CLINICAL MANAGEMENT GUIDELINES

WILMS TUMOUR

To be used in conjunction with IMPORT study protocol

Produced by the CCLG Renal Tumour Interest Group

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Revised March 2018 to correct a formatting error on the AVDm flow sheet (figure 7)

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The CCLG does not sponsor or indemnify the treatment detailed herein. These treatment recommendations are provided by the CCLG Renal Tumours Special Interest Group to inform and guide the sole discretion of treating clinicians who retain professional responsibility for their actions and treatment decisions. Treatment recommendations are based on current best practice and not what is necessarily proposed for any forthcoming clinical trial.
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1. Background and Rationale

Wilms tumour is seen as one of the success stories of paediatric oncology, with collaboration in terms of both treatment disciplines and inter-group working. Partly due to this success, focus has shifted to reducing the toxicity and late effects of treatment. The results of SIOP2001 suggest that the anthracycline, doxorubicin, can be removed from treatment regimens for intermediate risk stage 2 and 3 patients.

The outlook for the majority of relapsed patients is good; however it is apparent that subgroups with poor outlook still exist, despite maximal therapy. It is also clear that the majority of relapsing patients do so after treatment for low/intermediate risk disease.

Differences still exist between the 2 major treating groups in terms of use of pre-operative chemotherapy. The US based COG group remain committed to initial nephrectomy with focus on stratification of treatment, according to the co-existence (in a limited number of patients), of the adverse cytogenetic factors, 1p and 16q allele loss. The European based SIOP group continue to administer pre-operative chemotherapy in an attempt to reduce surgical complications, which have potential to upstage disease with resultant increase in therapy. Whilst this makes joint analysis difficult in some areas, it would appear that outcomes in terms of event free survival and overall survival are equivalent.

The intention of the SIOP Wilms Tumour Group is to now better stratify treatment of patients based on the preliminary results from the SIOP 2001 WT trial. This suggests that the subgroup of patients who remain at high risk of relapse, may do so as a result of the persistence of chemo-resistant blastemal cells. Work is underway to identify characteristics, which may act as biomarkers of such tumours. In the meantime, a true estimate of the volume of blastema remaining after pre-nephrectomy chemotherapy is important to further clarify this hypothesis. To best quantify this volume, it is essential that tumour volumes are measured and documented at diagnosis as well as at nephrectomy.

In an era of improved technological communication, an opportunity exists to combine the continued collection of vital data, with a pan-european project to centrally hold individual patient disease data. This will enable consistent central review and assignment of patient risk group and treatment. The currently open IMPORT study, will act as a feasibility study to ensure the infrastructure is in place for the next clinical trial. These clinical guidelines are intended to be used in conjunction with The IMPORT study protocol.

Guideline Summary

The recently closed SIOP 2001 trial set out to better stratify risk groups for patients with Wilms tumour, as well as asking a randomised question regarding the need for doxorubicin in intermediate risk stage 2 and 3 patients. Whilst these objectives have largely been met, and doxorubicin is no longer recommended for intermediate risk stage 2 and 3 tumours, further verification, regarding prognostic factors, is required before a full international trial question can be laid out.

The IMPORT study allows further investigation of factors implicated in prognosis, as well as continuing to obtain registration, treatment and outcome data for patients with renal tumours for the interim period.
2. **Specific Objectives of CCLG Clinical Guidelines**

1. To be used in conjunction with The UK IMPORT study. This study sets out to better identify biomarkers, for future use, in order to improve outcomes for children with renal tumours.
2. To continue to collect data pertaining to patient registration, treatment and outcomes according to risk adapted therapy as recommended in the SIOPWT2001 clinical trial, omitting doxorubicin for intermediate risk stage 2 and 3 patients.
3. To maintain standards set for central reference pathological review.
4. To introduce more standard protocols for imaging, with central review of radiology, encouraging the use of MRI where possible with sequences which can assess cellularity and response to treatment.
5. To ensure adequate data collection of factors relating to tumour size, both at diagnosis and pre-operatively. Particular attention should be paid to the measurement of the residual volume of blastema remaining after pre-operative chemotherapy. This may well be used as a biomarker for higher risk disease and be used for treatment stratification in future studies.
6. To better characterise somatic genetic change and relate these to risk groups, in particular blastemal types and relapsing tumours.

3. **Guideline Recommendations**

**Diagnosis**

The diagnostic and staging investigations for a child with suspected Wilms tumour are detailed below.

Percutaneous biopsy, to obtain histological diagnosis, continues to be mandated in the UK. Central review of pathology will continue to be provided by Professor Gordan Vujanic in Cardiff.

Increased emphasis is placed on the quality and standardisation of imaging. 3D volume measurements of the tumour, both at diagnosis and pre-operatively, are imperative to further our understanding of the prognostic implication of remaining blastema volume.

MR scanning is the recommended gold standard for abdominal imaging. Studies have shown better anatomical depiction of the tumour and along with new protocols (ADC mapping) allows assessment of tumour composition, which may be used as a biomarker for response to chemotherapy and histological subtype. Centralised radiology review is introduced as part of IMPORT to improve standardisation, as well as better define metastatic and bilateral disease, both at diagnosis and following chemotherapy.

Improved imaging may influence planned surgical resection, particularly where partial nephrectomy is considered. These methods will also help characterise lesions in the contralateral kidney, which are increasingly recognised and may represent precursor lesions, nephrogenic rests or small Wilms tumours. Initial and post chemotherapy (pre-nephrectomy) imaging may then be related to histopathology findings thereby increasing our understanding of the relevance of these lesions.
It is recommended that children under 6 months have upfront nephrectomy. This age threshold can be discussed with the chair of the Renal CCLG SIG if a child aged 3-5 months has a tumour where immediate surgery appears to present significant risks. In these circumstances, depending on the imaging appearances of the tumour, the possibility of either malignant rhabdoid tumour or Wilms tumour should be considered as the likely malignant tumours. It is of note that the incidence of congenital mesoblastic nephroma decreases significantly from the age of 3 months upwards.

See Appendix 3 for indications and subsequent management of patients receiving upfront nephrectomy

All children with a suspected intra-renal tumour should have:

- Clinical history and examination, to include evidence of any family history and, predisposing congenital malformation syndromes
- Measurement of blood pressure and urinary protein
- Abdominal ultrasound, to include both kidneys, looking for evidence of tumour within the renal vein or IVC and exclude liver metastases
- Chest X-ray as baseline for follow up and to visualize large lung lesions
- CT chest, with documentation of number and largest size of any visible lung lesions*
- 3D Cross sectional imaging of abdomen (MRI standard, CT if MRI not available)
- Submit imaging for real time central review as detailed in IMPORT study
- Expert panel review and discussion for bilateral cases. (See CCLG website for process)
- DMSA scan if bilateral renal lesions or if partial nephrectomy is planned (once, prior to surgery)
- Per-cutaneous cutting needle biopsy with ultrasound guidance to avoid necrotic/cystic areas (note biopsy is not mandatory in the following circumstances; if tumour is largely cystic; a difficult to access lesion; bilateral renal lesions with typical appearances of Wilms tumour, or if patient has a Wilms tumour associated malformation syndrome)
- Consent for CCLG tumour banking
- Consent for prospective clinical study (IMPORT) – *note families can consent separately for inclusion of their child’s clinical information and for the samples to be taken for the biological study
- Echocardiogram for patients receiving doxorubicin

Uncertainty exists regarding the use of CT thorax for diagnosis of lung lesions. Evidence suggests that children with CT scan diagnosed metastases, have a worse outcome than those without CT only nodules, when treated as localised disease. If we are to move to recommending the use of CT thorax for diagnosis of lung metastasis, we need centralised review of this imaging to provide a more standardised definition of pulmonary metastases and adequacy of response to treatment. Whilst CT scan is the modality most used in clinical situations, we should use this opportunity to define relevant findings. Currently clinicians are asked to judge the presence or absence of lung metastases; however, advice is available through the renal tumour interest group and includes the opinion of reference radiologist.

4. Pre-operative Chemotherapy
Pre-operative chemotherapy as laid out in SIOP2001 is recommended for all children > 6 months. Children < 6 months are still recommended to have upfront nephrectomy. See Appendix 3.

4.1 Localised unilateral tumour

Two drugs (VCR, ActD) x 4 weeks: (fig 1)

Vincristine: 1.5 mg/m² intravenous bolus (max 2mg) weeks 1, 2, 3, 4 (5th dose can be given if week 5 falls before planned surgery)

Actinomycin D: 45 microgram/Kg intravenous bolus (max 2mg), weeks 1, 3

*Give 66% of above doses for children weighing <12 Kg. If age < 6mths dose reduce to 50% of each drug.*

Reassessment imaging at week 4

Surgery should be planned for week 5-6

Fig 1.

\[
\begin{array}{c|cccc|c}
\text{ACT} & 45 \, \mu g/kg & \downarrow & \downarrow & \\
\text{VCR} & 1.5 \, mg/m^2 & \downarrow & \downarrow & \downarrow & \downarrow \\
\text{WEEKS} & 1 & 2 & 3 & 4 & \text{SURGERY}
\end{array}
\]
4.2 Metastatic Tumours:

3 Drugs (VCR, Act D, Doxorubicin) x 6 weeks: (fig 2)

Vincristine; 1.5 mg/m² intravenous bolus (max 2mg), weeks 1, 2, 3, 4, 5, 6 (7th & 8th doses can be given if week 7/8 fall before planned surgery)

Actinomycin D: 45 microgram/Kg intravenous bolus (max 2mg) , weeks 1, 3, 5

Doxorubicin 50 mg/m² intravenous infusion over 4-6 hours weeks 1, 5

Give 66% of above doses for children weighing <12 Kg. If age <6 mths dose reduce to 50% of each drug

Reassessment imaging (3D) at week 6

Surgery should be planned for week 7-8

Fig 2.

| ACT  | 45 µg/kg | ↓ | ↓ | ↓ | ↓ |
| VCR  | 1.5 mg/m² | ↓ | ↓ | ↓ | ↓ | ↓ |
| DOX  | 50 mg/m² | ↓ | | | | ↓ |
| WEEKS     | 1 2 3 4 5 6 Sx |

5. Bilateral Tumours: Stage V

Clinical Management Guidelines: Wilms Tumour
January 2015 (rev March 2018)
It is strongly recommended that details of these cases are sent to the CCLG Renal Interest Group for central review and opinion (see CCLG website for process). This will ensure the optimum and more standardised management in terms of time to operate, consideration of partial nephrectomy, pre and post-operative treatment.

*Minimum treatment duration for Stage V tumours is 6 months.*

**5.1 Pre-operative chemotherapy**

This is to be given as above (Fig. 1 for localised/ Fig. 2 for metastatic). In principle this should be continued for as long as the tumour shows signs of regression, in order to minimise renal tissue resected. Reassessment should be planned for week 5 (consider Ultrasound/MR imaging to avoid CT related irradiation). In the event of good response continue for further 4 weeks and reassess at week 8. In the context of on-going response continue alternate week dosing with bi-weekly VCR and Act D (omit interval VCR) and reassess every 4 weeks by ultrasound and every 8 weeks by MRI. Diffusion weighting may be important in assessing tumour response and planning timing of surgery.

Evidence from The GPOH Group, suggests that, in principle, pre-operative chemotherapy should not continue beyond 12 weeks, as there is no further benefit in reducing individual tumour stage and prolonged chemotherapy may lead to tumour anaplasia.

Apparent response to chemotherapy may be dependent on histological subtype (eg. stromal type in WAGR or Denys-Drash syndrome often do not show reduction in size of tumour). This must be considered in planning the timing of surgery as tumour may not reduce in size with further or intensification of treatment.

If Nephron Sparing Surgery (NSS), is not felt to be feasible on standard chemotherapy regimens, introduction of carboplatin-etoposide, may facilitate further tumour shrinkage enabling this approach.

In the case of differential response and challenging surgical picture, consider possibility of biologically distinct tumours. Biopsy of the lesions may be helpful. Please discuss with CCLG Renal Tumour Interest Group.

**5.2 Surgery for Bilateral Wilms’ Tumours**

(see Surgical Guidelines Appendix 1)

**5.3 Post-operative chemotherapy**

This is directed at the kidney with the highest stage lesion. When the individual tumours are both stage 1, the minimum post-operative chemotherapy should be regimen AV-2 (ie 2 drugs for 27 weeks). If nephrogenic rests are seen in the resected kidney in addition to the Wilms tumour, then VA should be continued every 28 days from the end of AV-2 until completion of a total of 12 months of chemotherapy.

In contrast to uni-lateral tumours, doxorubicin should still be considered standard of care for the post-op chemotherapy of individually stage II and III intermediate risk tumours. The
question regarding the value of doxorubicin was not tested in bilateral cases the SIOP WT 2001 trial. **Do not exceed total dose of 300mg/m² doxorubicin.**

Radiotherapy recommendations. See Appendix 5. However dose must not exceed 12Gy to remaining kidney.

### 6. Surgical Guidelines

See Appendix 1

### 7. Pathology Protocol

See Also Appendix 2

#### 7.1 Staging

Stage is one of the most important therapeutic and prognostic criteria for renal tumours. It has been shown in all multicentre trials that accuracy of staging still represents a major problem. This problem arises in part because renal tumours are usually very large at nephrectomy and often it is very difficult to assess their relationship with normal renal anatomical structures such as the renal capsule and the renal sinus. It is absolutely critical to take blocks from all sites that are important for staging and to carefully document the site from which each block is taken (please take photographs and mark the sites from which blocks have been taken).

Please remember that local (abdominal) staging of primary tumour is done following pre-operative chemotherapy and it is very important even in stage IV cases. The presence/absence of metastases is evaluated at presentation, on the basis of imaging studies.

**Stage I**

a) The tumour is limited to kidney or surrounded with a fibrous pseudocapsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated with the tumour but it does not reach the outer surface, and it is completely resected (resection margins ‘clear’)

b) The tumour may be protruding (‘bulging’) into the pelvic system and ‘dipping’ into the ureter (but it is not infiltrating their walls)

c) The vessels of the renal sinus are not involved

d) Intra renal vessel involvement may be present

*Fine needle aspiration or percutaneous core needle biopsy (‘tru-cut’) does not upstage the tumour.*

*The presence of necrotic tumour or chemotherapy-induced change in the renal sinus and/or within the perirenal fat should not be regarded as a reason for upstaging a tumour providing it is completely excised and does not reach the resection margins.*
Stage II

a) The tumour extends beyond kidney or penetrates through the renal capsule and/or fibrous pseudocapsule into peri-renal fat but is completely resected (resection margins ‘clear’)

b) Tumour infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchyma but it is completely resected

c) Tumour infiltrates adjacent organs or vena cava but is completely resected

Stage III

a) Incomplete excision of the tumour which extends beyond resection margins (gross or microscopic tumour remains post-operatively)

b) Any abdominal lymph nodes are involved

c) Tumour rupture before or intra-operatively (irrespective of other criteria for staging)

d) The tumour has penetrated through the peritoneal surface

e) Tumour implants are found on the peritoneal surface

f) The tumour thrombi present at resection margins of vessels or ureter, transsected or removed piecemeal by surgeon

g) The tumour has been surgically biopsied (wedge biopsy) prior to pre-operative chemotherapy or surgery.

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

Stage IV*

Haematogeneous 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 above classifications.

7.2 Histological Subtypes of pre-treated cases

LOW RISK TUMOURS

Mesoblastic nephroma
Cystic partially differentiated nephroblastoma
Completely necrotic nephroblastoma (100% necrosis)

INTERMEDIATE RISK TUMOURS

Nephroblastoma-epithelial type (<66% necrosis)
Nephroblastoma- stromal type (<66% necrosis)
Nephroblastoma- mixed type (<66% necrosis)
Nephroblastoma- regressive type (66%-99% necrosis)
Nephroblastoma- focal anaplasia
HIGH RISK TUMOURS
Nephroblastoma- blastemal type
Nephroblastoma- diffuse anaplasia
Clear cell sarcoma kidney
Rhabdoid tumour kidney (treatment recommendations now according to EuRhab protocol)

8. Post Operative Treatment; Localised Disease

based on stage and histology, see Table 1 and subsequent flow diagrams

Cases requiring ‘upfront’ nephrectomy see Appendix 3

Table 1.

<table>
<thead>
<tr>
<th></th>
<th>STAGE I*</th>
<th>STAGE II*</th>
<th>STAGE III*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW RISK</td>
<td>NO FURTHER TREATMENT</td>
<td>AV2</td>
<td>AV2</td>
</tr>
<tr>
<td>INTERMEDIATE RISK</td>
<td>AV1</td>
<td>AV2</td>
<td>AV2+flank irradiation</td>
</tr>
<tr>
<td>HIGH RISK</td>
<td>AVDloc</td>
<td>HRloc + flank irradiation (except blastemal type)</td>
<td>HRloc + flank irradiation</td>
</tr>
</tbody>
</table>

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.

8.1 Stage 1, Intermediate Risk Histology: Regimen AV1 (Fig.3)

The total duration of the post-operative chemotherapy is 4 weeks
**Vincristine**: 1.5 mg/m² intravenous bolus (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 microgram/kg intravenous bolus (max 2mg), at week 2 (day 7) of post-operative regimen. Delayed until the absolute neutrophil count is <1.0 x10⁹/l or platelet count <100 x 10⁹/l

*Note Dose reductions*

1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

### 8.2 Stage 1, High Risk Histology: Regimen AVDloc (Fig. 4)

*The total duration of the post-operative chemotherapy is 27 weeks*

**Vincristine** 1.5mg/m² intravenous bolus (maximum 2mg) 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 – ie total of 20 doses of Vincristine.

**Actinomycin D**: 45 microgram/kg intravenous bolus (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

**Doxorubicin** 50mg/m² intravenous infusion over 4-6 hours every 6 weeks to start in week two concurrently with the first dose of Actinomycin D and the second dose of Vincristine. Subsequent doses are given at weeks 2, 8, 14, 20 and 26 i.e. 5 doses- total 250mg/m²

*Note Dose reductions*

1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Actinomycin D and Doxorubicin should be delayed if the absolute neutrophil count is <1.0 x10⁹/l or platelet count <100 x 10⁹/l

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

*The total duration of the post-operative chemotherapy is 27 weeks. (Fig. 5)*

**Vincristine** 1.5mg/m² intravenous bolus (maximum 2mg), commenced 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 – ie total of 20 doses of Vincristine.
Actinomycin D: 45 microgram/kg intravenous bolus (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)
Delayed the absolute neutrophil count is >1.0 x10^9/l or platelet count >100 x 10^9/l

**Note Dose reductions**
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

8.4 Stage II/III High Risk Histology: High Risk Regimen HRloc (Fig. 6)

**Total duration of post-operative 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 the operation and clinical condition allows and within 21 days of pre-operative chemotherapy. Ideally radiotherapy commenced concomitantly, and chemotherapy courses manipulated to ensure doxorubicin is not given within 14 days of radiotherapy.

Each cycle commences when absolute neutrophil count is >/= 1.0x10^9/l and platelet >100 x 10^9/l

Use of Cotrimoxazole recommended for HR regimens

**Course 1. Cyclophosphamide and Doxorubicin**
Cyclophosphamide 450mg/m^2 intravenous infusion over one hour on days 1,2,3.
Doxorubicin 50mg/m2 intravenous infusion over 4-6 hours on day 1 of weeks 1, 7, 13, 19, 25 and 31. (total of 6 courses) with a 6 week interval.

The Doxorubicin can be started after the first dose of Cyclophosphamide.

**Course 2. Etoposide and Carboplatin**
Both Etoposide (VP16) 150mg/m2 intravenous infusion over 4 hours and Carboplatin 200mg/m2 (or AUC = 2.65 see Appendix 1) on days 1,2,3 of weeks 4, 10, 16, 22, 28 and 34 (a total of 6 courses) given every 6 weeks

**Note Dose reductions for all drugs**
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Stage II blastemal subtype tumours do not receive radiotherapy (see Appendix 4)
9. Post-Operative Chemotherapy Treatment; Metastatic Disease

Full surgical and radiotherapy guidelines in Appendix 1 and 4, respectively.

Table 2.

<table>
<thead>
<tr>
<th>Histology Standard Risk</th>
<th>Histology High Risk *</th>
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<tbody>
<tr>
<td><strong>Local Stage I and II</strong></td>
<td><strong>Local Stage III</strong></td>
</tr>
<tr>
<td><strong>In metastatic CR</strong> (chemotherapy or surgically obtained)</td>
<td>AVDm</td>
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<tr>
<td>Residual metastatic disease</td>
<td>HRm Pulmonary RT</td>
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</table>

9.1 Local Stage I/II/III, Low and Intermediate Risk Histology; Metastatic Clearance Obtained (by chemotherapy or surgery); Regimen AVDm (Fig. 7)

Total duration post-operative treatment 27 weeks.

**Vincristine** 1.5mg/m2 intravenous bolus (maximum 2mg) 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 – i.e. total of 20 doses of Vincristine.

**Actinomycin D**: 45 microgram/kg intravenous bolus (max 2mg), at week 2, 5, 8, 11, 14, 17, 20, 23, 26 (9 doses in total)

**Doxorubicin** 50mg/m² intravenous infusion over 4-6 hours every 6 weeks to start in week 2 concurrently with the first dose of Actinomycin D and the second dose of Vincristine. Subsequent doses are given at weeks 2, 8, 14, 20 i.e. 4 doses NO doxorubicin in week 26. Total dose including pre-op treatment= 300mg/m²

**Note Dose reductions**
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

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

Radiotherapy: Flank radiotherapy for all local Stage III only.

9.2 a. Local Stage II/III, Low and Intermediate Risk Histology with Residual Metastatic Disease

b. Local Stage I/II/III with High Risk Histology regardless of metastatic status

High Risk Regimen (HRm) (Fig. 8)

Total duration of post operative treatment is 34 weeks

Two courses of combination chemotherapy given at 21 day intervals. HRm differs from HRloc in that 2 cycles of carboplatin/etoposide are substituted for 2 cycles of cyclophosphamide/doxorubicin. This avoids excessive anthracycline exposure. The first course starts as soon as the patient has recovered from the operation and clinical condition allows and within 21 days of pre-operative chemotherapy.

Ideally radiotherapy is commenced concomitantly, and chemotherapy courses manipulated to ensure doxorubicin is not given within 14 days of radiotherapy.

Each cycle commences when absolute neutrophil count is >/= 1.0x10^9/l and platelet >100 x 10^9/l

Use of cotrimoxazole recommended for high risk regimens.

Course 1. Cyclophosphamide and Doxorubicin

Cyclophosphamide 450mg/m2 intravenous infusion over one hour on days 1,2,3. Mesna hydration as detailed in appendix 6. Drug Administration and Doxorubicin 50mg/m2 intravenous infusion over 4-6 hours on day 1 of weeks 1, 7, 19, and 31. (total of 4 cycles). Total dose including pre-operative chemotherapy 300mg/m².

The Doxorubicin can be started after the first dose of Cyclophosphamide.

Course 2. Etoposide and Carboplatin
Both Etoposide (VP16) 150mg/m² intravenous infusion over 1-4 hours and Carboplatin 200mg/m² (or AUC = 2.65 see Appendix 1) intravenous infusion over one hour on days 1, 2, 3 of weeks 4, 10, 13, 16, 22, 25, 28, and 34 (a total of 8 cycles)

**Note Dose reductions for all drugs**

1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.
Fig 3. REGIMEN AV-1

STAGE I, INTERMEDIATE RISK (see notes above)

ACT  45 µg/kg ↓
VCR  1.5 mg/m² ↓ ↓ ↓ ↓

1  2  3  4

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2 mg)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection

Note Dose reductions for all drugs

1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.
### Fig 4. REGIMEN AVDloc

**STAGE I, HIGH RISK** *(see notes above)*

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<tr>
<th>DRUG</th>
<th>DOSE</th>
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<tr>
<td>ACT</td>
<td>45 µg/kg</td>
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<tr>
<td>VCR</td>
<td>1.5 mg/m²</td>
<td>↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓</td>
</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
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- **ACT** = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2 mg)
- **VCR** = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg)
- **DOX** = doxorubicin = 50 mg/m²/ i.v. infusion in 4-6 hours

**Note Dose reductions for all drugs**
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Major intolerance: doses on the next course should be reduced to 66% (see appendix 5)
**Fig 5. REGIMEN AV-2**

**STAGE II / III, LOW AND INTERMEDIATE RISK** *(see notes above)*

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<td>VCR</td>
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ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2 mg)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg)

*Note Dose reductions for all drugs*

1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Major intolerance: doses on the next course should be reduced to 66% (see appendix 5)
Fig 6. HIGH RISK REGIMEN for localised disease HRloc
STAGE II/ III, HIGH RISK (see notes above)

Radiation
Stage II Blastemal-predominant high risk cases do not receive radiotherapy (table 1 above and appendix 4)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Weeks</th>
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<tbody>
<tr>
<td>VP16</td>
<td>150 mg/m²</td>
<td>1-4</td>
</tr>
<tr>
<td>CARBO</td>
<td>200 mg/m² (or AUC 2.65)</td>
<td>5-6</td>
</tr>
<tr>
<td>CYCLO</td>
<td>450 mg/m²</td>
<td>7-8</td>
</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
<td>9-10</td>
</tr>
</tbody>
</table>

Chemotherapy cycles can be manipulated to avoid use of Doxorubicin within 14 days of radiotherapy

- VP16 = etoposide = 150 mg/m²/i.v./infusion 1-4 hours
- CARBO = carboplatin = 200 mg/m²/i.v./infusion 1 hour (or AUC = 2.65)
- CYCLO = cyclophosphamide = 450 mg/m²/i.v./infusion 1 hour
- DOX = doxorubicin = 50 mg/m²/i.v./infusion 4-6 hours, just after the first CYCLO administration

Note Dose reductions for all drugs
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Major intolerance: doses on the next course should be reduced to 66% (see appendix 5)
**Fig 7. Regimen AVDm, Metastatic Disease, Local Stage I/II/III, Low and Intermediate Risk; Metastatic Clearance Obtained (by chemotherapy or surgery);**

Radiation
Local stage I/II no flank irradiation.
Local stage III, flank irradiation except blastemal subtypes

<table>
<thead>
<tr>
<th></th>
<th>ACT</th>
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<tbody>
<tr>
<td>VCR</td>
<td>1,5 mg/m²</td>
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<td>DOX</td>
<td>50 mg/m²</td>
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**WEEKS**
1 2<------- 3-------- 4------> 5 6 7 ◆ 8 9 10 11 12 13 14 15 16 17 18 19 ◆ 20 21 22 23 24 25 26Ø 27

28 ◆ Echocardiogram (ECHO)
Ø no DOX in week 26, so total dose does not exceed 300 mg/m²
Chemotherapy cycles can be manipulated to avoid use of Doxorubicin within 14 days of radiotherapy

*Reduce dose of ACT by 50% when within 7 days prior and 14 days following radiotherapy

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2 mg)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg)
DOX = doxorubicin = 50 mg/m²/i.v. infusion 4-6 hours

Note Dose reductions for all drugs
1. Give 66% of above doses for children weighing <12 Kg.
2. If age < 6mths dose reduce to 50% of each drug.

Major intolerance: doses on the next course should be reduced to 66% (see appendix 5)
Fig 8. HIGH RISK REGIMEN HRm, Metastatic Disease

a. Local Stage II/III, Low and Intermediate Risk Histology with Residual Metastatic Disease,
b. Local Stage I/II/III with High Risk Histology regardless of metastatic status.

Local Stage I and Stage II standard risk; no flank irradiation, pulmonary irradiation except blastemal subtypes (table 2 and appendix 4)
Local Stage II high risk and all Local Stage III, flank irradiation (except blastemal subtypes),

<table>
<thead>
<tr>
<th>VP16</th>
<th>150 mg/m²</th>
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<tr>
<td>CARBO</td>
<td>200 mg/m² (or AUC 2.65**)</td>
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<td>CYCLO</td>
<td>450 mg/m²</td>
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<tr>
<td>DOX</td>
<td>50 mg/m²</td>
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WEEKS

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\( \otimes \) 41 42 43 44 45 46 47 48 49 50

\( \otimes \) 51 52 53 54 55 56 57 58 59 60

\( \otimes \) 61 62 63 64 65 66 67 68 69 70

\( \otimes \) 71 72 73 74 75 76 77 78 79 80

\( = \) Echocardiogram (ECHO) if ECHO is abnormal, see appendix 5

\( \otimes \) = GFR (measure at every third course, or more frequently if there is evidence of renal dysfunction

Co-trimoxazole prophylaxis is recommended

Chemotherapy can be manipulated to avoid use of Doxorubicin within 14 days of radiotherapy

VP16 = etoposide = 150 mg/m²/i.v./infusion 1-4 hours
CARBO = carboplatin = 200 mg/m²/i.v./infusion 1 hour (or AUC = 2.65)
CYCLO = cyclophosphamide = 450 mg/m²/i.v./infusion 1 hour * MESNA Hydration see
DOX = doxorubicin = 50 mg/m²/i.v./infusion 4-6 hours, just after the first CYCLO administration

Dose reductions for all drugs 1. Give 66% of above doses for children weighing <12 Kg. 2. If age < 6mths dose reduce to 50% of each drug. Major intolerance: doses on the next course should be reduced to 66% (see Appendix 5)
10. **Supportive Care**

Pneumocystis prophylaxis should be given to patients on the HR regimen and those receiving pulmonary irradiation.

GCSF may be beneficial for patients receiving The HR regimen, in order to maintain treatment intensity. This may be given at clinician discretion.

11. **Radiotherapy guidelines**

See Appendix 4

12. **Toxicity and Dose Modification**

See Appendix 5
References
Characteristics and survival of 750 children diagnosed with a renal tumor in the first seven months of life: A collaborative study by the SIOP/GPOH/SFOP, NWTSG, and UKCCSG Wilms tumor study groups.

An international strategy to determine the role of high dose therapy in recurrent Wilms tumour.

Clinical significance of pulmonary nodules detected by CT and not CXR in patients treated for favorable histology Wilms tumor on national Wilms tumor studies-4 and -5: a report from the Children's Oncology Group.

Treatment of pulmonary metastases in children with stage IV nephroblastoma with risk-based use of pulmonary radiotherapy.

The contribution of chest CT-scan at diagnosis in children with unilateral Wilms tumour. Results of the SIOP 2001 study.


Patterns of shift in ADC distributions in abdominal tumours during chemotherapy-feasibility study.

Bilateral disease and new trends in Wilms tumour.

Mesoblastic nephroma: a report of the United Kingdom Children's Cancer and Leukaemia Group (CCLG).
Appendix 1. Surgical Guidelines

Introduction
The principles of nephrectomy for paediatric malignancy were established by Gross in 1953: a wide transverse trans abdominal incision and trans peritoneal approach with early ligation of the renal vessels (1-3). Pre-operative chemotherapy as demonstrated by SIOP studies 2, 5, 6, 9 and 93-01 makes nephrectomy easier and less hazardous. Furthermore, metastases may disappear or become resectable, vascular extension may regress and partial nephrectomy may become possible (4-10).

1. Please ensure familiarity of surgical guidelines in the context of The Wilms tumour management guidelines.
2. Excision of Wilms tumour is an elective procedure and should, therefore, be carried out by the most experienced team available.
3. An emergency may occur if the tumour ruptures and bleeds pre-operatively and conservative management is ineffective. In spite of these difficulties, it is usually possible to follow most of the treatment recommendations.

Imaging
The imaging at presentation and after chemotherapy should be carefully assessed prior to operation.

Magnetic resonance imaging (MRI) is now seen as the gold standard imaging (see earlier), but can be difficult to obtain for very young children. CT is sufficient in this case, in addition to Doppler ultrasonography. The surgeon must know the extent of the tumour, its location within the kidney, and its relation to the central vessels, diaphragm, liver, pancreas, spleen and adrenal glands before operation. Enlarged intra-abdominal (mainly para-aortic) lymph nodes, intra-abdominal metastases (mainly hepatic) and thrombus in the renal vein or vena cava should be looked for. Chest CT is advised if there is any doubt about the X-ray and if metastatectomy is planned.
Recommendations for needle biopsy

In the UK it is strongly recommended to obtain tissue for a histological diagnosis prior to commencing chemotherapy. The following guidelines are based on the experience of the UK surgeons in undertaking percutaneous core needle biopsy. Biopsy can be performed by surgeon or radiologist.

1. Ultrasound guidance is strongly recommended.
2. If compatible with a safe approach to the tumour, an anterior approach is recommended so that the needle track can be excised at the time of definitive nephrectomy.
3. A 12-14G cutting needle is commonly used. Automated needles such as a Biopty or Temno are better than the conventional Tru-cut needles.
4. Take several cores to ensure that the pathologist will have sufficient material to make a diagnosis, as Wilms tumours are often extensively necrotic.
5. In order to reduce the numbers of points of entry of the needle tract into the tumour, consider the use of a co-axial technique (discuss with your radiologists).

Recommendations for nephrectomy

Access
Long transverse abdominal incision

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

Thorough inspection of the opposite retroperitoneal space is obligatory only if pre-operative images indicate bilateral localisation of the tumour. In other cases it rarely gives more information than good quality imaging. The operating surgeon should decide whether or not to do it in individual cases. Unequivocal stage V cases will be treated following ‘Stage V treatment guidance’.
Nephrectomy
Early ligation of the renal vessels should be the aim and is possible in nearly every case. The renal artery should be ligated first in order to avoid swelling of the tumour with increase of its fragility and the possibility of dissemination via perforating perinephric veins. For right sided tumours an extensive Kocher’s-manoeuvre of the duodenum allows access to the vena cava and renal vessels. Whilst this approach can be used to gain control of the vessels in left sided tumours, an approach via the peritoneum lateral to the colon is perhaps preferable. The technique of the approach should be indicated in the surgery form if the patient is consented on IMPORT. If the tumour is very large and infiltrating and the primary ligation of renal vessels is difficult and considered too risky, the tumour should be dissected from surrounding structures first, and vessels ligated when possible. The tumour should be removed together with its adipose capsule and Gerota’s fascia, and where indicated all invaded surrounding structures. Extensive and mutilating resections, such as pancreatectomy are not recommended, as these tumours are both chemo- and radiosensitive. This should be precisely described in the surgical form if the patient is consented on IMPORT.

Renal Vein, Vena Cava
Although intravascular extension of the tumour is usually apparent on the pre-operative imaging, the vena cava and renal vein should be carefully examined during the operation. If thrombus is found, it should be removed. A short thrombus in the renal vein may be resected together with the vein. A thrombus extending to the infra-hepatic vena cava should be removed through a vena cavotomy, after controlling the contra lateral renal vein and cava above and below the thrombus. The thrombus should be removed and the venotomy closed. A longer thrombus, (intra-hepatic, supra-hepatic, or right atrial), may require the assistance of a vascular or cardiac surgeon and cardiopulmonary by-pass.
In cases with very extensive infiltration of the vena caval 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. The SIOP 9 study showed that this is a valid option.

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

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

Lymph Nodes
The NWTS 1 trial showed that 8/224 (3.6%) of lymph nodes that were declared negative by the surgeon showed metastases on histological examination and 25/64 (39.1%) of cases that were declared positive, did not. The tumour must not be upstaged if there is no histological confirmation of lymph node involvement. Recent studies revealed a higher incidence of local recurrence in patients enrolled in NWTS-4 in whom biopsy of lymph node was not performed. This suggested that inadequate staging led to under-treatment of local disease in these children.

Sampling and histological examination of lymph nodes is imperative for accurate staging and subsequent treatment. Hilar and para-aortic lymph nodes at
the origin of the renal artery (regional nodes) and nodes below or above this level (extra regional nodes) should be sampled even if not suspicious. **It is recommended that at least 7 nodes are sampled.** Involved or suspicious lymph nodes must be excised without rupture. They must be carefully labelled and sent to the pathologist separately with an accurate description of their position and character. **The above information affects staging, treatment and therefore outcome. Radical lymph node dissection does not enhance survival and therefore is not part of the surgical therapy.**

**Stage IV surgical recommendations**

In the UK it is recommended to give pulmonary radiotherapy to lung metastasis that have not achieved complete remission on CXR after preoperative chemotherapy with 3 drugs. Early surgical excision should be reserved for small numbers of operable metastasis, where the finding of completely necrotic tumour or scar tissue may lead to the avoidance of radiotherapy. Similar consideration should be given to other sites of metastasis.

Lung metastasis should be excised if possible. Operation should be performed either as soon after nephrectomy as possible and when the patient’s condition permits, or after the beginning of post-operative chemotherapy. This should be decided upon by both surgeon and oncologist. Bilateral resectable lung metastases should be excised either via two thoracotomies or a median-sternotomy depending on surgical choice and anatomy. Wedge resections can frequently be radical. If wedge resection will not achieve complete excision, then segmentectomy or lobectomy is acceptable. Pneumonectomy is not justified.

For isolated liver metastases a wedge resection should also be appropriate in these cases. Extensive and potentially mutilating resections are not recommended before the possibility of further chemotherapy is explored. Metastases outside lung or liver should be excised completely provided the operation can be done without mutilation, or loss of vital organs.

**Complete excision of metastases is extremely important as it may remove the need for irradiation. It is not recommended to operate on metastases that have progressed through pre-operative chemotherapy as complete excision is rarely successful in such circumstances. Alternative chemotherapy and/or radiotherapy should be explored first.**

The sampling or hilar and perihilar lymph nodes is just as important as in patients with metastases as it is for those with localised disease.
**Bilateral disease surgical recommendations**

Bilateral cases should be treated individually. Surgical intervention requires an extremely experienced team. Surgery is planned after tumour reduction with chemotherapy. The goal is bilateral partial nephrectomies (or wedge resection) preferably in two separate operations performed 1-2 weeks apart. The less involved kidney should be operated on first. Complete nephrectomy on one side with partial nephrectomy on the opposite side is acceptable providing enough functional renal tissue can be preserved. Enucleation or complex longitudinal partial nephrectomies are not recommended unless there is no possibility of any other type of nephron sparing surgery on at least one kidney. If in spite of favourable appearances on imaging, the tumours appear inoperable at surgery, the tumours could be biopsied, preferably with the Tru-cut needle, and the patient treated with further chemotherapy. However, in some cases complete nephrectomy may be the only surgical option. The options for radiotherapy as local treatment are limited after partial nephrectomy but there are examples from the SIOP 9 study which indicate that low dose radiotherapy (10Gy) and chemotherapy may result in long term remission even after incomplete excision. This possibility should be taken into account in patients for whom bilateral nephrectomy would be the only means to achieve complete excision. If bilateral nephrectomy is performed, vascular access for dialysis (Permcath) should be inserted at the time of the second nephrectomy. Peritonel 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, both tumours should be biopsied (contrary to unilateral cases), preferably with Tru-cut needle, and the patient treated with chemotherapy. Subsequent therapy should be as described above. If the lesion is small, the biopsy should be excisional.

**Partial nephrectomy/Nephron Sparing Surgery (NSS)**

Partial nephrectomy/NSS may assure local control and is becoming more commonly performed. For bilateral tumours this approach is usually the surgical management of choice. Unilateral cases may also benefit from partial nephrectomy, but the advantages and risks have to be precisely evaluated for each individual case. Contra-lateral urological and nephrological disorders and genetic syndromes of an increased risk of Wilms rather than a risk of hyperperfusion nephropathy in the remaining kidney are important criteria when this option is considered.

Partial nephrectomy/NSS is acceptable in all cases of unilateral Wilms tumour provided the following criteria are met:
Indications for partial nephrectomy/NSS in unilateral Wilms tumours

1. Tumour restricted to one pole of kidney or peripheral at mid-kidney (<300ml volume)
2. Excision can be performed with oncologically safe margin
3. Kidney remnant has useful function

At least 50% 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.

Contraindications for a partial nephrectomy/NSS in unilateral Wilms tumours

1. Pre-operative tumour rupture
2. Tumour infiltrating extra renal structures
3. Intraabdominal metastases or lymph nodes seen on preoperative imaging
4. Thrombus in the renal vein or vena cava
5. Tumour involving more than 1/3rd of the kidney (at least 50% of renal tissue should be spared after the tumour resection with a margin of healthy tissue, to give any worthwhile protection against hyperperfusion)
6. Multifocal tumour
7. Central location
8. For teams with little experience of partial nephrectomy (consider discussion or transfer of patient to unit/surgical team with more experience or )

Remarks

1. A significant volume reduction after preoperative chemotherapy suggest a better chance of successful partial nephrectomy
2. Functional imaging of the kidney (DMSA scan) of the kidneys should be considered prior to surgery
3. Resection must be performed with margins of healthy renal tissue, enucleation is not adequate local treatment unless bilateral tumours and no other option for NSS. Evidence from adult practice shows that no set margin (>5mm) is necessary, provided the margins are clear. Histologically. If histological examination suggests a marginal resection a completion nephrectomy should be considered.
4. Intraoperative ultrasound scanning can be useful in defining the intrarenal tumour extent.
5. Following partial nephrectomy, the kidney should be 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.
6. Nephroblastomatosis in the renal parenchyma of the partial nephrectomy specimen, may give rise to metachronous nephroblastoma in the residual kidney. These patients should be followed very carefully.
7. The decision for partial nephrectomy should be taken by all members of MDT and feasibility finally confirmed by the surgeon at operation.
8. SIOP is currently developing a descriptive methodology to identify what type of
surgery and what percentage of native kidney is left following NSS.

Optional: Laparoscopic Nephroureterectomy
Laparoscopic or laparoscopically assisted nephrectomy is acceptable in unilateral cases of Wilms tumours provided the following criteria are met:

**Indications for laparoscopic nephrectomy:**

1. Resection must adhere to oncological principles and include lymph node sampling
2. Small, central tumours with rim of “normal” renal tissue (<300ml volume)

**Contraindications for laparoscopic nephrectomy:**

1. Pre-operative tumour rupture
2. Tumour infiltrating extra renal structures
3. Intra-abdominal metastases or lymph nodes seen on pre-operative imaging
4. Thrombus in the renal vein or vena cava
5. Tumour involving more than 1/3 of the kidney
6. Multifocal tumour
7. Peripheral location
8. Little or no experience in laparoscopic nephrectomy (consider transfer to another unit or obtain more experienced help).

Recommended surgical treatment of relapse
First relapse, whether metastatic or local, is curable in a high proportion of patients. Treatment should therefore be conducted with the intention of cure. The first treatment is with chemotherapy. Exceptions are the late solitary lung metastasis, and any metastasis in the central nervous system. 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 is 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. This is the goal of surgery which should aim for clear resection margins. The tumour bed and any suspicious residual disease should be marked with titanium clips and radiotherapy targeted to this site.

If the relapse occurs in the field of radiotherapy, surgery remains the only local treatment, and 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.

Closing remarks
The standard metal clips, although useful for many reasons, should be avoided if CT or MRI is planned. Please use titanium clips which do not interfere with either CT or MRI. If only pre-operative MRI was performed, consider using titanium clips to mark the upper and lower border of the tumour to facilitate targeting of radiotherapy.

For Wilms tumour, a minimal invasive surgical technique does not offer any outcome advantages over the classical open surgical approach. For metastectomy, endoscopic techniques do not allow palpation of the lungs or liver for small parenchymal nodules which may frequently be missed on imaging. However, this is rarely an issue in Wilm’s tumour.

All suspicious structures should be biopsied or resected, marked, described precisely and sent to the pathologist in separate containers. The intact surgical specimen should be delivered fresh (not fixed in formalin and immediately) 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.

At nephrectomy, areas of dubious complete excision should be marked and described precisely on both surgery and pathology forms. A copy of the complete surgical report should accompany the surgery form.

Please complete the drawing enclosed with the form for every surgical procedure, and add comments after review with your pathologist. This should be included with the completed forms.

Please fill in IMPORT FORM 3: Operative Findings “metastatectomy form”. Since nephrectomy and metastatectomy may be performed in different hospitals, the responsible paediatric oncologist should ensure that both operating surgeons complete the relevant form.
Appendix 2. Pathology Protocol

*These recommendations are those recommended to use with The IMPORT study, and can be found within the study documentation.*

1.0 Introduction

This study seeks to accurately identify the volume of blastema remaining following pre nephrectomy chemotherapy. Institutional pathologists are asked to record an actual percentage of tumour necrosis/chemotherapy-induced changes and, within the viable tumour, an actual percentage of residual blastema. Please also assess and record percentages of other tumour components (epithelial and stromal).

Histological subtype is assigned by institutional pathologist, with central pathology review by Professor Gordan Vujanic in Cardiff. SIOP histological criteria (Table 1) and staging system should be used, considering clinical information regarding tumour rupture and metastatic status. Assignment to treatment risk groups **WILL NOT** be done by institutional pathologists, but centrally, by the Study centre.

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>Histological criteria (SIOP WT 2001)</th>
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<tbody>
<tr>
<td></td>
<td>CIC</td>
</tr>
<tr>
<td>Completely necrotic</td>
<td>100%</td>
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<tr>
<td>Regressive</td>
<td>&gt;66%</td>
</tr>
<tr>
<td>Mixed</td>
<td>&lt;66%</td>
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<tr>
<td>Epithelial</td>
<td>&lt;66%</td>
</tr>
<tr>
<td>Stromal</td>
<td>&lt;66%</td>
</tr>
<tr>
<td>Blastemal</td>
<td>&lt;66%</td>
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</table>

CIC - chemotherapy-induced changes

2.0 Nephrectomy Specimens

The *intact* surgical specimen should be presented to the pathologist *without being opened by the surgeon*. A report of the operation (form 3A) with sufficient information necessary for correct staging should be made available to the pathologist.

2.1 Handling the fresh specimen, step by step:

1) **Weigh, measure** and **photograph** the whole specimen. Look carefully for ruptures and fissures and locate any suspicious areas and/or ink it in different colours from the rest of the specimen. Decapsulation makes determination of growth beyond the capsule impossible and therefore should not be done. **It is critical to accurately measure the tumour in all three dimensions as it will be used for calculating tumour volume.**

2) Look for and dissect the peri-renal and perihilar **lymph nodes**. Block these separately recording the site. (These are rare).
3) **Identify renal vein, artery and ureter** and take transverse section block of each near the resection margin.

4) **Ink** the surface of the whole specimen (or at least areas in which excision margins are dubious) and renal sinus with Indian ink and let it dry **before** opening the specimen. This is a critical step and should always be done as otherwise it might be impossible to stage the tumour correctly and give adequate therapy.

5) **Open** by a longitudinal incision to bivalve the specimen and reveal the tumour and its relation to the kidney, capsule, and renal sinus.

6) **Photograph** the cut surface, record macroscopic appearance. **Measure** the size of the tumour. It is crucial to **assess the percentage of a necrotic tumour** (this percentage has to be filled in on the Form F4) and also to describe and photograph the multicystic cut surface, if present.

7) **Samples required** for biology studies:
   - **Tumour**: At least two pieces (0.5 - 1 cm³ each) of morphologically different parts of the tumour should be sampled and snap frozen in liquid nitrogen or at −70°C (Freeze more aliquots if available). If a biopsy is performed prior to commencing pre-operative chemotherapy, then a sample of this should also be frozen, if adequate tissue is available.
   - **A ‘mirror’ sample** of tumour adjacent to the frozen sample should be fixed in formalin and studied for histology. Please submit this wax block along with the frozen tissue, when requested.
   - **Adjacent normal kidney**: two pieces (0.5 – 1 cm³) snap frozen in liquid nitrogen or at −70°C.
   - **Nephrogenic rests** should be sampled as above.
   - **Peripheral blood** in EDTA (if national procedure for storage available).
   - Samples should be stored at −70°C or under liquid nitrogen until transported to the appropriate national research laboratory on dry ice.

   The time interval between removal of the tumour and the freezing of the samples should be as short as possible and certainly not exceed a period of 30 - 60 minutes. (See also section 13: 13.5).

8) **The specimen** should be **fixed** in 4% buffered formalin for 24 to 48 hours, according to the usual procedure of the laboratory. Several additional cuts can be made parallel to the initial cut to divide the specimen into “slabs” for better fixation. (Alternatively, instead of parallel longitudinal sections, you may find that making horizontal sections and sampling the tumour in this way will give a better view of the renal sinus and a tumour-sinus relationship.)

9) **The samples for histological examination should include**:
   - **a)** at least one longitudinal slice of tumour and kidney surface, completely sampled (see Figure 1) (please consider using mega-blocks as it makes histological assessment much easier, and they are less time consuming for both pathologists and their labs – Figure 2)
In addition, please sample the following, too:

b) the macroscopically different areas of the tumour (it is advised to take at least one block per cm of the largest diameter of the tumour, not forgetting to take blocks from grossly necrotic areas, too); mostly from the periphery rather than from the central areas of the tumour;

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;

m) at least 2 blocks of the normal kidney and blocks from abnormal looking areas in the remaining renal tissue.

Please make sure to have a ‘block guide’ (as in Figure 1), i.e., all the samples should be numbered and their sites recorded as well as all other samples taken at the time of operation, i.e. adrenals, lymph nodes and various biopsies.

In Histopathology report, please clearly state all relevant findings and block/slide number (for example, “there is renal sinus invasion in block A7”) as it makes central pathology review easier.

Figure 1. Recommended sampling of renal tumours
**Figure 2.** Mega-cassette and normal-sized cassette

<table>
<thead>
<tr>
<th>In Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Weigh and accurately measure the specimen and tumour (in 3 dimensions)</td>
</tr>
<tr>
<td>- Sample tumour according to the Guidelines (above)</td>
</tr>
<tr>
<td>- Consider using mega-cassettes</td>
</tr>
<tr>
<td>- Take fresh samples for biological studies</td>
</tr>
<tr>
<td>- Assess the percentage of chemotherapy-induced changes</td>
</tr>
<tr>
<td>- Assess the percentages of viable tumour components</td>
</tr>
<tr>
<td>- In your report, clearly state in which blocks the relevant findings are</td>
</tr>
</tbody>
</table>

SEND THE CASE FOR **RAPID CENTRAL PATHOLOGY REVIEW**
Pathology References


Appendix 3. Recommended treatment for Wilms tumours receiving immediate nephrectomy

The recommended management of infants less than 6 months of age with a primary intrarenal tumour is immediate nephrectomy. The infant dose modifications for chemotherapy are as for the main protocol. Risk group assignment in cases treated with immediate nephrectomy is based solely on tumour stage and presence of unfavourable histology (ie anaplasia).

**Staging**
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 stage I and stage II correctly, as these patients receive reduced chemotherapy compared to previous SIOP protocols. Lymph nodes must be adequately sampled at time of nephrectomy (see surgical guidelines). For patients with stage I disease, they must have a CT chest to confirm absence of pulmonary micrometastases (data from the UK suggest that vincristine monotherapy is inadequate in this group and they should be treated with regimen 2, i.e. two drugs).

**Histological classification**
The SIOP histological risk grouping 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.

**Primary Nephrectomy Pathology**
Tumours in italics are non-Wilms tumours and have their own treatment recommendations. The following treatment recommendations apply to Wilms tumours only. Note that mesoblastic nephroma is a benign tumour that usually requires treatment with surgery only. Cases with tumour spillage should be discussed with the national group (CCLG Renal Tumour Interest Group)

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

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

**HIGH RISK TUMOURS**
- *Nephroblastoma – diffuse anaplasia*
- *Clear cell sarcoma and Rhabdoid tumour of the kidney*
Post-operative chemotherapy regimens for Wilms tumours having primary excision

Dose modifications for infants aged <6 months and children <12 kg.

Children <12 kg receive 66% of the doses of all the drugs calculated either by surface area (vincristine and doxorubicin) or per kg (actinomycin D). Children aged <6 months should receive a dose reduction to 50% of standard doses.

<table>
<thead>
<tr>
<th>Regimen 1 (intensive VCR): - Stage I, intermediate risk (excluding focal anaplasia).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine 1.5 mg/m² intravenous bolus (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.</td>
</tr>
<tr>
<td>Note dose modifications above.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen 2 (AV): - Stage II, low and intermediate risk and Stage I, focal anaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine 1.5 mg/m² intravenous bolus (maximum dose 2 mg) weekly for 11 weeks and then three weekly, at weeks 14, 17, 20, 23 and 26 (16 doses in total)</td>
</tr>
<tr>
<td>Actinomycin D 45 ug/kg intravenous bolus (maximum dose 2 mg) at weeks 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total).</td>
</tr>
<tr>
<td>Note dose modifications above.</td>
</tr>
<tr>
<td>Total duration of therapy: 26 weeks.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Regimen 3 (sequential AVD): Stage III intermediate risk (includes focal anaplasia).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine 1.5 mg/m² intravenous bolus (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), plus:</td>
</tr>
<tr>
<td>Actinomycin D 45 ug/kg intravenous bolus (maximum dose 2 mg), 50% dose at week 2* then full dose at weeks 10, 16, 22, 28 (5 doses in total).</td>
</tr>
<tr>
<td>Doxorubicin 50 mg/m² intravenous bolus over 4-6 hours at weeks 7, 13, 19, 25 (4 doses (200 mg/m²) in total).</td>
</tr>
<tr>
<td>Note dose modifications above.</td>
</tr>
<tr>
<td>Flank radiotherapy (15 Gy) to be given weeks 2 – 4.</td>
</tr>
<tr>
<td>Total duration of therapy: 28 weeks.</td>
</tr>
</tbody>
</table>
Stage IV patients with local stage III disease 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 CXR. Subsequent chemotherapy is dictated according to whether or not metastatic complete remission has been achieved by chemotherapy +/- surgery, as per the main protocol recommendations, i.e. complete responders continue the three drug regimen; incomplete responders switch to the high risk post-operative regimen.

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

Diffuse anaplasia

Stages I - IV – use the SIOP ‘high risk’ post-operative chemotherapy regimen according to tumour stage, i.e.

- Stage 1 diffuse anaplasia – regimen AVDloc no radiotherapy
- Stages II and III diffuse anaplasia high risk post-operative chemotherapy HRloc plus flank radiotherapy
- Stage IV diffuse anaplasia – give the stage III, High risk post operative chemotherapy HRloc Lung radiotherapy is given to all stage IV cases with lung metastases, regardless of metastatic response to chemotherapy/surgery.

Mesoblastic nephroma

Mesoblastic nephroma is a benign tumour that usually requires treatment with surgery only for stage I and II tumours. Cases with tumour spillage (stage III) should be discussed with the extended MDT (national group) as chemotherapy is often not indicated, given the very young age of the majority of these patients. In such cases, tumour should be sent for molecular diagnostic studies for the TEL-TRKC translocation that characterises the cellular subtype (testing available through Professor Neil Sebire, Histopathology Dept, Great Ormond Street). Close observation with two monthly ultrasounds for the first year is advised. If chemotherapy is considered, then alternative regimens such as low dose VAC may be indicated.
Flow diagrams for recommended chemotherapy for Wilms tumour cases receiving immediate nephrectomy

Chemotherapy regimens

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

10 weekly injections of vincristine 1.5 mg/m² intravenous bolus (maximum 2mg) as a single agent.

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

11 weekly injections of vincristine, then three weekly for 5 further doses, together with actinomycin D every three weeks starting at week 2 for a total of 9 doses. Total duration of treatment 6 months.
Regimen 3 (sequential AVD): Stage III intermediate risk (including focal anaplasia).

“Sequential AVD”, consisting of 10 weekly doses of vincristine, followed by 6 further doses at three-weekly intervals; actinomycin D 22.5 μg/kg at week 2 just prior to radiotherapy and then at 45 μg/kg at week 10, 16, 22, 28; doxorubicin 50 mg/m² at six weekly intervals alternating with actinomycin D, starting at week 7. Total duration of treatment 28 weeks. Total doxorubicin = 200 mg/m².

| VCR   | 1.5 mg/m² ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ |
| ACT-D | 45 μg/kg ↓ |
| DOX   | 50 mg/m² RT (15 Gy in 10#) ↓ |
| WEEKS | ♦ 1 2 3 4 5 6 7 8 9 |
| Then Weeks | 10................................. 13 |
|         | 16.................................19 |
|         | 22.................................♦25 |
|         | 28 |

* 50% dose of actinomycin D given within 7 days of start and 14 days following radiotherapy

♦ = ECHOCARDIOGRAM. This should be performed prior to the first dose of doxorubicin then at week 25, prior to receiving 200 mg/m² then again at end of treatment (within 3 months of last dose of doxorubicin)
Appendix 4. Radiotherapy Guidelines

AIMS OF RADIOTHERAPY

1. To achieve control of abdominal disease in patients with significant risk of intra-abdominal relapse.

2. To increase control of pulmonary metastases in patients not achieving complete remission following chemotherapy and surgery or those with high risk abdominal tumours in stage IV patients regardless of metastatic response.

3. To increase control of hepatic metastases in patients who do not achieve complete remission following chemotherapy and surgery in intermediate risk tumours or in high risk histology regardless of completeness of metastatic response.

4. To increase control of brain and bone metastases.

5. To increase control of bone metastasis.

TIMING OF RADIOTHERAPY

Whilst the available evidence suggests benefit in commencing RT, when indicated within 2 weeks of nephrectomy, this is often not feasible and so RT should commence as soon as is practicable. Where there is a need to make a decision on the need for RT to the lungs at a later time point than for the flank/abdominal tumour, then it may be safer to postpone the abdominal component of the RT for a few weeks to allow both fields to be planned and given together, to reduce the risk of overlap toxicity. It is therefore essential that all children with Wilms tumours are referred to a clinical oncologist as soon as the initial diagnosis is confirmed, to optimise their subsequent treatment pathway, even though many children will not ultimately require radiotherapy. It is at the discretion of the treating clinical oncologist as to whether to use pulmonary RT (when indicated) concurrently with flank RT. Advantages include adequate management of field overlap and minimisation of number of GAs, disadvantages being early pulmonary irradiation when metastatectomy may be indicated following high risk chemotherapy and also that delaying pulmonary RT until completion of all chemotherapy minimises the risk of chemo/RT interactions and unacceptable acute toxicity.
INDICATIONS FOR RADIOTHERAPY

Post-operative Flank RT indications; (see table 1 & 2 above)
To commence as soon after abdominal surgery as possible unless delayed for pulmonary treatment.

1. Histological intermediate risk, stage III (node +ve, residual disease after surgery, tumour rupture).
2. Histological high risk stage II and III – except stage II blastemal type
3. Stage IV and V disease treated according to local stage.

There is to be NO LYMPH NODE BOOST given for microscopic LN involvement, whether viable or necrotic. However a 10 Gy boost should be considered for areas of bulk residual disease after pre-op chemo that could not be resected (such a situation is rare and should be discussed with the Chair of the renal SIG)

Pulmonary RT indications;

1. Patients with residual pulmonary disease following chemotherapy and/or metatastectomy as visible on Chest X-Ray or CT Scan. Centralised radiology review introduced to standardise disease classification

In case of doubt of the nature of the pulmonary nodule, eg solitary nodule unchanged by preoperative chemotherapy, consider surgical excision prior to a final decision on need for irradiation.

To commence at discretion of treating physician (may be in combination with flank RT)

Whole abdominal RT indications;
Reserved for diffuse abdominal disease or gross pre or peri-operative rupture

Hepatic RT indications;
Inoperable residual lesions following chemotherapy or in case of high risk histology regardless of completeness of response

Other metastatic sites;
Brain (whole brain RT) and Bone regardless of chemotherapy response
TARGET VOLUME

SIMULATION/LOCALISATION

All patient should undergo localisation using a CT-simulator. It may be possible to electronically fuse the pre-operative CT scan images with planning CT scan images to assist with target volume definition. Placement of reference tattoos should be as per local departmental policy.

Target Volumes are defined according to ICRU 50 and ICRU 62 guidelines (1).

CLINICAL TARGET VOLUME (CTV)

Localisation of primary tumour and kidney for flank/abdominal RT

For RT planning the pre-operative (post-chemotherapy) tumour extent should be localised according to the pre-operative cross sectional imaging.

The boundaries of the tumour and kidney are generally no longer marked during surgery although surgeons are encouraged to use clips to mark areas of concern regarding residual microscopic or macroscopic disease.

The pre-operative scan should be used to re-construct the tumour volume on the planning CT scan and could usefully be labelled as GTV Tu Bed. The surgical notes and histopathological reports can provide further valuable information at the RT planning stage.

A GTV to CTV margin of one cm should be taken superior, lateral and inferior of these clips.

The medial border should be extended to encompass the full width of the vertebral bodies.

In the case of pre-operative or intra-operative rupture the anatomic location and the intra-abdominal space (intra/retro-peritoneal) should be clearly indicated in the surgical note and drawing. Infiltration into the peri-renal fat, involved lymph nodes, macroscopic incomplete resection, microscopic or macroscopic ruptures have to be stated clearly.

If macroscopic tumour is left behind a post-operative scan may be performed to delineate the tumour.

Boosts for residual macroscopic disease

CTV should encompass the extent of macroscopic residual disease after surgery with a margin of 1 cm. Nodal boosts are no longer performed as long as the involved lymph nodes have been excised. If there is an indication for RT of the paraaortic lymphnodes the cranial field border should be at the thoracic vertebra T-10-TV-11 level while almost 50% of the coeliac axis arises from the aorta at the level of the pedicle of the 12th vertebral body. Again the full width of the vertebral bodies should receive a homogeneous dose.
Whole abdominal RT
CTV includes the entire abdominal contents and peritoneum extending from the dome
of the diaphragm to the pelvic floor (lower border of obturator foramen).

Pulmonary RT
CTV encompasses both lungs including the apices and costo-diaphragmatic recesses.
If abdominal radiotherapy also has to be given, both fields should be matched in order
to avoid any gap or overlap.

Liver RT
CTV includes the extent of incompletely resected tumour with a margin of 2 cm.

RT for brain metastases
CTV includes the whole brain

RT for haematogenous metastases to bone
CTV: For bone metastases it is not necessary to treat the entire bone. The field
includes the obvious disease visible on imaging examination, with a margin of not less
than 3 cm in any direction.

PLANNING TARGET VOLUME (PTV)
Margins for PTV will be influenced by individual departmental policy. In general the
margins that will be applied will be as follows:

CTV to PTV margin 1cm in all directions. Care may be taken to reduce cardiac
irradiation for left-sided tumours, and avoid irradiation to the remaining (contralateral)
kidney. These decisions are taken on an individual basis by the treating clinical
oncologist
Especially for left sided tumours RT of the heart should be avoided if possible.

ORGAN AT RISK VOLUMES (ORV)
It is considered good practice to contour and calculate dose-volume histograms
(DVHs) for:
- Contralateral kidney, dose to the contralateral kidney should not exceed 12 Gy.
- Liver, dose to the whole liver should not exceed 19 Gy, 21 Gy is acceptable for
  one lobe.
- Heart (left sided tumours)
- Breast tissue (female patients)
- Gonads (low-lying tumours).
- Lung V20 should be less than 25%/Mean Lung Dose should be less than 5 Gy.
  (if lungs irradiated)
- Thyroid if lungs irradiated
TREATMENT DOSE

Prescription Point: the mid-plane of the central axis for parallel-opposed fields (ICRU 50 definition).

Flank RT:

Total dose is dependent on stage and pathology. Fraction dose is conditioned by the age of the child and the volume encompassed.

**Stage III intermediate risk:** 14.4 Gy, boost to the macroscopic residual disease after surgery: 10.8 Gy (giving a total dose of 25.2 Gy).

**Stage II, stage III, high risk:** 25.2 Gy

Whole abdominal RT:
The entire peritoneal cavity should be irradiated to a maximum of 21 Gy, with consideration of a boost to a limited area (as for flank RT). The remaining (contralateral) kidney should be shielded at 12Gy. Dose per fraction should be lowered to 1.5 Gy. In children under one year of age total dose should be reduced to 10-12 Gy.

Brain RT:

The whole brain is treated to a dose of 25.5 Gy. A small boost may be given (4.5 Gy) at the discretion of the treating clinical oncologist.

Liver RT:

A dose of 20 Gy may be given to the area of R1 resection of metastases.

Bone RT:

For bone metastases the metastasis may be treated with a dose of 30 Gy.

Pulmonary RT:

For whole lung RT the total dose is 15 Gy for both lungs (with correction of tissue heterogeneity). The dose per fraction is 1.5 Gy delivered within 10 treatment days. A boost of 5-10 Gy could be considered for areas of gross residual disease after surgery. This would be dependent on the volume of the residual disease and should not allow the V20 to exceed 25% and the mean lung dose to exceed 5Gy.
TIME DOSE CONSIDERATIONS

Daily dose

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.

Flank RT

The dose per fraction is 1.8 Gy, but may be lowered when large volumes are treated (e.g. whole abdomen).

Total abdominal RT

The dose per fraction is 1.5 Gy, but may be lowered to 1.25 Gy in case of toxicity and very young children (< 2 years).

Whole lung RT

The dose per fraction is 1.5 Gy (with inhomogeneity correction).

Brain RT: The dose per fraction is 1.5 Gy.

Liver RT: The dose per fraction is 1.5 Gy.

Bone metastases: The dose per fraction is 3 Gy.

Number of fractions per day

Daily fraction, five days per week, Monday-Friday.

Rests/ Interruptions

Rests must be kept to an absolute minimum. Interruptions to treatment machine service and public holidays must be avoided unless absolutely necessary.

Interruptions for myelotoxicity

RT should be interrupted if the neutrophil count falls below 0.5 x 10^9/l and should not be resumed until the count is at least 1.0 x 10^9/l.

RT should be interrupted if the platelet count falls below 25 x 10^9/l and should not be resumed until the count is at least 50 x 10^9/l.

The haemoglobin level should be maintained at a minimum of 10 g/dl during RT with correction by transfusion if necessary.

G-CSF may be used in the case of the neutrophil count falling below 0.5, and continued until it is greater than 1.0.
Radiotherapy References


Taylor RE. Morbidity from abdominal radiotherapy in the First United Kingdom Children's Cancer Study Group Wilms Tumour Study. United Kingdom Children's Cancer Study Group. Clinical Oncology (Royal College of Radiologists), 1997, vol./is. 9/6(381-4), 0936-6555;0936-6555 (1997)


Paulino AC. Relapsed Wilms tumor: is there a role for radiation therapy?. American Journal of Clinical Oncology, August 2001, vol./is. 24/4(408-13), 0277-3732;0277-3732 (2001 Aug)


ICRU Report 50 and 62. International Committee on Radiation Units and Measurements. ICRU Publications, 7910 Woodmont Avenue, suite 800, Bethesda+
Appendix 5. Dose Modifications and Toxicity

a. Adjustment of dose to body weight and for age < 6 months
Children with a body weight of less than 12 kg will have a dose reduction to 66% of the original dose of all drugs, mainly to reduce the risk of veno-occlusive disease. Children aged less than 6 months receive all drugs at 50% doses.

b. Radiation
If liver or large fields such as the entire abdomen, the entire thorax or both are irradiated, actinomycin D should be avoided during radiotherapy and any dose given within a week prior to commencing radiotherapy or within two weeks following end of radiotherapy should be reduced to 50% in all patients.

c. Toxicity
1. Haematological toxicity
- Neutropenia: absolute neutrophil count (ANC) has to be > 1.0 x 10⁹/l to start a course with actinomycin D or doxorubicin.
  Vincristine when given alone may be continued without taking the ANC into account if the patient is clinically well.
- Thrombocytopenia: platelet count has to be > 100 x 10⁹/l to start a cycle. Chemotherapy should be interrupted if the platelet count falls below 50 x 10⁹/l and in case of 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.
- Anaemia alone should be treated by transfusion if necessary (Hb 7 g/l) but is not an indication to modify the treatment schedule.

If a course of treatment results in a nadir of WBC count below 1500/mm³ or in a nadir of ANC below 1000/mm³, associated with mucositis and/or fever or if a nadir of platelet count below 50,000, associated with marked enlargement of the liver and or haemorrhages: The doses on the next course should be reduced to 2/3 and if the next course of chemotherapy is well tolerated full doses will be tried again in subsequent ones.

2. 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.
- Diarrhoea with or without vomiting particularly occurs after irradiation of the whole abdomen of young children. This may require the treatment to be withheld for a few days and sometimes irradiation has to be abandoned. Antispasmodics, intestinal antiseptics and intravenous fluids have to be given as required.
- Constipation is common with vincristine. The drugs should be omitted in case of paralytic ileus and restarted at a 50% dose.
3. Hepatic complications
May occur at any time during treatment and is generally related to Actinomycin D treatment. Risks are increased for tumours of the right kidney and irradiation of the whole abdomen and associated doxorubicin. Patients with signs of liver dysfunction should be monitored carefully. Patients with severe liver disease (VOD) should not be given actinomycin D until the main abnormalities have returned to normal. Alternative chemotherapy agents should be considered or cautiously re-introduce actinomycin D at half the dose and escalated thereafter if felt appropriate. If the symptoms reappear during actinomycin D treatment, this drug should be withdrawn permanently. Vincristine may also enhance hepatopathy.
If there are problems in interpreting or applying the protocol in children with hepatic disease, the CCLG Wilms Tumour Group Chairman should be contacted in writing for advice.

4. Exposure to infection with varicella or herpes
Patients who develop varicella or herpes should receive Aciclovir and chemotherapy should not be restarted until one week after the resolution of the rash.

5. Cardiac toxicity
There are no generally accepted guidelines available on which dose modification of doxorubicin can be based. There is some evidence that by the use of a 24 hour continuous infusion schedule, the risk of long term cardio-toxicity may be reduced. Monitoring with echocardiography should be done before the first administration of Doxorubicin, prior to 200 mg/m² cumulative dose and, for localised disease patients, at end of treatment (within 3 months of the last anthracycline dose). For patients with stage IV disease or those receiving the high risk protocol, echocardiography should be performed before the first administration of Doxorubicin and repeated prior to 200 and 300 mg/m² cumulative dose (i.e. prior to the doses scheduled at weeks 19 and 31) and again, at end of treatment (within 3 months of last anthracycline dose). Dose modification must be considered if fractional shortening falls below 28% or a reduction of > 10% is seen. If this occurs, do not delay chemotherapy but give 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 stop doxorubicin until the fractional shortening has normalized.
Cardiac toxicity is more likely 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 the End Systoli wall Stress*, as an evaluation of increasing afterload, seen as a consequence of the wall muscle thinning, due to myocyte killing.
6. 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 injection of vincristine should be omitted and the next dose decreased to 2/3.

7. Bladder and renal toxicity
Cyclophosphamide can cause haemorrhagic cystitis if the details for its prescription are not met. For haemorrhagic cystitis, the treatment is only stopped if haematuria is macroscopic and repetitive. In the case of haemorrhagic cystitis: to increase diuresis a diuretic may be added: furosemide (Lasix) (0.5 mg/kg) 2 and 6 hours after the injection. Mannitol is also used under these circumstances
Appendix 6. Drug Administration

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, to avoid veno-occlusive disease.

a. Actinomycin D, Vincristine
   Are usually given directly into the vein without the use of an infusion, care should be taken to establish a good veno-puncture as, if extravasation occurs during injection, severe pain and tissue necrosis will occur. A method often used is to test the correct position of the needle in the peripheral vein by injections of physiological saline and by flushing the needle afterwards in the same way.

b. Doxorubicin
   In order to minimise cardiac toxicity, it is generally agreed that doxorubicin should be given by prolonged intravenous infusion. There is not yet sufficient evidence that prolonging infusion beyond six hours is advantageous in further reducing toxicity, although it is possible that this will be the case. It is recommended therefore that each dose of doxorubicin be given by a slow intravenous infusion over a period of not less than 4 hours according to local policy. Regular monitoring with echocardiography is recommended during and after therapy (see 8.35 cardiac toxicity). Central venous access is mandatory.

c. Etoposide (VP-16)
   Etoposide is made up in normal saline and should be infused over a period of 2-4 hours depending on volume. Concentrations > 0.5 mg/ml may precipitate before administration. The preferred concentration of this drug is 0.4 mg/ml. If more than 100 mg is to be given, this means that the total amount of infusion fluid is more than 250 ml. If given in less than 4 hrs one should pay attention to this. No additional hydration is required for etoposide itself.

d. Carboplatin
   The drug is dissolved in 100 - 250 ml glucose 5% solution (maximum dilution 0.5 mg/ml) and given over 1 hour.

e. Cyclophosphamide
   The drug is reconstituted with sterile water to a concentration of 20 mg/ml and should be administered as an IV infusion over 60 minutes. Each dose must be accompanied by mesna and hydration to prevent bladder toxicity when given at this total dose per course (see under Mesna). Although at this daily dose, outpatient administration is theoretically possible providing the patient can maintain adequate hydration (at least 2 l/m2/24hrs), there is limited experience in the UK with oral Mesna in children, particularly uninephric children. We therefore recommend that this course is given as an inpatient. If the child is adequately hydrated on admission, IV hydration fluids may commence immediately prior to the infusion of the first dose of cyclophosphamide. IV hydration should continue at a rate of 2 l/m2/24hrs until 12 hrs after completion of the last cyclophosphamide infusion.

f. Mesna

Clinical Management Guidelines: Wilms Tumour
January 2015 (rev March 2018)
g. **G-CSF**
G-CSF at a dose of 5 μg/kg is administered once daily, either subcutaneously or as a 30 minutes i.v. infusion.