxorubicin × 25 weeks. Baseline primary nephrectomy OR biopsy with subsequent feasibility for nephrectomy assessed at week 6. Stage and site-specific radiation therapy. Note, stage IV patients with lung metastases and 1q gain should receive pulmonary irradiation even if rapid early response	• Stage I/II FHWT with LOH 1p/16q • Stage III FHWT without LOH 1p and 16q • Stage IV FHWT without LOH 1p and 16q and rapid early response of pulmonary metastases • Stage I to III focal anaplasia WT • Stage I diffuse anaplasia WT
VAD	Vincristine, actinomycin D, doxorubicin induction x 6 weeks then reassess based on delayed nephrectomy histology. Stage and site-specific radiation therapy	• Bilateral WT • Stage IV unilateral WT with radiological contralateral nephrogenic rests or predisposition syndrome
M	Vincristine, actinomycin D, doxorubicin, cyclophosphamide, and etoposide x 31 weeks. Site-specific radiation therapy	• Stage III or IV FHWT with LOH 1p and 16q • Stage IV with slow early response of pulmonary metastases
rev UH1	Vincristine, doxorubicin, cyclophosphamide, carboplatin, etoposide x 30 weeks. Site-specific radiation therapy	• Stage II/III diffuse anaplasia
rev UH2	Vincristine/doxorubicin/cyclophosphamide/carboplatin/etoposide + vincristine/irinotecan x 36 weeks. Site-specific radiation therapy	• Stage IV diffuse anaplasia
COG, Children's Oncology Group; NWTS, National Wilms Tumor Study; FHWT, favourable histology Wilms tumour; VLR, very low-risk; LOH, loss of heterozygosity; LOI, loss of imprinting; DHPLN, diffuse hyperplastic perilobar nephroblastomatosis.		

Supplementary table 4: Standard SIOP chemotherapy regimens after preoperative chemotherapy[5,15,16,18–20]		
Regimen	**Regimen description**	**Patient features**
AV-1	Vincristine, actinomycin D × 4 weeks	Stage I, IR histology
AV-2	Vincristine, actinomycin D × 27 weeks	Stage II/III LR and HR histology with tumour volume after preoperative chemotherapy <500 ml, or stromal type or epithelial type any tumour volume
AVD	Vincristine, actinomycin D, doxorubicin × 27 weeks (cumulative dose of doxorubicin 250 mg/m^2)	Stage I HR histology; or stage II/III IR histology (excluding stromal and epithelial types) with tumour volume >500 ml after preoperative chemotherapy
HR-1	Doxorubicin/cyclophosphamide, etoposide/carboplatin x 34 weeks	Stage II/III HR histology
AVD150	Vincristine, actinomycin D, doxorubicin × 27 weeks (cumulative dose of doxorubicin 150 mg/m^2)	Stage IV, LR or IR disease with early complete clearance of lung metastases of 3-5 mm by chemotherapy ± surgery
		Stage IV, LR with residual lung nodules after chemotherapy, but no viable tumour in a representative number of resected nodules
AVD250	Vincristine, actinomycin D, doxorubicin × 27 weeks (cumulative dose of doxorubicin 250 mg/m^2)	Stage IV, LR or IR with early complete clearance of lung metastases >5 mm by chemotherapy ± surgery
		Stage IV, IR with residual lung nodules after chemotherapy, but no viable tumour in a representative number of resected nodules
		Stage IV, LR with residual lung nodules after chemotherapy, and viable tumour in a representative number of resected nodules
HR-2	4-drug regimen: doxorubicin, cyclophosphamide, etoposide, carboplatin x 34 weeks	Stage IV, IR, lung metastases are viable and incompletely resected or representative resection not feasible when still remaining at week 10
New regimen	Doxorubicin, cyclophosphamide, etoposide, carboplatin, irinotecan, vincristine, high-dose melphalan[5]	Stage IV, HR histology, regardless of metastatic response to chemotherapy or surgery
IR, intermediate-risk; LR, low-risk; HR, high-risk		

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