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SECTION 1
AIMS AND OBJECTIVES

The Nephroblastoma clinical trial and study SIOP 2001 continues the philosophy of the former SIOP studies and is based on international collaboration for the collection of reliable data which can be used to answer questions of direct clinical relevance to patients.

1.1 SPECIFIC OBJECTIVES FOR SIOP 2001

1. To continue a risk-adapted stratification of therapeutic intensity, incorporating response to pre-operative chemotherapy, in all children with Wilms tumour and other renal tumours of childhood.

2. To test the treatment hypothesis that doxorubicin is not necessary in patients with intermediate risk tumours and local stage II or III by a multicentre prospective randomised trial.

3. To determine prospectively the prognostic significance of specific histological subtypes following pre-operative chemotherapy, as specified in the protocol. In particular, the study aims to:
   ♦ confirm the adverse prognostic significance of the blastemal predominant subtype and whether this can be offset by intensifying therapy and
   ♦ investigate the hypothesis that the epithelial and stromal-predominant subtypes have a favourable prognosis and
   ♦ investigate the prognostic significance of the percentage necrosis after pre-operative chemotherapy in relation to the type and amount of residual viable tumour.

4. To minimise acute and late toxicity without jeopardising event free and overall survival by reducing treatment for:
   ♦ patients with focal anaplasia, and
   ♦ patients with stage I, intermediate risk tumours.

5. To determine prospectively the prognostic significance of tumour volume following pre-operative chemotherapy and its relation to histological subtype.

6. To determine prospectively the prognostic significance of specimen weight at time of nephrectomy and its relation to histological subtype.

7. To reduce the number of drug administrations, hospital visits and thereby costs in the preoperative phase.
1.2 AIMS FOR THE BIOLOGICAL STUDY

1. To correlate allele loss at 16q, 1p and other chromosomal regions of interest with relapse-free and overall survival of children with Wilms tumour treated within the SIOP 2001 nephroblastoma trial and study.

2. To correlate the above allele losses with clinical risk factors defined following pre-operative chemotherapy (i.e. histological appearance and tumour volume).

3. To establish, on a national basis, a Wilms tumour biological samples bank containing frozen tumour and normal kidney and/or blood, that will be available to conduct further research into molecular prognostic factors and Wilms tumour biology.

4. To evaluate prospectively laboratory indicators of myocardial damage.
Cure rates of nephroblastoma have been increasing all over the world. This is largely due to good co-operation between multidisciplinary teams in several parts of the world. For Europe and some countries outside the continent, the SIOP studies have been the key to developing treatment strategies. For North America, this has been the National Wilms' Tumor Study Group (NWTSG). Other national groups such as the United Kingdom Children's Cancer Study Group (UKCCSG) and the Brazilian Wilms' Tumor Study Group have also contributed to the now outstanding results. A schematic summary of the design and results of the most important studies follows.

### 2.1 SIOP STUDIES

**SIOP 1**  
This study ran from September 1971 to October 1974 and registered 398 patients. There were two randomized questions about the role of pre-operative radiotherapy and duration of postoperative chemotherapy.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>RT - S - RT</td>
<td>4% ruptures (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31% stage 1</td>
</tr>
<tr>
<td>S - RT</td>
<td></td>
<td>32% ruptures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14% stage 1</td>
</tr>
<tr>
<td>Surgery</td>
<td>R</td>
<td>no difference in DFS/S</td>
</tr>
<tr>
<td></td>
<td>Act-D 1 course</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Act-D 6 courses</td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** Pretreatment reduces the number of ruptures and produces a more favourable stage distribution after surgery. There is no evidence that prolonged Act-D post-operatively contributes to a better disease free survival and/or survival (1).
SIOP 2
This study ran from October 1974 to December 1976 and registered 138 patients. It was a non-randomized study to confirm the findings of SIOP 1.

<table>
<thead>
<tr>
<th>Outline of the study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months</td>
<td>DFS/S equal</td>
</tr>
<tr>
<td>VCR added. to Act-D postop</td>
<td></td>
</tr>
<tr>
<td>15 months</td>
<td></td>
</tr>
<tr>
<td>Preop. RT</td>
<td>5%</td>
</tr>
<tr>
<td>Ruptures</td>
<td>(p=0.0025)</td>
</tr>
<tr>
<td>Primary surgery</td>
<td>20%</td>
</tr>
<tr>
<td>Various reasons:</td>
<td></td>
</tr>
<tr>
<td>e.g. small tumours</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions:
It is not necessary to give a two drug combination for more than 9 months postoperatively. Beware of the temptation to operate on small tumours!

SIOP 5
This study ran from January 1977 to July 1979 and registered 433 patients.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis R</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>No difference between the two gps for tumour rupture or stage distrib.</td>
</tr>
<tr>
<td>(VCR/ActD x 4wks)</td>
<td></td>
</tr>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>(+ 1 course of Act-D)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions:
Chemotherapy is comparable to radiotherapy in efficacy of preparing the tumour for surgery. Due to fewer late effects, it is preferable to use chemotherapy rather than radiotherapy (2).

SIOP 6
This study ran from July 1980 to October 1987 (except for stage IIN0 patients in whom the stopping rule was activated in April 1986). 1095 patients were registered. There were three randomized questions regarding reduction of post-operative treatment: the duration (stage I) or need for an anthracycline (stages IIN+/III) in post-operative chemotherapy and the need for radiotherapy in stage IIN0.
### Randomization and Outcome

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIN0</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:**
After pre-operative chemotherapy and surgery, 17 weeks is as effective as 38 weeks post-operative chemotherapy with VCR + ActD in stage I patients (2yr DFS 92% v 88%, n.s.). In stage IIN0, the stopping rule was activated due to an apparent increase in abdominal relapses in the non-irradiated group. However, in the final analysis, this was not confirmed, with a 2 yr DFS of 72% v 78% for stage IIN0 patients receiving (n = 64) or not receiving (n = 59) radiotherapy. For stage IIN+/III patients, the doxorubicin arm had a better 2 yr DFS (74% v 49%) but equivalent 5 yr OS (80% v 77%) (3). However, other factors such as overall chemotherapy dose intensity may have explained this difference – the intensive VCR arm received ActD only every 7 – 9 weeks (total of 6 courses over 40 wks) whereas the DOX arm received doxorubicin every 3 weeks during the first 15 weeks (6 courses) of post-operative treatment (total of 11 courses over 38 wks).

**SIOP 9**
This study ran from November 1987 to November 1991 and registered 852 patients. 382 patients with eligible localised tumours were randomised for duration of pre-operative chemotherapy.

### Randomization and Outcome

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (4 weeks)</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:** 4 weeks is equivalent to 8 weeks pre-operative chemotherapy for localised tumours in terms of proportion of stage I (64% v 62%), intra-operative rupture rate (1% v 3%), 2yr EFS (84% v 83%) and 5yr overall survival (92% v 87%) (4).
SIOP 93-01  This study ran from July 1993 to August 1999 and had registered 1104 patients by December 1998. The study asked a randomised question about the duration of postoperative chemotherapy in stage I tumours with intermediate risk histology or anaplasia.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT – S</td>
<td></td>
</tr>
<tr>
<td>Risk. +</td>
<td>As far as data are available</td>
</tr>
<tr>
<td>CT - R</td>
<td>(1999) equivalence between</td>
</tr>
<tr>
<td>Anaplasia</td>
<td>both arms for DFS/S</td>
</tr>
<tr>
<td></td>
<td>No further therapy</td>
</tr>
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</table>

Conclusions: A further reduction in duration of postoperative chemotherapy, from 18 to 4 weeks appears to be safe in this group of patients. The results are preliminary. Potential prognostic markers have been identified from a careful evaluation of histological appearance and tumour volume reduction following preoperative chemotherapy.

2.2 NATIONAL WILMS TUMOUR STUDY GROUP

NWTS 1  This study ran from October 1969 to December 1973 and registered 606 patients.

<table>
<thead>
<tr>
<th>Outline of the study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT – Act-D</td>
<td>Patients over two years</td>
</tr>
<tr>
<td>Act-D</td>
<td>have a barely significant better</td>
</tr>
<tr>
<td>Act-D</td>
<td>RFS in the RT arm</td>
</tr>
<tr>
<td>VCR</td>
<td>The 2-drug combination is</td>
</tr>
<tr>
<td>Act-D + VCR</td>
<td>significantly better for</td>
</tr>
<tr>
<td></td>
<td>RFS (p=0.002)</td>
</tr>
<tr>
<td>VCR-S</td>
<td>No indication that pre-op. therapy</td>
</tr>
<tr>
<td>Group IV</td>
<td>RT – Act-D + VCR improves patients’ survival</td>
</tr>
<tr>
<td>diagnosis</td>
<td>(but very small numbers!)</td>
</tr>
</tbody>
</table>

Conclusions: Post-operative radiotherapy is effective for selected patients. The combination of VCR and Act-D is better than either drug alone. No evidence for a role of preoperative VCR, but too small numbers to be conclusive (5).
NWTS 2  The study ran from January 1975 to July 1978 (group I from October 1974) and registered 775 patients.

<table>
<thead>
<tr>
<th>Outline of the study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>Act-D + VCR 6 months&lt;br&gt;Act-D + VCR 15 months</td>
</tr>
<tr>
<td>Group II, III, IV</td>
<td>Act-D + VCR</td>
</tr>
</tbody>
</table>

**Conclusions:** There is no indication that prolonged postoperative treatment is of any value. Doxorubicin is an effective drug in Wilms’ tumour (6).
**NWTS 3**

This study ran from May 1979 to May 1985 (November 1985 for stage I, FH) and registered 2496 patients.

<table>
<thead>
<tr>
<th>Design</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group I</strong></td>
<td></td>
</tr>
<tr>
<td>Act-D + VCR 10 weeks</td>
<td>Equivalence</td>
</tr>
<tr>
<td>Act-D + VCR 6 months</td>
<td></td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td></td>
</tr>
<tr>
<td>No RT</td>
<td>Act-D + VCR + DOX</td>
</tr>
<tr>
<td>RT 20 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Equivalence</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group III</strong></td>
<td></td>
</tr>
<tr>
<td>RT 10 Gy</td>
<td>Act-D + VCR + DOX</td>
</tr>
<tr>
<td>RT 20 Gy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sign. diff. (p=0.04)</td>
</tr>
<tr>
<td></td>
<td>in RFS for 3 drug arm</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>UH, any stage</td>
<td>RT – Act-D + VCR + DOX</td>
</tr>
<tr>
<td>FH + UH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CPM does not improve</td>
</tr>
<tr>
<td></td>
<td>results</td>
</tr>
</tbody>
</table>

**Conclusions:**

It is shown that in low-stage tumours, postoperative chemotherapy could be further shortened. Radiotherapy, if necessary, does not have to be of high dose. Doxorubicin adds to the effect of the well known two drug combination. Addition of cyclophosphamide as a fourth drug does not lead to any further improvement in survival (7).

**NWTS 4**

The study ran from August 1986 to September 1994 and 905 previously untreated children were randomized, either for duration of treatment and/or for single dose versus divided dose of drug administration. This study was to evaluate the efficacy, toxicity and costs of the administration of different regimens for the treatment of WT.

**Conclusions:**

The short administration (6 months) for the treatment of children with WT is no less effective than the long one (15 months) and can be administered at a substantially lower total treatment cost (8).
2.3 UNITED KINGDOM WILMS TUMOUR STUDIES

UKW1  This study ran from 1980-86 and recruited 384 patients (~80% of all UK cases of Wilms tumour). Immediate nephrectomy was recommended for all non-metastatic tumours. Aims were 1) to reduce treatment for low stage, FH disease (omit RT for stage I, omit doxorubicin and reduce dose RT for stage II, without impairing survival, and 2) to intensify treatment for stage III and IV and for UH tumours to improve survival.

<table>
<thead>
<tr>
<th>Outline of study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (n=104)</td>
<td>single agent VCR x 26 wks, omit RT 89% 6yr EFS, 96% OS.</td>
</tr>
<tr>
<td>Stage II (n=54)</td>
<td>two drugs VCR/ActD x 26 wks, RT 85% 6yr EFS, 93% OS</td>
</tr>
<tr>
<td>Stage III (n=106)</td>
<td>Sequential VA + DOX x 1 yr, RT 82% 6yr EFS, 83% OS</td>
</tr>
<tr>
<td>Stage IV (n=40)</td>
<td>VA + DOX + cyclo x 1yr, lung RT only if no remission at wk 12. 50% 6yr EFS, 65% OS</td>
</tr>
</tbody>
</table>

Conclusions: Outcome for FH stage I disease equivalent to NWTS 2 – 4 and avoids use of ActD. Similar outcome to NWTS 2 & 3 for stage II and III tumours suggests pulsed ActD is as effective as fractionated regimen. Inferior results for stage IV disease may be due to small number receiving RT (4/40) compared to NWTS approach (9).

UKW2  This study ran from 1986-91 and recruited 448 patients (> 90% of all UK cases of paediatric Wilms tumour). Immediate nephrectomy was recommended for all non-metastatic tumours. Aims were 1) to further reduce treatment for low stage, FH disease by reducing duration of VCR to 10 weeks for stage I and omitting RT for stage II disease, 2) to improve outcome for stage IV, primary ‘inoperable’ and UH tumours by intensifying chemotherapy with simultaneous administration of ActD and DOX (“intensive AVD”).

<table>
<thead>
<tr>
<th>Outline of study</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I (n=136)</td>
<td>VCR x 10 wks 87% 4yr EFS, 94% OS.</td>
</tr>
<tr>
<td>Stage II (n=57)</td>
<td>two drugs (VA) x 26 wks, no RT 82% 4yr EFS, 91% OS</td>
</tr>
<tr>
<td>Stage III (n=122)</td>
<td>Sequential VA + DOX x 1 yr, RT 82% 4yr EFS, 84% OS</td>
</tr>
<tr>
<td>Stage IV (n=60)</td>
<td>intensive AVD x 1yr, lung RT recommended for all 70% 4yr EFS, 75% OS</td>
</tr>
</tbody>
</table>
Conclusions: Excellent outcome for stage I FH maintained with only 10 weekly VCR. Stage II FH requires only 2 drugs (VA) and no RT. Improved stage IV survival but still inferior to NWTS results – may be due to reduced use of RT despite protocol recommendation (only 37/60 received lung RT) (10).

2.4 RATIONALE FOR SIOP 2001

SIOP 2001 is based on the results of the previous SIOP trials and studies as well as on the results of the NWTS protocols. The study design and the logistics of the study were made as simple as possible because of the world wide participation of centres.

2.5 PRE-OPERATIVE TREATMENT
The previous SIOP studies have shown the effectiveness of pre-operative chemotherapy:
♦ by reducing the risk of tumour rupture during surgery
♦ by inducing a favourable stage distribution with 60% stage I patients requiring less post-operative therapy
♦ by selecting "good responders" in stage IV patients.

The use of pre-operative chemotherapy will be continued in SIOP 2001. It will be given to all patients between 6 months and 18 years of age, if imaging studies confirm the diagnosis of nephroblastoma. Based on the now mature results of SIOP 9, 4 weeks preoperative chemotherapy with vincristine and actinomycin D is considered the standard therapy for localised tumours. Patients with metastases at diagnosis will continue to receive 6 weeks preoperative therapy with three drugs, including doxorubicin. The treatment schedules are shown in Sections 6 and 7.

2.6 RISK STRATIFICATION FOLLOWING PREOPERATIVE CHEMOTHERAPY

2.6.1 Post-operative local stage
Regarding SIOP stage and prognosis there is no discrimination between the stage IIN+ and stage III, therefore, in SIOP 2001, a stage IIN+ tumour will be defined as stage III, allowing better comparison between SIOP and NWTSG studies.
2.6.2 Post-operative histological classification

A retrospective analysis of SIOP 93-01 data looking for prognostic factors in localised tumours showed that the histological classification of the tumour as low, intermediate or high risk is more important than tumour stage (compare fig. 1 with figs 3/4). Furthermore the use of pre-operative chemotherapy changes the distribution pattern as well as the prognostic value of the different histological subtypes compared to tumours treated with immediate surgery (Fig. 2). This information can be used as a measure of response to pre-operative chemotherapy and helps to better stratify post-operative chemotherapy according to the individual risk of the patient.
Figure 2

*Distribution of histological subtypes in registered patients from the GPOH subgroup of SIOP 9 and SIOP 93-01 according to the initial treatment.*

A new pathological risk stratification will be used in SIOP 2001 (see section 5). Note that this only applies to tumours treated with preoperative chemotherapy. The new classification is based on the retrospective observations that tumours with persistent viable cells occupying more than two thirds of the tumour and composed predominantly of blastema behave much more akin to diffuse anaplasia than other histologies (figs 3/4).

Figure 3

*Event free survival including all stages for the different histological subtypes of the intermediate risk group. [Inter (rest) includes all intermediate risk tumours without epithelial, stromal and blastemal predominant; panel diagnosis].*
By contrast, there is a suggestion that viable tumours in which the predominant cell type is either epithelial or stromal have a better than average prognosis and may be candidates for further reductions in therapy in the future (fig. 3). The latter potential prognostic factor will be studied prospectively in SIOP 2001 whereas blastemal predominant tumours will move into the high risk group.

Figure 5
Event free survival according to tumour volume after preoperative chemotherapy.
There have been changes to the classifications in all three risk groups. In the low risk tumour group there is only one tumour type: completely necrotic nephroblastoma (cystic partially differentiated nephroblastoma and mesoblastic nephroma, when diagnosed on imaging studies, should be treated with surgery only). The intermediate risk tumour group consists of five types including epithelial, stromal, mixed and regressive type and focal anaplasia. Focal anaplasia has a better prognosis than diffuse anaplasia with an event free survival lying within the range of other intermediate risk tumours and so is treated accordingly. Finally, the high risk tumour group now includes blastemal predominant nephroblastoma as well as diffuse anaplasia.

2.6.3 Tumour volume reduction following pre-operative chemotherapy
This has been identified as a potential prognostic factor in a retrospective analysis of patients from the GPOH subgroup of SIOP 9 and SIOP 93-01 (fig. 6). However, interpretation is complicated by the observation that certain histological subtypes (epithelial and stromal predominant) fail to shrink and yet have a favourable outcome. Hence, the hypothesis that tumour volume might be a useful parameter for response to pre-operative chemotherapy and a predictor of survival will be tested prospectively in SIOP 2001. In order to answer this question, it is mandatory to measure precisely the tumour volume at diagnosis and particularly after preoperative chemotherapy. The measured tumour volume will be correlated to the specimen weight, to find the best and easiest way to measure "tumour volume".

Figure 6
*Tumour volume at diagnosis and after preoperative chemotherapy according to histology.*

2.7 POST-OPERATIVE TREATMENT
Post-operative treatment is given in all patients according to local stage and histology. Only patients receiving preoperative chemotherapy will be stratified according to the new histological classification.

In Germany, tumour volume (> 500 ml) after pre-operative chemotherapy will also be used for stratification of postoperative treatment in intermediate risk tumours, excluding those with epithelial and stromal predominant histology.
From the preliminary results of the randomised question of SIOP 93-01, the short arm of this trial will be used as postoperative treatment for all patients with stage I and an intermediate risk tumour according to the new definition, if they have received preoperative chemotherapy. However these patients will be followed up very carefully because the final analysis is not yet available (see Section 5).

Patients with local stage II and III intermediate risk tumours after surgery and no metastasis at diagnosis will be randomised for postoperative treatment. The randomisation is between chemotherapy with or without Doxorubicin. This randomisation will reduce treatment intensity in about 1/3 of all eligible patients.

The event free survival for these patients in the SIOP 93-01 study is:
- stage II, 88% (80-92) at 2 years (C.I. 95%) and 88% (66-92) at 5 years
- stage III, 78% (66-86) at 2 years and 75% (49-84) at 5 years.

Treatment reduction is also given to all patients with tumours showing focal anaplasia.

Because of their poorer prognosis, patients with a blastemal predominant subtype after preoperative chemotherapy will receive intensified postoperative treatment.

The treatment schedules are outlined in Section 6 and 7.

Postoperative chemotherapy recommendations for patients treated with immediate surgery for whatever reason are given in Appendix 3. They are based on UKCCSG and NWTSG protocols and survival data.

2.8 ADMINISTRATION OF ACTINOMYCIN D
In NWTS 4 it was clearly shown that a single dose of actinomycin D of 45 µg/kg body weight is as efficient as giving actinomycin D in divided doses. This way of administering the drug is therefore recommended as the new standard, resulting also in less severe haematologic toxicity and the requirement for fewer physician and hospital encounters (11).

2.9 ANTHRACYCLINE THERAPY
Anthracyclines are potentially cardiotoxic drugs. The risk of cardiotoxicity is dependent on the total cumulative dosage and the infusion duration as well as the type of anthracycline used. In SIOP 9 and 93-01, with the exception of the German centres, epirubicin was used. A comparison regarding efficacy and toxicity of the two drugs will be made. Regarding the early cardiotoxicity of doxorubicin, a retrospective analysis of GPOH patients from studies SIOP 9 and 93-01 has been completed. Post-therapy left ventricular fractional shortening was reduced in this analysis in 4 out of 157 (2.5%) patients. Two of the 4 children had clinically reduced tolerance to exercise and received anticongestive therapy. Abnormal ECG findings that were not detectable prior to therapy were found in 7/124 children. This incidence is low although it may increase with longer term follow up. These data suggest it is possible to use the less expensive drug doxorubicin for all patients without increasing the risk of cardiotoxicity.

Because cardiotoxicity is one of the most severe late effects, further reduction of this drug for patients with Wilms tumour is worthwhile. The better risk stratification of patients according to their histological subtype allows us to ask again a randomised question on the role of doxorubicin in the postoperative treatment of stage II and III intermediate risk patients. The risk of a slightly poorer outcome for the "Non-Doxorubicin" arm is deemed acceptable in this
setting (12). It should be noted that both of the previous randomised studies that attempted to address this question for stage III patients (SIOP 6 and NWTS3) had relatively small numbers of patients in each arm. Although early disease free survival showed a significant advantage to the inclusion of doxorubicin, there was no difference in overall survival at long term follow up. Furthermore, in SIOP 6, there were other differences in postoperative treatment intensity that may have accounted for the apparent benefit of doxorubicin. In NWTS3, the advantage of doxorubicin was only seen in stage III patients receiving reduced dose (10 Gy) radiotherapy whereas patients in SIOP 2001 will continue to receive a somewhat higher dose (15 Gy).

A reduction of cardiotoxicity in SIOP 2001 could also result from prolonging the infusion time from 4 to a minimum of 6 hours and by stopping anthracyclines in all patients after a cumulative dose of 300 mg/m² (Only necessary in stage IV patients).

2.10 HIGH RISK PROTOCOL
The toxicity of the high risk protocol of SIOP 93-01 was high. In 60 % of GPOH patients receiving this protocol, treatment violations were observed because of toxicity. Haematological toxicity was especially high. At least 4 patients received G-CSF after every treatment cycle. Delays to therapy were also common and in nearly all patients the total duration of therapy was significantly prolonged (fig 7). Nine patients had their treatment stopped prematurely, 5 due to toxicity and 4 due to progressive disease.

Figure 7 shows the duration of the protocol for the 82 documented high risk patients of GPOH.

Figure 7: Duration of the high risk protocol in 82 GPOH patients.

Therefore the schedule of the high risk protocol is changed. VP16 and carboplatin are given over 3 days with reduced dosages (VP16: 5 x 100 mg/m² à 3 x 150 mg/m²; CARBO: 600 mg/m² à 3 x 200 mg/m²).

Ifosfamide is substituted by cyclophosphamide, because of the potential risk of tubular damage to the remaining kidney. The dosage of the anthracycline is unchanged but the infusion time is prolonged. After a cumulative dose of 300 mg/m², no further anthracyclines are given.

Because treating patients according to the protocol ends up with a significantly higher event free survival, the percentage of Protocol patients should be as high as possible. This is also of importance, because of the fact that treatment reduction might be at the limit, where further reduction can harm patients.
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1. Preoperative versus postoperative radiotherapy, single versus multiple courses of Actinomycin D in the treatment of Wilms' tumor. Preliminary results of a controlled clinical trial conducted by the International Society of Paediatric Oncology (SIOP).

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5. The Treatment of Wilms' Tumor. Results of the National Wilms' Tumor Study.
D'Angio G.J. et al.
Cancer, 38, 1976, 633-646.


7. Treatment of Wilms tumor. Results of the Third National Wilms Tumor Study.
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SECTION 3

STUDY DESIGN AND PATIENT SELECTION

3.1 STUDY DESIGN
This is a multi-centre study with centres mainly from Europe, but also from other parts of the world. It includes prospective single arm studies and prospective randomised trials for stage II and III, intermediate risk patients. Furthermore, there are groups of patients with bilateral tumours and nephroblastomatosis for whom the intention is to diagnose and treat them according to proposals made by the committee and to prospectively follow these patients to find out more about their behaviour, prognostic factors, treatment results, etc. For specific design of all the treatment arms see section 6, 7 and appendices 4, 5 and 6.

3.2 INCLUSION AND EXCLUSION CRITERIA

All renal tumours
At diagnosis all patients with a renal tumour have to be registered. At this time they are divided into:
- localised disease patients
- metastatic disease patients
- simultaneous bilateral tumour patients

3.2.1 Localised disease patients
These patients are eligible for the protocol if:
1. Age: more than 6 months or less than 18 years at time of diagnosis.
2. Unilateral tumour with clinical and ultrasonic characteristics compatible with nephroblastoma or with a biopsy proven histological diagnosis.
3. No previous anti-tumour treatment.
4. No metastasis.
5. Written informed consent and national ethical committee approval.

3.2.2 Metastatic disease patients
These patients are eligible for the protocol if:
1. Age: any age up to 18 years.
2. Unilateral tumour with clinical and ultrasonic characteristics compatible with nephroblastoma or with a biopsy proven histological diagnosis.
3. No previous anti-tumour treatment.
5. Written informed consent and national ethical committee approval.

3.2.3 Simultaneous bilateral tumour patients
These patients are treated according to the recommendations for patients with bilateral tumours at diagnosis. They will be followed prospectively.
3.2.4 Protocol patients
All localised and metastatic patients that fulfil the criteria to be eligible for the SIOP 2001 protocol. They will be treated according to the treatment principles set out in this protocol.

3.2.5 Patients eligible for randomisation
These are protocol patients that turn out to be stage II / III, intermediate risk histology, after a pretreatment according to the protocol and after the operation and are randomized to receive a treatment according to one of the randomization arms.

For Randomisation Instructions see Appendix 2.

3.3 STUDY PATIENTS
All other patients that do not fulfil the eligibility criteria of the protocol and those for whom there is no strict protocol available are study patients. They are excluded from the protocol. More precisely these exclusion criteria are:
1. Under 6 months or over 18 years old at the time of diagnosis.
2. Bilateral tumours (stage V) with or without metastases.
3. Renal tumours other than Wilms tumour diagnosed at registration.
4. Patients who are unable to follow the protocol for reasons of associated pathology or social, geographical problems or when follow-up is not possible.
5. Patients who have already been given radiotherapy or chemotherapy other than stated in the protocol before surgery or patients referred to the centre after surgery.
7. Surgical emergency or immediate surgery for whatever reason.
8. Doubt in diagnosis after relevant investigations and operated as a consequence (relevant investigations include needle biopsy if necessary).

However, these patients will be documented by:
- Form 1, Registration Form.
- Form 3A, Operative findings Form.
- Form 3B, Surgery related complications Form.
- Form 4, Pathology Form and the histological sections.
- Form 14, Follow-up Form.
SECTION 4

/PRE-TREATMENT INVESTIGATIONS

The following investigations are the minimum required observations and the results should be recorded in the patient’s personal file.

4.1 PHYSICAL EXAMINATION
1. Weight and height
2. Side and size of the tumour (see also ultrasonography)
3. Size of the liver (axillary/mammilla/midline)
4. Blood Pressure
5. Suspect lymph nodes or other masses
6. Congenital anomalies (e.g. aniridia, hemihypertrophy, urogenital malformations and other).

4.2 LABORATORY EXAMINATION
1. Hemoglobin, Ht
2. WBC and platelet count
4. Urinanalysis: Presence or absence of protein, white and red cells. Verify that urinary excretion of catecholamine (HVA VMA DOPA) is normal.

4.3 RADIOLOGICAL EXAMINATIONS
1. Ultrasonic examination of abdomen is mandatory
   It is simple, fast and non invasive. It can help distinguish between a cyst and a tumour and is very helpful in detecting small tumours on the opposite kidney, tumour thrombi in the inferior vena cava, liver and abdominal metastases. Size of the renal mass, tridimensional, should be measured on two occasions, first before initial treatment and second, following completion of preoperative chemotherapy, immediately prior to surgery. It is the first choice investigation in cases of suspected WT. One should try to measure just the tumour and not the whole kidney. It should be clearly stated how the tumour was measured (see form 1).
   Separate masses should be measured separately and this should be clearly stated on the forms. The pre-operative measurements should be taken just before surgery and correlated to the weight of the specimen.
   
   \[ V = a \times b \times c \times 0.523. \quad \text{units} = \text{cm}^3 \]

2. CT-scan of the abdomen
   May be helpful if ultrasound gives insufficient information and in case of doubtful anomalies in the contralateral kidney or liver.

3. P.A. and lateral views of the chest should be done as a routine in order to detect pulmonary metastases. CT-scan only in case of doubt.
Note that any patient undergoing immediate nephrectomy and having a stage I intermediate risk tumour should have a CT thorax to exclude pulmonary micrometastases, as these are probably not adequately treated with single agent vincristine (see appendix 3).

4. **Selective renal arteriography** is usually only necessary in bilateral cases, in horseshoe kidney tumours and other situations in which the surgeon needs that information. It should be done preferably just before surgery by a radiologist skilled in performing the examination in young children to document the size and site of the tumours.

5. **Needle biopsy** performed by an experienced person using a posterior approach is permitted without changing the stage.

6. **Echocardiography:** Fractional shortening, Ejection fraction and End systolic wall stress should be documented. Storage of serum for Troponin levels is strongly recommended for research purposes. These investigations should be done before the first dose of Doxorubicin in stage II, III and IV patients and all high risk patients and at other points indicated on the forms.

**4.4 DOCUMENTATION IN STAGE IV PATIENTS**

All stage IV patients are protocol patients. Initial detailed and quantitative evaluation of the extension of the disease should be performed and mentioned on the form. CT scan of the site of the metastases is optional.

**4.5 DOCUMENTATION IN SIMULTANEOUS BILATERAL CASES**

In SIOP 2001, patients with bilateral disease at diagnosis will be studied prospectively (see Appendix 4).
### 4.6 PRACTICAL GUIDE TO THE DIAGNOSIS

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP ONE</strong></td>
<td></td>
</tr>
</tbody>
</table>
| 1. Start to collect 24 hrs. Urine while on a standardized diet. | To exclude neuroblastoma.  
To establish renal function. |
| 2. Ultrasound | To make 3 dimensional measurements.  
To establish if this is an intrarenal process.  
To investigate the opposite kidney. Is the tumour cystic, solid or both? To search for other abnormalities in the abdomen. Intravascular extension, etc. To exclude hepatic metastases. |
| 3. Plain X-ray of the chest in 2 directions | To exclude pulmonary metastases. |

### IF NO SOLID DIAGNOSIS YET

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP TWO</strong></td>
<td></td>
</tr>
</tbody>
</table>
| CT-scan abdomen if appropriate | To confirm intrarenal lesion with certain characteristics, relations to other structures.  
Lymph nodes, invasion of vessels, other organs and structures. Also useful for measurements. |
| CT-scan thorax if any doubt on chest x-ray | To further exclude metastases or to confirm. |

### IF STILL NO SOLID DIAGNOSIS

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STEP THREE</strong></td>
<td></td>
</tr>
<tr>
<td>Needle Biopsy.</td>
<td>Consult the recommendations for this procedure. (see over)</td>
</tr>
</tbody>
</table>
4.7 RECOMMENDATIONS FOR THE USE OF NEEDLE BIOPSY IN RENAL TUMOURS IN CHILDREN

CONSIDER NEEDLE BIOPSY IN CASE OF:

Unusual clinical presentations:
- Age > 5-6 years
- Urinary infection
- Septicemia
- Psoas inflammation

Unusual findings by imaging:
- Calcification
- Voluminous adenopathies
- Renal parenchyma not visible
- Almost totally extrarenal process

Contraindications for the use of Needle Biopsy:
- Age < 6 months
- Suspicion of rupture or hemorrhage
- Needle biopsy is unlikely to be of benefit in pure cystic structures with no solid component. Immediate surgery to establish the diagnosis is recommended in such cases.

PROCEDURE:
1. Normal blood coagulation tested.
2. General anaesthetic.
3. All retroperitoneal tumours should be biopsied from the posterior side.
4. Ultrasound guided biopsy preferably.
5. Pathologist at hand for tissue handling.
6. Discuss with local radiologist regarding a coaxial needle technique.
SECTION 5
PATHOLOGY PROTOCOL

All renal tumours diagnosed in children up to 18 years of age as well as typical renal tumours of childhood found in older adolescents should be registered. Typical renal tumours of childhood are nephroblastoma, clear cell sarcoma of kidney, rhabdoid tumour of kidney, and mesoblastic nephroma. Consultation for all cases will be provided without charge, and any use of material for teaching purposes or publication will credit the contributing pathologist.

5.1 ROLE OF THE PATHOLOGIST IN A PARTICIPATING CENTRE

The local pathologist has an essential role in both the clinical trial and the prospective study, as follows:

1. DIAGNOSIS: He/she makes the diagnosis of the renal tumour.
2. HISTOLOGICAL SUBTYPE AND RISK GROUP. He/she assigns the tumour to a histological subtype, i.e. low risk, intermediate risk or high risk.
3. STAGING: He/she makes a precise evaluation of the abdominal stage of the tumour (even in children with stage IV disease, local staging is critical to determine the utilisation of radiotherapy). The pathologist should have information regarding pre- or intraoperative tumour rupture (from the surgeon) and clinical information regarding distant metastases. For the purpose of the Trial, please use the SIOP staging system (see 5.5) (the pTNM staging system can be of additional support but should not be used instead of the SIOP staging system).

Patients will be treated according to different therapeutic protocols depending on tumour histology and stage. As outlined elsewhere in the Trial protocol (Sections 6 and 7), low risk tumours, stage I, will be treated with no post-operative chemotherapy while high risk tumours will be treated with more intensive chemotherapy after surgery. Therefore, it is of the utmost importance for these tumours to be classified correctly – in order to confirm the diagnosis prior to post-operative treatment, all low and high risk tumours should be sent for rapid review immediately after the operation. Please submit a full set of H&E slides and one paraffin block from an area of viable tumour, accompanied by the SIOP Institutional Pathology Form and a copy of your report, to the Referring Pathologists (see 5.4). (Consider asking technician to cut another set of H&E slides at the same time he/she is preparing one for you – it is much easier and quicker to do it at that time than later. Please do not send unstained slides only as it will delay the answer). In case of local relapse(s) or surgically removed metastases, please also send a full set of slides with the appropriate forms.

Do not delay sending the sections for pathology review for whatever reasons, even if you are not sure whether the patient will be entered into the Trial. Although registration of the patient might have been delayed and no trial number yet allocated, please send your slides and you will still have the panel pathologist’s opinion in time for making a decision on further postoperative treatment.
5.2 THE REVISED S.I.O.P. WORKING CLASSIFICATION OF RENAL TUMOURS OF CHILDHOOD (2001)

A. FOR PRE-TREATED CASES

LOW RISK TUMOURS
- Mesoblastic nephroma
- Cystic partially differentiated nephroblastoma
- Completely necrotic nephroblastoma

INTERMEDIATE RISK TUMOURS
- Nephroblastoma - epithelial type
- Nephroblastoma - stromal type
- Nephroblastoma - mixed type
- Nephroblastoma - regressive type
- Nephroblastoma - focal anaplasia

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

B. FOR PRIMARY NEPHRECTOMY CASES

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 of the kidney
- Rhabdoid tumour of the kidney
5.3 DEFINITIONS OF NEPHROBLASTOMA AND ITS SUBTYPES, AND OTHER TYPICAL RENAL TUMOURS OF CHILDHOOD

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

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

The SIOP (Stockholm) Working Classification of Renal Tumours of Childhood has recently been revised to incorporate the results of the latest SIOP Trials and Studies and it will be followed in this Trial and Study. Some entities that existed in the previous classification, such as nephroblastoma with fibroadenomatous structures and highly differentiated epithelial nephroblastoma, have been either excluded or grouped with other subtypes. Unlike in the previous classification, subtyping of nephroblastomas in the Intermediate risk group is now required (see diagram below).

It is important to emphasise that for treatment purposes, in addition to anaplasia, only three major types of nephroblastoma need to be recognised: completely necrotic nephroblastoma (low risk tumours), blastemal (high risk tumour) and others (intermediate risk tumours), but pathologists are encouraged to record and enter in their reports a percentage of different components (regressive changes, blastemal, epithelial and stromal) as these features will be analysed prospectively in order to identify those that might have further prognostic significance. (Cystic partially differentiated nephroblastoma should be diagnosed on imaging studies and treated with surgery alone).

![Diagram showing the classification of nephroblastomas based on post-chemotherapy specimens](image-url)
5.4 STUDY OF THE 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.

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.

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 cm$^3$ 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 cm$^3$) snap frozen in liquid nitrogen or at −70°C.
   - If present, **nephrogenic rests** should be sampled as above.
   - 10 ml 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) 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;

b) 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);

c) sinus lymph nodes when present;

d) other lymph nodes.

e) 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;

f) tumour-kidney interface

g) tumour-kidney capsule

h) areas of the capsule that are suspected of being invaded by the tumour;

i) areas of perirenal fat suspected for tumour infiltration (important for assessment whether the tumour is completely resected);

j) areas of adhesions of the tumour to surrounding tissues;

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

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. **Please use a pre-prepared diagram in the SIOP Institutional Pathology Form F4 or a photograph.**

### 5.5 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 is partly because of the fact that 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 use a pre-prepared diagram in the SIOP Institutional Pathology Form F4 or, preferably, a photograph and mark the sites from which blocks have been taken).

Please remember that local (abdominal) staging of primary tumour is done following prenephrectomy 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.

**Criteria for staging:**

**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) Intrarenal vessel involvement may be present

Fine needle aspiration or percutaneous core needle biopsy ('tru-cut') does not upstage the
tumour but the size of the needle gauge should be mentioned to the pathologist.

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

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 microscopical 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 a 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 substaged according to above
classifications.

If in any doubt about a tumour’s stage or for its confirmation, please send it for urgent
review to the referring pathologist.
HISTOLOGICAL DESCRIPTION OF THE SUBTYPES OF NEPHROBLASTOMA AND OTHER RENAL TUMOURS OF CHILDHOOD

5.6 LOW RISK TUMOURS

MESOBLASTIC NEPHROMA

Mesoblastic nephroma is a renal tumour that usually occurs in the first year of life. The oldest child with confirmed mesoblastic nephroma in the National Wilms’ Tumor Study (NWTS) files was diagnosed at age of 29 months. Cases of ‘mesoblastic nephromas’ in older children have been shown to be Metanephric Stromal Tumours – a recently described new entity. However, for both entities treatment is surgery and prognosis is excellent, so the distinction between them has no important therapeautic implications.

There are two histological subtypes of mesoblastic nephroma: the classical and the cellular type. The distinction between the two types has no implication for therapy so far. Classical mesoblastic nephroma is a monomorphous tumour composed of spindle cells with large, vesicular nuclei, noticeable nucleoli and abundant cytoplasm. The cells are arranged in interlacing bundles and mitotic figures are usually present. The tumour-kidney border is irregular and long radial extensions (finger-like extensions) of tumour tissue into the adjacent renal tissue are a characteristic finding. Also, within the tumour small rests of connective tissue with entrapped tubules are usually seen. Cellular mesoblastic nephroma has a sharper, pushing tumour-kidney border, increased cellularity and numerous mitoses. Both types show infiltrative growth and may infiltrate the adjacent perirenal fat and spread into the renal sinus. Complete, wide surgical resection is the only recommended treatment for localised disease. Local recurrences and metastases have been described in a few cases, especially in children older than six months of age, although some children were < 1 month old at diagnosis. The vast majority of relapses occur within 12 months of nephrectomy and in about 70% of relapsed cases the tumour is of the cellular type.
In the differential diagnosis, metanephric stromal tumour, blastemal and stromal nephroblastoma, clear cell sarcoma and rhabdoid tumour of kidney must be considered (in difficult cases, please consult excellent tables in 3rd series of AFIP Fascicle on ‘Tumors of the kidney, bladder, and related urinary structures’, 1994). Recently, cytogenetic abnormalities of chromosome 11 and a translocation involving chromosome 15 have been reported in cellular mesoblastic nephroma. The finding of ETV6-NTRK3 gene fusions and trisomy 11 has established a histogenetic link between cellular mesoblastic nephroma and congenital fibrosarcoma.

**CYSTIC PARTIALLY DIFFERENTIATED NEPHROBLASTOMA (CPDN)**

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

a) it is composed entirely of cysts and their thin septa;
b) the thin septa are the only ‘solid’ portion of the tumour;
c) the tumour forms a discrete mass, well demarcated from the non-cystic renal parenchyma;
d) the cysts are lined by flattened, cuboidal or hobnail epithelium; and
e) the septa contain blastemal cells in any amount, with or without other embryonal stromal or epithelial cell types.

Thus, variable differentiated glomeruli, tubules, mesenchyme, striated muscle, cartilage, fibrous tissue, and fat may be admixed with blastemal cells in septa. The presence of well-differentiated tubules only is not enough to make a diagnosis of this tumour and separate it from cystic nephroma. However, from a therapeutic and prognostic point of view there is no need to distinguish between CPDN and cystic nephroma as they are both treated with surgery alone and both share the same, excellent prognosis. However, intermediate risk nephroblastomas may present with numerous cysts but they also contain solid areas and septa are usually thicker and show chemotherapy-induced changes. Be aware that other renal tumours, such as clear cell sarcoma and rhabdoid tumour, may have a predominantly cystic appearance.

**COMPLETELY NECROTIC NEPHROBLASTOMA**

Pre-operative chemotherapy given in SIOP trial patients results in so-called ‘chemotherapy-induced change’ in many nephroblastomas. Depending on their initial histological pattern, some nephroblastomas are completely or almost completely necrotic, while others show less marked or minimal/moderate changes. The relationship between the percentage of these chemotherapy-induced changes and prognosis has been shown in other tumours such as osteosarcoma as well as in a recent SIOP study on nephroblastoma in which completely necrotic nephroblastomas had an excellent prognosis with 100% survival in all stages.

The histological criteria for making a diagnosis of completely necrotic nephroblastoma are:

a) the absence of any viable tumour tissue on gross and microscopic examination of multiple blocks taken from different areas of a tumour, according to the recommended protocol (ie at least one block per cm of tumour); the presence of scattered mature tubules is allowed as they may represent remnants of nephrogenic rests.
b) the presence of regressive and/or necrotic changes caused by chemotherapy.
Although complete tumour necrosis makes histological sub-typing of nephroblastoma impossible, ‘ghost’ tumour structures (mainly blastema, occasionally epithelial elements) can be recognised, and are helpful in distinguishing nephroblastoma from other renal tumours. In addition, the presence of nephrogenic rests, which are virtually never associated with non-Wilms tumour and are generally not affected by chemotherapy, is a very reliable clue that the tumour has been a nephroblastoma before chemotherapy. Finally, it is well known that regression of other renal tumors such as clear cell sarcoma, rhabdoid tumor or renal cell carcinoma, is minimal to moderate under the actinomycin D - vincristine protocol, and their histological features can be easily recognised even in treated cases.

The typical histological appearance of treated nephroblastoma is a mixture of necrosis, fibromyxomatous stroma containing lipid- and/or haemosiderin-laden macrophages, and haemorrhage. In some cases scattered mature tubules may be seen within necrotic areas – this may represent remnants of pre-existing rests and should not be regarded as viable tumour tissue. The main pattern of the necrotic area is coagulative-type necrosis of small round cells or tubules, with the majority of ‘ghost’ structures consisting of large sheets of small, pink, necrotic nuclei, consistent with coagulative necrosis of blastemal cells or tubules. (If in doubt whether the necrotic tumour is a nephroblastoma, the reticulin staining may help to identify scarce epithelial or mesenchymal ‘ghost’ structures.) The presence of identical changes in a lymph node is regarded as a proof of its involvement with a tumour and it is, therefore, very important to sample and microscopically examine all lymph nodes removed. Beware of Tamm Horsfall protein which is sometimes accompanied by discrete epithelium in a lymph node – this must not be interpreted as a metastasis (for other lesions and changes which may mimic lymph node metastases, see paper by Weeks et al. 1990).

5.7 INTERMEDIATE RISK TUMOURS

Beckwith and Palmer’s criteria for histological subtyping of nephroblastomas state that one component has to comprise at least 2/3 (66%) of a tumour mass for the tumour to be subclassified accordingly. However, pre-operative chemotherapy alters the original histological features of nephroblastomas and often results in areas of necrosis and regression. Therefore the criteria applicable to subclassification of primarily operated tumours have to be modified to take these changes into account. The reason that only viable tumour is taken into account when subclassifying nephroblastomas which are not completely necrotic is based on previous studies which have shown that chemotherapy-induced changes are a prognostically favourable effect of treatment (Zuppan et al., 1991; Boccon-Gibod et al., 2000). On the other hand, the presence of blastema after pre-operative chemotherapy clearly indicates its non-responsiveness to chemotherapy and has been shown to be associated with poorer outcome (Weirich et al., 2001). For all these reasons, we believe modification of the criteria for certain subtypes of nephroblastoma is justified. We are aware that the assessment of percentage of necrosis/regression is subjective, but since it is very important for subclassification of nephroblastomas, it should be done on both gross and histological examination.

Histological types of nephroblastoma from this group are described below, but a simple approach can be the following (please, also see a diagram in section 5.3):
1) Assess the percentage of necrosis/regressive changes caused by chemotherapy
2) If regressive changes comprise more than 2/3 of a tumour mass – it is a regressive type
3) If regressive changes comprise less than 2/3 of a tumour mass – look for a predominant histological component and subclassify a tumour accordingly (blastemal, epithelial or stromal type). If no component is predominant, it is a mixed type.

4) Even if focal anaplasia is found, try to subclassify the tumour as below.

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

**NEPHROBLASTOMA - EPITHELIAL TYPE**

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

- a) only the viable part of a tumour is assessed and it has to comprise more than 1/3 of a tumour mass;
- b) at least 2/3 of the viable tumour consists of epithelial structures
- c) the stromal component may comprise the rest of the viable tumour; and
- d) scattered small foci of blastema comprising less than 10% of the tumour may occur

*the finding of larger nodules of blastema comprising about 10% of the viable tumour mass is not acceptable and such tumours should be subclassified as mixed subtype).

The epithelial elements are regarded as follows:

- a) *tubules* – spaces lined by columnar epithelial cells arranged in a fairly regular manner radially around the central space; cell margins are sharp, they have basal, crowded nuclei, and mitotic activity may be marked; tubules are usually back-to-back, with virtually no supporting stroma;
- b) *rosettes* – circular arranged tumour cells with elongated ovoid nuclei, but no central lumen is present;
- c) *papillary structures* – finger-like projections of a stroma covered with epithelial cells;
- d) *glomerular structures* – tuft-like masses of malignant cells surrounded by a well-formed capsule or rather flattened tumour cells.

The stromal elements are regarded as follows: undifferentiated stromal cells, myxoid, fibroblastic, smooth muscle, skeletal muscle, adipose cells, cartilage and osteoid formations.

The presence of genuine anaplasia classifies the tumour as anaplastic nephroblastoma even if otherwise completely epithelial (see 5.8 for criteria anaplasia). Epithelial nephroblastoma usually occurs in younger children (median age 9 months in a SIOP series), and about 80% of cases are in stage I. Beware of epithelial nephroblastoma in older children and look carefully for anaplasia.

**NEPHROBLASTOMA – STROMAL TYPE**

Stromal nephroblastoma represents a subtype in which the stromal elements are a predominant component of the tumour. The fetal rhabdomyomatous nephroblastoma, which in the past was regarded as a nephroblastoma with better prognosis, is also included here.
The histological criteria for making a diagnosis of stromal type nephroblastoma are as follows:

a) only the viable part of a tumour is assessed and it has to comprise more than 1/3 of a tumour mass;
b) at least 2/3 of the viable tumour consists of stromal elements;
c) the epithelial component may comprise the rest of the viable tumour; and
d) scattered small foci of blastema comprising less than 10% of the tumour may occur
   *(the finding of larger nodules of blastema comprising about 10% of the viable tumour mass is not acceptable and such tumours should be subclassified as mixed subtype).*

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

Stromal nephroblastoma usually occurs in younger children and usually shows minimal to moderate chemotherapy-induced changes since stromal tissue seems to be resistant to chemotherapy. Fetal rhabdomyomatous nephroblastoma is bilateral in 30% of cases.

**NEPHROBLASTOMA – MIXED TYPE**

Mixed type nephroblastoma represents a subtype in which none of the viable component is predominant.

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

a) only the viable part of a tumour is assessed and it has to comprise more than 1/3 of a tumour mass;
b) the viable tumour consists of blastemal and/or epithelial and/or stromal elements but none of them comprise more than 2/3 of the viable tumour.

As for the other subtypes, please try to assess the percentage of different (viable) tumour component as well as the percentage of necrosis/regression.

**NEPHROBLASTOMA – REGRESSIVE TYPE**

Nephroblastoma – regressive type is regarded as a tumour in which chemotherapy-induced changes comprise more than 2/3 of the tumour mass. Please note that assessment of percentage of necrosis/regression is done on both gross and histological examination, so blocks should be taken not only from viable parts of the tumour mass but also from those that show necrotic/regressive changes.
The histological criteria for making a diagnosis of regressive type nephroblastoma are:

a) the presence of more than 2/3 of non-viable tumour tissue (regressive and/or necrotic changes caused by chemotherapy) on gross and microscopical examination of multiple blocks taken from different areas of a tumour, according to the recommended protocol (see 5.4).

b) the viable tumour elements are histological components of nephroblastoma including blastemal, epithelial and stromal elements.

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

NEPHROBLASTOMA WITH FOCAL ANAPLASIA

Nephroblastoma with focal anaplasia has been moved into the Intermediate risk group since both NWTS and SIOP studies have shown that it has the same prognosis as non-anaplastic nephroblastomas (other than blastemal type, in the SIOP trials). Diagnostic criteria for focal anaplasia have been described with diffuse anaplasia (see below).

5.8 HIGH RISK TUMOURS

NEPHROBLASTOMA - BLASTEMAL TYPE

This nephroblastoma type has been moved into the high risk tumours but only if diagnosed after pre-operative chemotherapy. The reason for this change is based on the results of previous SIOP trials showing that tumours with chemotherapy-resistant blastema had a worse prognosis and require more intensive treatment. In cases diagnosed after primary nephrectomy, blastemal nephroblastoma remains in the Intermediate risk tumours.

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

a) only the viable part of a tumour is assessed and it has to comprise more than 1/3 of the tumour mass;

b) at least 2/3 of the viable tumour consists of blastema

c) other components of nephroblastoma may be present in varying proportions.

The blastemal elements are regarded as undifferentiated round or elongated cells which are usually closely packed and show no evidence of epithelial and/or stromal differentiation. There are several distinctive patterns in which blastemal cells may occur and it is not uncommon to find more than one pattern in the same tumour. They include the diffuse, serpentine, nodular, and basaloid patterns but they are of no prognostic or therapeutic significance (for detailed criteria for different blastemal patterns, please see 3rd series of AFIP Fascicle on ‘Tumors of the kidney, bladder, and related urinary structures’, 1994).
NEPHROBLASTOMA WITH ANAPLASIA

Anaplasia was recognised as an unfavourable histological feature of nephroblastoma in earlier trials. The histological criteria for making a diagnosis of anaplastic nephroblastoma are the presence of all three criteria for anaplasia including:

a) the presence of atypical tri/multipolar mitotic figures;
b) marked nuclear enlargement, with diameters at least three times those of adjacent cells; and
c) the presence of hyperchromatic tumour cell nuclei.

Anaplasia may occur in the blastemal, epithelial or stromal component of nephroblastoma and it can be focal or diffuse. The recent (topographic) definition of focal anaplasia emphasizes the distribution of anaplasia which has to be sharply demarcated within the primary tumour. This proved to be of prognostic significance in both primarily operated and pre-nephrectomy treated cases.

Focal anaplasia has now been defined as the presence of a clearly defined focus within a primary intrarenal tumour, without evidence of anaplasia or prominent nuclear atypia in extrarenal tumour sites.

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

This topographic definition of focal anaplasia makes it mandatory that pathologists carefully document the exact site from which every section is obtained (e.g. on a diagram, specimen photocopy, and/or photograph of the gross specimen). Please use a pre-prepared diagram in the SIOP Institutional Pathology Form F4 or a photograph.

Anaplasia occurs in about 5% of patients with nephroblastoma. Preoperative chemotherapy does not obliterate or produce anaplasia but it makes its recognition easier since non-anaplastic areas are destroyed by chemotherapy while anaplastic foci remain unchanged. This provides further support to the hypothesis that anaplasia represents a more resistant rather than a more aggressive cell line. The age distribution of anaplastic nephroblastoma differs from non-
anaplastic nephroblastoma: anaplasia never occurs in the first six months of life, it is very rare between 6-12 months (1-2%), median age at diagnosis is 61 months and >50% of children are over five years of age (for non-anaplastic nephroblastoma median age is 45 months, and 25% of children are over five years of age).

Although the criteria for anaplasia have been well established, it still represents a diagnostic problem resulting in either missed or ‘overdiagnosed’ cases, while only in rare instances it is confused with other renal tumours. It is important to bear in mind that all three criteria for the diagnosis of anaplasia have to be met and that some histological changes may mimic anaplasia including calcification, fused or smudged masses of nuclear chromatin due to technical artefact, stain precipitate, circulating megakaryocytes, overlapping cells in thick sections, and bizarre nuclei resulting from chemotherapy with the formation of hyperchromatic multinucleated and bizarre macronucleated skeletal muscle cells in response to injury. However, the diagnosis of anaplasia in the skeletal muscle must be made if atypical mitoses and other histological criteria are present.

CLEAR CELL SARCOMA OF THE KIDNEY (CCSK)

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

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

The classical pattern of CCSK is relatively simple to diagnose, but others including the myxoid, sclerosing, cellular, epithelioid, palisading, spindle cell, storiform, and anaplastic pattern can cause problems in reaching the diagnosis. In some CCSKs, there can be extensive hyalinisation and these tumours may be confused with cases of nephroblastoma with sclerosis due to pre-operative treatment, or rhabdoid tumour. In the differential diagnosis blastemal nephroblastoma, mesoblastic nephroma, PNET and rhabdoid tumour must be considered (in difficult cases, please consult excellent tables in 3rd series of AFIP Fascicle on ‘Tumors of the kidney, bladder, and related urinary structures’, 1994, and the paper by Argani et. al., Am J Surg Pathol 2000).

The histogenesis of the tumour is uncertain. The tumour cells are only positive for vimentin and are generally negative for cytokeratin, factor VIII associated antigen, epithelial membrane antigen, desmin, and S100 protein.
RHABDOID TUMOUR OF THE KIDNEY

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

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

Immunohistochemistry shows consistent positivity of tumour cells for vimentin with frequent co-expression of cytokeratin, while many other markers including epithelial membrane antigen, S-100 protein, neurofilaments, neuron-specific enolase, desmin, myoglobin, alpha-1-antichymotrypsin have been reported but are not found consistently. CD99 (Mic-2) positive staining may be seen too. In some cases abnormalities of chromosome 22 and 11p13 have been described.

5.9 NEPHROGENIC RESTS

Nephrogenic rests are foci of embryonal cells which persist after 36 weeks of gestation and they are considered as potential precursors of nephroblastoma. They have been found not only in 25-40% of patients with nephroblastoma but also in 1% of routinely examined perinatal postmortem kidneys. However, they have not been described associated with other typical renal tumours of childhood and their finding in problematic cases should be regarded as a very useful clue that the tumour is nephroblastoma. Two main types of nephrogenic rests have been recognised: perilobar and intralobar rests. They can be further subclassified as dormant, sclerosing, or hyperplastic, and all these appearances may be present in an individual case.

The rests may regress to fibrous tissue or progress to nephroblastoma. Hyperplastic rests may be difficult to distinguish from a small nephroblastoma but it is usually of no therapeutic significance since both hyperplastic rests and nephroblastoma should be treated (see appendix 5). Perilobar rests occur in hemihypertrophy and Beckwith-Wiedemann syndrome while intralobar rests are associated with WAGR and Denys-Drash syndromes.
5.10 Differential Diagnosis of Renal Tumours of Childhood

The results of the SIOP 9 and SIOP 93 01 trials showed that there were a number of cases of both low and high risk tumours that were misdiagnosed, including cystic partially differentiated nephroblastoma, highly differentiated epithelial type nephroblastoma, anaplastic nephroblastoma, clear cell sarcoma and rhabdoid tumour of the kidney. Since many of them were seen by the Panel retrospectively, this resulted in either over-treatment (for low risk tumours) or under-treatment (for high risk tumours). As groups of low and high risk tumours have changed in this Trial, it has become even more important to reach a correct diagnosis before any post-operative treatment is administered.

There are some clinical, macroscopical and histological features of renal tumours of childhood which might be a useful clue in reaching a correct diagnosis.

Age at diagnosis is a rather reliable criterion. Anaplastic nephroblastoma has never been described in the first six months and is extremely rare in the first year of life, but after 5 years of age it comprises 10% of nephroblastomas. Clear cell sarcoma of kidney hardly occurs in the first 6 months of life, while mesoblastic nephroma and rhabdoid tumour of kidney are extremely rare in children over 3 years of age.

Grossly, many renal tumours may show areas with cysts but only CPDN and cystic nephroma are entirely cystic neoplasms, with no solid areas.

There are some unique features of nephroblastoma which are very useful in distinguishing it from other renal tumours including:

a) nephroblastoma is the only typical renal tumour of childhood which may be bilateral (in 5% of cases) or multifocal;
b) nephrogenic rests are commonly present in nephroblastoma but not in other tumours (there is only one report of nephrogenic rests associated with mesoblastic nephroma and CCSK, respectively)
c) the presence of skeletal muscle, adipose tissue and genuine neoplastic tubules has only been seen in nephroblastoma (although fat may be present in metanephric stromal tumours, other features should be sufficient to make a correct diagnosis).
d) nephroblastoma has been diagnosed in a child with a syndrome predisposing to nephroblastoma (WAGR, Beckwith-Wiedemann, Denys-Drash syndrome) while mesoblastic nephroma is the only other renal tumour that has occasionally been described with Beckwith-Wiedemann syndrome.

When in doubt about either the histological type or the stage, please immediately send a full set of histological sections to the national reference pathologist (see 5.11).

Other tumours included in the study:

In addition to the more common renal tumours of childhood discussed above, there are numerous other tumours which may occur at any age. Although these tumours are not entered in the Trial, they should be registered and submitted as they may provide important information in our understanding of renal tumours in general.
These include:
1. Metanephric tumours
   (metanephric stromal tumour, metanephric adenofibroma, metanephric adenoma)
2. Adenomas (all other types)
3. Cystic nephroma
4. Renal cell carcinoma (all variants)
5. Transitional cell carcinoma
6. Neuroepithelial tumours (renal neuroblastoma, renal PNET, renal carcinoid)
7. Miscellaneous sarcomas (without evidence of blastemic cells and/or epithelial component in five different blocks)
8. Renal lymphoma
9. Angiomyolipoma
10. Other tumours (adrenal tumours, teratoma) and lesions (xanthogranulomatous pyelonephritis, etc), if preoperative chemotherapy for nephroblastoma has been given
11. Metastases from other sites
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SECTION 6
THERAPY PROTOCOL FOR LOCALISED DISEASE

6.1 INTRODUCTION
As soon as the work-up is completed and the diagnosis of renal tumour, most probably nephroblastoma is made the pre-operative chemotherapy should be given to the patient. For scheduling see 6.5 and for dose adjustment see 8.1. For major intolerance in this phase of the treatment see also 8.4.
See also 8.5 for supportive care recommendations.

Pay attention to the observations and actions in this part of the treatment, before surgery, directly post-surgery and include a copy of the checklist (see 6.3) in your patient file.

Post-operative therapy is based on stage and histology. The responsible clinician should see to it that the tissue is handled properly from the point of view of diagnosis, but also for the purpose of the necessary biological studies.
For post-operative treatment see the appropriate schedules on the pages in this chapter. An overview follows.

6.2 RECOMMENDED CHEMOTHERAPY REGIMENS FOR NEWLY DIAGNOSED LOCALISED DISEASE TUMOURS

6.2.1 PRE-OPERATIVE TREATMENT
Vincristine 1.5 mg/m² (maximum dose 2 mg) weekly for 4 weeks (4 doses in total).
Note: doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.

Actinomycin D 45 µg/kg (maximum dose 2 mg) at week one and three (2 doses in total).
Note: doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.

Both drugs are given i.v. push.

6.2.2 POST-OPERATIVE TREATMENT

6.2.2.1 REGIMEN AV-1
STAGE I, INTERMEDIATE RISK ONLY
Vincristine 1.5 mg/m² (maximum dose 2 mg) 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 last dose of pre-operative chemotherapy.
Note: doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.
Actinomycin D 45 µg/kg (maximum dose 2 mg) at week two (day 7) of the post-operative regimen.  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.  
Both drugs are given by i.v. push.  

### 6.2.2.2 REGIMEN AVD

#### STAGE I, HIGH RISK and STAGE II/III INTERMEDIATE RISK RANDOMISED TO THIS REGIMEN

Vincristine 1.5 mg/m$^2$ (maximum dose 2 mg) weekly for 8 weeks (8 doses), the first dose to be given once peristalsis is established following surgery and within 21 days of last dose of pre-operative chemotherapy.  
Thereafter 6 courses of Vincristine on day one and seven with a two week interval between courses (12 doses in total) to start at week 11.  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.  
Actinomycin D 45 µg/kg (maximum dose 2 mg) at week 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total).  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose and Actinomycin D should be reduced for all patients to 50% of the recommended dose during radiation and the first following course.  
Doxorubicin 50 mg/m$^2$ in a 4-6 hours infusion every 6 weeks to start in week two concurrently with the first dose of Actinomycin D and the second dose of Vincristine.  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.  
The total duration of the post-operative chemotherapy is 27 weeks.

### 6.2.2.3 REGIMEN AV-2

#### STAGE II, LOW RISK and STAGE II/III INTERMEDIATE RISK RANDOMISED TO THIS REGIMEN

Vincristine 1.5 mg/m$^2$ (maximum dose 2 mg) weekly for 8 weeks (8 doses). The first dose is to be given once peristalsis is established following surgery and within 21 days of last dose of pre-operative chemotherapy.  
Thereafter 6 courses of Vincristine on day one and seven with a two week interval between courses (12 doses in total) to start at week 11.  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose.  
Actinomycin D 45 µg/kg (maximum dose 2 mg) at week 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total).  
**Note:** doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose and Actinomycin D should be reduced for all patients to 50% of the recommended dose during radiation and the first following course.  
The total duration of post-operative chemotherapy is 27 weeks.
STAGE II, INTERMEDIATE RISK  RANDOMISATION

REGIMEN AVD  (the same as stage I high risk)

REGIMEN AV-2  (the same as stage II low risk)

6.2.2.4 HIGH RISK TREATMENT REGIMEN

All high risk histology tumours of stage II or III

There are two alternating courses of chemotherapy. Both combinations consist of 2 drugs. The first course starts as soon as the patient has recovered from the operation and his/her condition allows this chemo. Preferably together with the radiotherapy and within 21 days of last dose of pre-operative chemotherapy. The order of the chemotherapy blocks can be altered if necessary to allow doxorubicin not to be given within 14 days of RT, depending on when it can be arranged.

Cyclophosphamide 450 mg/m$^2$ for 3 consecutive days with Doxorubicin 50 mg/m$^2$ on day one of this course (total of 6 courses) with a 6 week interval. I.e. on weeks 1, 7, 13, 19, 25 and 31. Doxorubicin just before the first dose of Cyclophosphamide.

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

Etoposide (VP16) 150 mg/m$^2$ for three consecutive days together with Carboplatin 200 mg/m$^2$ also for three consecutive days (a total of 6 courses) given every 6 weeks from week 4 on. I.e. on weeks 4, 10, 16, 22, 28 and 34.

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

Infusion times for the various drugs are one hour for Cyclophosphamide, Carboplatin and Etoposide and 4-6 hours for Doxorubicin.

STAGE III, LOW RISK receive regimen AV-2 without radiotherapy

STAGE III, INTERMEDIATE RISK  RANDOMISATION

The same chemotherapy regimens are used as in stage II intermediate risk. In these patients however radiotherapy is given from week 2 on and Actinomycin D should be reduced for all patients to 50% of the recommended dose during radiation and the first following course.

STAGE III, HIGH RISK receive the 'high risk' regimen with abdominal radiotherapy
Copy this form and put it in your patients file!!

6.3 OBSERVATIONS AND THEIR TIME SCHEDULE

| ACT  45 µg/kg | ↓ | ↓ | ↓ | SURG. | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
|-------------|---|---|---|------|---|---|---|---|---|---|---|---|---|---|---|
| VCR 1,5 mg/m² | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| WEEKS       | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |


Peripheral bloodsample of patient and patients for biology study.

Surgical report. Specimen + histological form immediately to pathologist.

Sampling of material for biological studies!

Diagnosis

In case of doubt about stage or histology

Final diagnosis

56
### 6.4 SUMMARY OF POSTOPERATIVE TREATMENT STRATEGIES FOR LOCALISED TUMOURS

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW RISK</strong></td>
<td>No further treatment</td>
<td>AV-2</td>
<td>AV-2</td>
</tr>
</tbody>
</table>
| **INTERMEDIATE RISK** | AV-1                  | DOX + (AVD)  
                   |                      | DOX - (AV-2)       |
|                     | R <                    | R < RT / DOX +  
                   |                      | (AVD) RT / DOX -   |
| **HIGH RISK**       | AVD                    | HIGH RISK + RT    | HIGH RISK + RT    |
LOCALISED DISEASE

PRE-OPERATIVE TREATMENT

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>45 µg/kg</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VCR</td>
<td>1.5 mg/m²</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>WEEKS</td>
<td>1 2 3 4</td>
<td>SURGERY</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ACT** = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)

**VCR** = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see 8.4)
STAGE I, LOW RISK

PRE-OPERATIVE TREATMENT

<table>
<thead>
<tr>
<th>ACT 45 µg/kg</th>
<th>↓</th>
<th>↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR 1.5 mg/m²</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>SURGERY</td>
<td>NO FURTHER TREATMENT</td>
<td></td>
</tr>
<tr>
<td>WEEKS</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

POST-OPERATIVE TREATMENT

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000µg!)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses should be reduced to 2/3 (see section 8)
REGIMEN AV-1

STAGE I, INTERMEDIATE RISK

PRE-OPERATIVE TREATMENT                      POST-OPERATIVE TREATMENT

<table>
<thead>
<tr>
<th>ACT</th>
<th>45 µg/kg</th>
<th>↓</th>
<th>↓</th>
<th>ACT</th>
<th>45 µg/kg</th>
<th>↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR</td>
<td>1.5 mg/m²</td>
<td>↓</td>
<td>↓</td>
<td>VCR</td>
<td>1.5 mg/m²</td>
<td>↓</td>
</tr>
<tr>
<td>WEEKS</td>
<td></td>
<td>1</td>
<td>2</td>
<td>WEEKS</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

WEEKS 1 2 3 4  SURGERY  WEEKS 1 2 3 4

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)

VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)

If body weight < 12 kg: dose reduction to 2/3 for each drug.
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
REGIMEN AVD

STAGE I, HIGH RISK, POST-OPERATIVE TREATMENT

| WEEKS | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|-------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)
DOX = doxorubicin = 50 mg/m²/i.v. in 4-6 hours

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
REGIMEN AV-2

STAGE II, LOW RISK, POST-OPERATIVE TREATMENT

| ACT    | 45 μg/kg ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓
STAGE II, INTERMEDIATE RISK, POST-OPERATIVE TREATMENT

ACT  45 µg/kg  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓
VCR  1.5 mg/m²  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓
DOX  50 mg/m²  ♦  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓
WEEKS  1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 ♦ 26 27

REGIMEN AVD

♦ means echocardiogram

REGIMEN AV-2
ACT  45 µg/kg  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓
VCR  1.5 mg/m²  ♦  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓  ↓
WEEKS  1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 ♦ 26 27

ACT = actinomycin D  = 45 µg/kg/i.v. bolus injection (max 2000 µg!)
VCR = vincristine  = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)
DOX = doxorubicin  = 50 mg/m²/i.v. 4-6 hours
If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
STAGE II, HIGH RISK, POST-OPERATIVE TREATMENT

<table>
<thead>
<tr>
<th>VP16</th>
<th>150 mg/m²</th>
<th>↓↓↓</th>
<th>↓↓↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARBO</td>
<td>200 mg/m²</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>CYCLO</td>
<td>450 mg/m²</td>
<td>↓↓↓</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

WEEKS 1<---- 2------ 3----> 4 5 6 7 8 9 10 11 12 13 14 15
16 17 18 19 20 21 22 23 24 25 26 27
28 29 30 31 32 33 34

VP16 = etoposide = 150 mg/m²/i.v./in 1 hour
CARBO = carboplatin = 200 mg/m²/i.v./in 1 hour
CYCLO = cyclophosphamide = 450 mg/m²/i.v./in 1 hour
DOX = doxorubicin = 50 mg/m²/i.v./in 4-6 hours, just before the first cyclo administration

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)

◊ Stage II Blastemal-predominant high risk cases do not receive radiotherapy
# REGIMEN AV-2

## STAGE III, LOW RISK, POST-OPERATIVE TREATMENT

|     | ACT 45 µg/kg | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
|-----|--------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| VCR | 1.5 mg/m²    | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
|     |              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| WEEKS | 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 |

**ACT** = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)

**VCR** = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)

If body weight < 12 kg: dose reduction to 2/3 for each drug

Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
### STAGE III, INTERMEDIATE RISK, POST-OPERATIVE TREATMENT

| WEEKS | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |

#### REGIMEN AVD

| ACT | 45 µg/kg | ↓ | ↓* | ↓ | ↓ | ↓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| VCR | 1.5 mg/m² | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DOX | 50 mg/m² | ♦ |  |  |  |  | ♦ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

* For all patients: ACT should be reduced to 50% of the recommended dose during radiation and the first following course (week 5).

Major intolerance: doses on the next course should be reduced to 2/3 (see section 8).

#### REGIMEN AV-2

| WEEKS | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)

VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)

DOX = doxorubicin = 50 mg/m²/i.v. 4-6 hours

If body weight < 12 kg: dose reduction to 2/3 for each drug.

* means echocardiogram
## STAGE III, HIGH RISK, POST-OPERATIVE TREATMENT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Schedule</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP16</td>
<td>150 mg/m²</td>
<td>↓↓↓</td>
<td>4</td>
</tr>
<tr>
<td>CARBO</td>
<td>200 mg/m²</td>
<td>↓↓↓</td>
<td>5</td>
</tr>
<tr>
<td>CYCLO</td>
<td>450 mg/m²</td>
<td>↓↓↓</td>
<td>6</td>
</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
<td>↓↓↓</td>
<td>7</td>
</tr>
</tbody>
</table>

WEEKS: 1<---- 2------ 3----> 4  5  6  7  8  9  10  11  12  13  14  15  16  17  18  19  20  21  22  23  24  25  26  27  28  29  30  31  32  33  34

VP16 = etoposide = 150 mg/m² i.v./in 1 hour
CARBO = carboplatin = 200 mg/m² i.v./in 1 hour
CYCLO = cyclophosphamide = 450 mg/m² i.v./in 1 hour
DOX = doxorubicin = 50 mg/m² i.v./in 4-6 hours, just before the first cyclo administration

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
SECTION 7

THERAPY PROTOCOL FOR METASTATIC DISEASE

7.1 INTRODUCTION
All metastatic sites are included in this study. Initial detailed and quantitative evaluation of the extension of the disease should be performed and documented on the appropriate forms. Pulmonary metastases are documented with a plain X-ray of the chest (CXR). CT-scan is used if there is any doubt about the presence of metastasis. Those centres that use CT-scan of the thorax as routine work-up are allowed to do so, but should take part in the prospective collection of data on the clinical significance of micrometastases that are only visible on CT scan and not on CXR. All the other sites are documented in the most appropriate way. IMPORTANT: If at diagnosis a CXR is negative and a CT-scan is positive, the initial treatment will consist of the two drug regimen as in localised disease. For the postoperative treatment, see hereafter.

7.2 PRE-TREATMENT
The three drug schedule with Vincristine, Actinomycin D and Doxorubicin will be used. Duration of pre-operative treatment is 6 weeks.

Thereafter surgery for the primary tumour is performed. As soon as possible after the surgical procedure for the renal tumour the metastatic site will be evaluated.

7.3 POST-OPERATIVE TREATMENT
From this point on the treatment protocol will be determined by the local stage of the abdominal tumour, the histological type of this tumour and the result of the evaluation of the metastatic sides. For pulmonary evaluation plain X-ray is sufficient from the protocol point of view.

For pulmonary metastases there are three starting points:

A Metastasis absent or completely removed by the surgeon.
B Metastasis incompletely removed or multiple inoperable metastases.
C Patients with high risk histology of the primary tumour.

Treatment guidelines are given on the next pages. For non pulmonary metastasis the treatment principle is the same. The responsible doctor will have to work the details for each individual case.
Strategy for management of pulmonary micrometastases, visible only on CT

CXR negative
CT-scan positive

Pretreatment according to localised disease

EVALUATION AFTER NEPHRECTOMY

NO DISCREPANCY
Continue to treat according to stage of localised abdominal disease

CXR negative
CT-scan still positive

RESECTABLE

NOT RESECTABLE

Surgery

BIOPSY?
Response to pre-op. CT?

VIABLE TUMOUR
NO VIABLE TUMOUR CELLS

According to stage IV protocol. Decide on extra DOX for completeness of cumulative dose at the end of therapy.

According to stage of localised abdominal disease

Contact study office (too individualised for standardization)

7.4 CHEMOTHERAPY REGIMENS FOR METASTATIC DISEASE

PRE-OPERATIVE TREATMENT

Vincristine 1.5 mg/m² (maximum dose 2 mg) weekly for 6 weeks (6 doses in total).
Actinomycin D 45 µg/kg (maximum dose 2 mg) at week 1, 3 and 5 (three doses in total).
Doxorubicin 50 mg/m² in week 1 and 5 (2 doses in total).

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

Vincristine and Actinomycin D are given as an i.v. push.
Doxorubicin is given in a 4-6 hours infusion.
POST-OPERATIVE TREATMENT

ARM A

Vincristine 1.5 mg/m² (maximum dose 2 mg) weekly starting at week 1 to week 8 and thereafter in week 11, 12, 14, 15, 17, 18, 20, 21, 23, 24, 26 and 27 (20 doses in total).

Actinomycin D 45 µg/kg (maximum dose 2 mg), a single dose in week 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total).

Doxorubicin 50 mg/m², a single dose in week 2, 8, 14 and 20 (4 doses in total).

No doxorubicin in week 26.

Note: doses in patients with a bodyweight <12 kg are reduced to 2/3 of the original dose and Actinomycin D should be reduced for all patients to 50% of the recommended dose during radiation and the first following course.

Vincristine and Actinomycin D are given as an i.v. push.
Doxorubicin is given in a 4-6 hours infusion.

Radiotherapy: flank irradiation for stage III only.

ARM B

Post-operative therapy should start preferably on day one of the radiotherapy and within two weeks from surgery.

There are two combinations of drugs: VP16 and Carboplatin, and Cyclophosphamide combined with Doxorubicin.

VP16 150 mg/m² for three consecutive days in a one hour infusion in week 4, 10, 13, 16, 22, 25, 28 and 34 (24 doses in total).

Carboplatin 200 mg/m² for three consecutive days in a one hour infusion in week 4, 10, 13, 16, 22, 25, 28 and 34 (24 doses in total).

Cyclophosphamide 450 mg/m² for three consecutive days in a one hour infusion in week 1, 7, 19 and 31 (12 doses in total).

Doxorubicin 50 mg/m² in a 4-6 hours infusion for one day only in week 1, 7, 19 and 31 (4 doses in total).

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

Radiotherapy: stage I and II no abdominal irradiation, stage III abdominal irradiation.
For pulmonary irradiation evaluate at week 9.
**ARM C**

Post-operative therapy should start preferably on day one of the radiotherapy and within two weeks from surgery.

There are two combinations of drugs: VP16 and Carboplatin, and Cyclophosphamide combined with Doxorubicin.

VP16 150 mg/m$^2$ for three consecutive days in a one hour infusion in week 4, 10, 13, 16, 22, 25, 28 and 34 (24 doses in total).

Carboplatin 200 mg/m$^2$ for three consecutive days in a one hour infusion in week 4, 10, 13, 16, 22, 25, 28 and 34 (24 doses in total).

Cyclophosphamide 450 mg/m$^2$ for three consecutive days in a one hour infusion in week 1, 7, 19 and 31 (12 doses in total).

Doxorubicin 50 mg/m$^2$ in a 4-6 hours infusion for one day only in week 1, 7, 19 and 31 (4 doses in total).

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

Pulmonary irradiation is given to all patients.
7.5 STAGE IV

PRE-OPERATIVE TREATMENT

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT</td>
<td>45 µg/kg</td>
<td>↓</td>
</tr>
<tr>
<td>VCR</td>
<td>1.5 mg/m²</td>
<td>↓</td>
</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
<td>↓</td>
</tr>
</tbody>
</table>

WEEKS 1 2 3 4 5 6 SURGERY

ACT = actinomycin D = 45 µg/kg/i.v. bolus injection (max 2000 µg!)
VCR = vincristine = 1.5 mg/m²/i.v. bolus injection (max 2 mg!)
DOX = doxorubicin = 50 mg/m²/i.v./in 4-6 hours

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
STAGE IV, POST-OPERATIVE TREATMENT

A. METASTASES ABSENT OR COMPLETELY RESECTED BY THE SURGEON
(see C for HIGH RISK PRIMARY TUMOUR)

- Local stage I - II: Local stage II treatment, three drugs arm
- Local stage III: Local stage III treatment, three drugs arm + flank irradiation

B. MULTIPLE INOPERABLE METASTASES OR INCOMPLETELY RESECTED

- Local stage I - II: High risk treatment, no abdominal irradiation
  Evaluate the status of the pulmonary metastases at week 9:
  - if CR → no pulmonary irradiation
  - if no CR → pulmonary irradiation
  In any other situation, please contact central office.
- Local stage III: High risk treatment, with abdominal irradiation

C. HIGH RISK PRIMARY TUMOUR

- Local stage I: High risk treatment. No abdominal irradiation. Pulmonary irradiation
- Local stage II - III: High risk treatment with abdominal and pulmonary irradiation
  (except Stage II Blastemal-predominant high risk tumours, which do not receive radiotherapy)
STAGE IV, POST-OPERATIVE TREATMENT

A. METASTASES ABSENT OR COMPLETELY RESECTED BY THE SURGEON
(See C for HIGH RISK PRIMARY TUMOUR)

LOCAL STAGE I - II: NO IRRADIATION

LOCAL STAGE III: ABDOMINAL IRRADIATION

| ACT     | 45 µg/kg | ↓ | ↓ | ↓* | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| VCR     | 1.5 mg/m² |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |
| DOX     | 50 mg/m² |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |↓ |
| WEEKS   | 1 2<------ 3-------- 4------> 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26♦ 27 28 |

♦ no DOX in week 26, so that the total dose does not exceed 300 mg/m²

* Reduce dose of ACT for 50% when RT is within 14 days of this administration (week 5).

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
### STAGE IV, POST-OPERATIVE TREATMENT

#### B. MULTIPLE INOPERABLE METASTASES OR INCOMPLETELY RESECTED

**LOCAL STAGE I - II:** NO ABDOMINAL IRRADIATION  
**LOCAL STAGE III:** WITH ABDOMINAL IRRADIATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP16</td>
<td>150 mg/m²</td>
<td>↓↓↓</td>
</tr>
<tr>
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<td>CYCLO</td>
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</tr>
<tr>
<td>DOX</td>
<td>50 mg/m²</td>
<td>↓</td>
</tr>
</tbody>
</table>

Pulmonary irradiation: ♦ evaluate and decide on pulmonary irradiation in week 9  
Pneumocystis carinii pneumonia prophylaxis in case of pulmonary irradiation

If body weight < 12 kg: dose reduction to 2/3 for each drug  
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
STAGE IV, POST-OPERATIVE TREATMENT

C. HIGH RISK PRIMARY TUMOUR

LOCAL STAGE I: NO ABDOMINAL IRRADIATION, WITH PULMONARY IRRADIATION

LOCAL STAGE II - III: BOTH ABDOMINAL AND PULMONARY IRRADIATION
(except Stage II Blastemal-predominant high risk tumours, which do not receive radiotherapy)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP16</td>
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<tr>
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</tr>
<tr>
<td></td>
<td></td>
<td>16 17 18 19 20 21 22 23 24 25 26 27</td>
</tr>
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Pulmonary irradiation: the start of the pulmonary irradiation will be decided by the local radiotherapist. Pneumocystis carinii pneumonia prophylaxis with cotrimoxazol to be started at week 9.

If body weight < 12 kg: dose reduction to 2/3 for each drug
Major intolerance: doses on the next course should be reduced to 2/3 (see section 8)
Chemotherapy regimens (see Section 6 and 7)

No dose of actinomycin D or doxorubicin and no course of carboplatin, cyclophosphamide or etoposide should be initiated if the absolute neutrophil count is <1.000 /mm$^3$ or the platelet count is < 100.000 mm$^3$.

8.1 DRUGS AND DOSAGE

a. Actinomycin D (Lyovac$^O$, Cosmegen$^O$)
   MSD
   Vials 0.5 mg lyophilized powder

   45 µg/kg/once course for children who weigh 12 kg or more.
   30 µg/kg/once course for children who weigh less than 12 kg.
   No single dose should exceed 2000 µg.

b. Vincristine sulfate (Oncovin$^O$)
   Eli Lilly
   Vials 1 mg/1 ml, 2 mg/2 ml, 5 mg/5 ml solution.

   1.5 mg/m²/once weekly for children who weigh 12 kg or more.
   1 mg/m²/once weekly for children who weigh less than 12 kg.
   No single dose should exceed 2 mg.

c. Doxorubicin
   Pharmacia & Upjohn SA
   Vials 10 mg, 20mg, 50 mg, 100 mg or 150 mg lyophilized powder
   Vials 10 mg/5 ml, 20 mg/10 ml, 50 mg/25 ml or 200 mg/100 ml

   50 mg/m²/once/course for children who weigh 12 kg or more.
   33 mg/m²/once/course for children who weigh less than 12 kg.
   Total cumulative dose given should not exceed 300 mg/m².

d. Etoposid (VP-16), (Etoposide$^O$)
   Pierre Fabre Oncologie
   Vials of 5 ml containing 20 mg/ ml.
   Or
   Etoposid phosphate (Etopophos$^O$)
   Bristol-Myers Squib
   Vials of 100 mg lyophilized powder
150 mg/m²/daily for 3 consecutive days for children who weigh 12 kg or more. 100 mg/m²/daily for 3 consecutive days for children who weigh less than 12 kg. **Total cumulative dose given should not exceed 2700 mg/m². Except for stage IV, arm B and C, where the cumulative dose is 3600 mg/m².**

e. **Carboplatin** (Paraplatin®)  
Bristol-Myers Squib  
Vials of 50 mg/5 ml, 150 mg/15 ml and 450 mg/45 ml solution.

200 mg/m²/daily for 3 consecutive days for children who weigh 12 kg or more.  
2/3 dose (mg/m²) daily for 3 consecutive days for children who weigh less than 12 kg.  

**Nephro-toxicity** is of importance at high doses and in patients with prior renal dysfunction. Precautions: reduction of the dose in proportion to creatinine clearance. **Total cumulative dose given should not exceed 3600 mg/m². Except for stage IV, arm B and C, where the cumulative dose is 4800 mg/m².**

f. **Cyclophosphamide** (Endoxan®)  
Asta  
Vials of 100 mg, 500 mg or 1 gr lyophilized powder

450 mg/m²/daily for 3 consecutive days for children who weigh 12 kg or more.  
300 mg/m²/daily for 3 consecutive days for children who weigh less than 12 kg.  
**Total cumulative dose given should not exceed 8100 mg/m².**

g. **Mesna** (Uromitexan®)  
Asta  
Vials of 400 mg/4 ml, 1 gr/10 ml or 5 gr/50 ml solution.

h. **G-CSF** (Filgrastim)  
(Neupogen®)  
Amgen-Roche  
Vials of 300 mcg/1 ml or 480 mcg/1.6 ml of rH G-CSF solution

5 µg/kg/daily 24 hours after the last dose of chemotherapy and given until ANC > 1000 and past the nadir of myelo suppression or a minimum of 1 week.  
**Should be stopped for 48 hours before restarting chemotherapy.**

8.2 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 as an intravenous infusion over 24 hours/ 200 ml normal saline. 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, and no longer than 6 hours, according to local policy. Regular monitoring with echocardiography is recommended during and after therapy (see 5 cardiac toxicity).
   Central venous access is mandatory.

c. **Etoposide**( VP-16) Vepesid
   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 one hour one should pay attention to this. No additional hydration is required for etoposide itself.

d. **Carboplatin** (Paraplatin)
   The drug is dissolved in 250 ml glucose 5% solution and given over 1 hour.

e. **Cyclophosphamide** (Endoxan)
   Must be accompanied by mesna (Uromitexan) to prevent bladder toxicity if given in higher doses. Hydration should precede the infusion and continue during 12 hours, paying attention to the diuresis: patients should be asked to void at least every 2 hours during the 12 hours period immediately following a dose of 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.

f. **Mesna** (Uromitexan)
   30 minutes before the cyclophosphamide administration 20% of the cyclo-dose in mg of Mesna. Thereafter every 4 hours again 20% of the cyclo-dose until 24 hours after the last cyclo-administration. This is recommended for cyclo-doses of $\geq 500$ mg/m$^2$.

g. **G-CSF** (Neupogen)
   Is administered once daily subcutaneously or i.v. without dilution.

**8.3 DOSE MODIFICATIONS**
a. **Adjustment of dose to body weight**
Children with a body weight of less than 12 kg will have a dose reduction of 2/3 of the original dose mainly to prevent the risk of veno-occlusive disease.

b. **Radiation**
If liver or large fields such as the entire abdomen, the entire thorax or both are irradiated, doses of actinomycin D should be reduced for all patients to 50% of the recommended dose during radiation and the first following course.

c. **Toxicity**
1. **Hematological toxicity**
   Hemoglobin level, WBC and platelet counts should be performed before each course of chemotherapy.
   - **Neutropenia:** absolute neutrophil count (ANC) has to be above 1000/mm$^3$ to start a course with actinomycin D or doxorubicin.
     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 > 100,000/mm$^3$ to start a course.
     The course in progress should be interrupted if the platelet count falls below 50,000/mm$^3$ and in case of such a sudden fall, the patient should be monitored carefully for signs of VOD or sepsis/line infection, with daily full blood count and liver function tests. Platelets transfusion is indicated only in case of haemorrhages.
   - **Anemia 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 WBC count below 1500/mm$^3$ or in a nadir ANC below 1000/mm$^3$, associated with mucositis and/or fever or in a nadir platelet count below 50,000, associated with marked enlargement of the liver 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 antisepsics and intravenous fluids have to be given as required.
   - **Constipation** is common with vincristine. One has to see that loose stools are produced. The drugs should be omitted in case of paralytic ileus and restarted at a 50% dose.

3. **Hepatic complications**
   May occur at the time of treating nephroblastoma of the right kidney and irradiation
of the whole abdomen associated with actinomycin D or doxorubicin. This may be related too to actinomycin D alone. 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 and half the dose should be given for the first following course. If the symptoms reappear during actinomycin D treatment, this drug should be withdrawn permanently. Vincristine may also enhance hepatopathy. If there are problems in interpreting or applying the protocol in children with hepatic disease, the Secretariat 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 and thereafter every 200 mg/m$^2$ cumulative dose. Dose modification must be considered if fractional shortening falls below 28% or a reduction of > 10% is seen between two consecutive administrations. If seen, do not delay chemotherapy by giving VA alone. Repeat echo after 3 weeks and if improved, proceed with doxorubicin, but perform echocardiography before each administration of doxorubicin. A reduction above 20% of baseline is a reason to stop doxorubicin until the fractional shortening has normalized. Cardiac toxicity is more prone to occur in a patient who has received thoracic radiotherapy and has a left sided nephroblastoma stage III. We recommend measuring fractional shortening, ejection fraction and the End Systolic wall Stress*, as an evaluation of increasing afterload, one major problem, 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. See also 8.2.f.

8.4 MAJOR INTOLERANCE DURING PRE-OPERATIVE THERAPY
It is an indication to cease chemotherapy if during the pre-operative chemotherapy the following complications occur.

a. Profound thrombocytopenia (thrombocytes < 50x10⁹/l) with or without haemorrhages associated with veno-occlusive disease:
   - abdominal pain with diarrhoea, ascites, oedema, marked enlargement of the liver,
   - oliguria, fever and jaundice
b. or with cutaneous erythema with desquamation or pruritis.
c. Severe neurological complications as intolerable paresthesias with paralysis, convulsion, coma or amaurosis.

If any of the above occur, they should be immediately reported to the office in Amsterdam.
See Appendix 8.

8.5 SUPPORTIVE CARE

The physician can prescribe whatever he thinks appropriate for pain, vomiting, constipation, etc. However, antimitotic agents and immunotherapy must not be prescribed.

Laxatives should be prescribed when Vincristine is given to prevent constipation.
A diet containing no lactose, saccharose and gluten has to be given as a prophylactic measure during the irradiation.

Pneumonitis prevention: In patients receiving the high risk regimen and those who are treated with lung irradiation it is recommended to give cotrimoxazole.

G-CSF Especially in the high risk regimen it might be necessary to use growth factors if bone marrow recovery is not sufficient before the next course. Also in case of severe infections in aplastic patients one could decide to use G-CSF (see also section 8.1).
For patients treated according to the other regimens, supportive treatment with growth factors is permitted but not considered as essential.

Transfusion: Full blood and platelet transfusions may be given on centre recommendations and/or clinical protocols.
SECTION 9
SURGICAL TECHNIQUE, RECOMMENDATIONS AND ADVICE

9.1 INTRODUCTION

The principles of nephrectomy for paediatric malignancy were established by Gross in 1953: a wide transverse transabdominal incision and transperitoneal 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).

The present study deals with further risk-adaptation of treatment. A number of patients will receive less treatment. Thus, quality of resection and accurate reporting are of the utmost importance.

9.2 GENERAL REMARKS

1. Please ensure familiarity with the contents of this Section and the surgical forms prior to surgery.
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 protocol requirements.

9.3 IMAGING

Abdominal ultrasonography, plain chest X-ray in two planes and 24 hr urine collection to assess the catecholamines excretion, kidney function and the presence of haematuria, are sufficient to establish the correct diagnosis in the majority of cases (see the scheme for the diagnostic work-up: 'Guide to the diagnosis').

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

Ultrasonography (US), with high quality Doppler (coloUr or power) and computed tomography (CT) are of most value to the surgeon. The CT makes excretion urography (EU) unnecessary, but not the Doppler US. Magnetic resonance imaging (MRI) is very effective but in most cases is unnecessary. An ambiguous sonogram should always be supplemented with CT or MRI. 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.
9.4 THE OPERATION

Access
Long transverse transabdominal incision.

Inspection of the abdominal cavity
The abdominal cavity should always be inspected prior to tumour removal. Metastases in the liver, lymph nodes and peritoneum should be searched for. Since SIOP 6 and 9 studies have shown the value of excision for both pulmonary and intra-abdominal metastases, every effort must be made to remove these completely (11-12). Every lesion should be excised (if resectable) or biopsied (if unresectable) and its position marked. This includes lymph nodes, which should be sampled even if they appear normal (see below). Excised material must be sent to the pathologist in a separate container and its origin clearly indicated. Complete excision should be attempted even if the diagnosis of nephroblastoma is uncertain. If the tumour is considered inoperable, it should be biopsied, preferably with a Tru-cut needle.

Thorough inspection of the opposite retroperitoneal space is obligatory only if pre-operative imaging indicates bilateral localisation of the tumour. In other cases it rarely gives more information than good quality imaging. The operating surgeon should decide whether or not to do it in individual cases. Unequivocal stage V cases will be treated following "Stage V treatment suggestions".

Nephrectomy
Early ligation of the renal vessels should be the aim and is possible in nearly every case. The renal artery should be ligated first in order to avoid swelling of the tumour with increase of its fragility and the possibility of dissemination via perforating perinephric veins. An extensive Kocher-manoeuvre of the duodenum is a convenient approach to the renal vessels for a large tumour whether on the right or left. An approach via the peritoneum lateral to the colon is also acceptable. The technique of the approach should be indicated in the surgery form. If the tumour is very large and infiltrating and the primary ligation of renal vessels is difficult and considered too risky, the tumour should be dissected from surrounding structures first, and vessels ligated when possible. This should be precisely described in the surgery form. The tumour should be removed together with adipose capsule and, if possible with all invaded surrounding structures. Heroic and mutilating resections such as pancreatectomy are not recommended as these tumours are both chemo- and radiosensitive (1-3).

Renal Vein, Vena Cava
Although intravascular extension of the tumour is usually apparent on the pre-operative imaging, the vena cava and renal vein should be carefully examined during the operation. If thrombus is found, it should be removed. A short thrombus in the renal vein may be resected together with the vein. A thrombus extending to the infra-hepatic vena cava should be removed through a vena cavotomy, after occluding the contra lateral renal vein and cava above and below the thrombus. The thrombus should be removed and the venotomy closed. A longer thrombus, (infra-hepatic, supra-hepatic, or right atrial), may require the assistance of a vascular or cardiac surgeon and cardiopulmonary by-pass (2,3,13,14).
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 not all such cases are lost (10).

**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 nodes was not performed. This suggested that inadequate staging led to under-treatment of local disease in these children (15).

**Sampling and histological examination of lymph nodes is imperative for accurate staging and subsequent treatment.** Hilar and para-aortic lymph nodes at the origin of the renal artery (regional nodes) and nodes below or above this level (extra regional nodes) should be sampled even if not suspicious. Involved or suspicious lymph nodes must be excised without rupture. They must be carefully labelled and sent to the pathologist separately with an accurate description of their position and character. **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 (16,17).**

**9.5 STAGE IV TREATMENT RECOMMENDATIONS**

1. As demonstrated by previous studies, lung metastases should be excised if possible (4,11,12). Operation should be performed either as soon after nephrectomy as the patient’s condition permits, or after the beginning of the postoperative chemotherapy. This should be decided upon by both surgeon and chemotherapist. Bilateral resectable lung metastases should be excised either via two thoracotomies or one 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.

1. Experience from SIOP 6 and 9 justifies a similar approach for extra pulmonary metastases, especially for the second most frequent – in the liver (12). 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 (12). Metastases outside lung or liver should be excised completely provided the operation can be done without mutilation, or loss of vital organs (4,11,12).

2. **Complete excision of metastases is extremely important as it removes 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.

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

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9.6 BILATERAL DISEASE TREATMENT RECOMMENDATIONS
(Refer also to Appendix 4 – Management of Bilateral Wilms Tumour)

Bilateral cases should be treated individually. This intervention requires an extremely experienced team. Surgery is planned after tumour reduction with chemotherapy. The goal is **bilateral partial nephrectomy (or wedge resection)** preferably in two separate operations performed 1-2 weeks one after another, either in situ or extra corporally with subsequent auto transplantation. 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 (18,19). Enucleation is 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 should be biopsied, preferably with the Tru-cut needle, and the patient treated with further chemotherapy. 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 (10 Gy) and chemotherapy may result in long-term remission even after incomplete excision (20). 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, 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 accidentally, during operation in a previously untreated patient, both tumours should be biopsied (contrary to the unilateral cases), preferably with the 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.

For surgical management of nephroblastomatosis – consult Appendix 5 – Management of Nephroblastomatosis. Note that the nephron sparing surgery is often adequate in such cases.

9.7 OPTIONAL: PARTIAL NEPHRECTOMY

Partial nephrectomy may assure local control in Wilms tumour (21-27). Most reports deal with bilateral tumours in which this approach is the 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 (21-27). Contra-lateral urological and nephrological disorders and genetic syndromes of an increased risk of Wilms rather than a risk of hyper perfusion nephropathy in the remaining kidney are important criteria when this option is considered (28).

We do not recommend partial nephrectomy in a classical unilateral nephroblastoma which is not related with the above disorders. We would, however, like to collect data on all patients subjected to partial nephrectomy provided that the contraindications listed below are respected. These patients will not be excluded from the study.

**Contraindications for partial nephrectomy:**

1. pre-operative tumour rupture or biopsy
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 (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)
6. multifocal tumour
7. central location
8. involvement of calyces
9. haematuria
10. little experience in partial nephrectomy.

**Remarks:**

1. A significant reduction of tumour volume after the preoperative chemotherapy suggests a better chance for successful partial nephrectomy.
2. Resection must be performed with the margin of healthy renal tissue, enucleation is not adequate local treatment.
3. Intra-operative ultrasound scanning is very useful in defining the intrarenal tumour extent.
4. Following partial nephrectomy the kidney should be assessed with Doppler sonography (or IVP) two days after surgery. The contribution of the spared renal tissue in the total urinary excretion should be assessed scintigraphically 6 months later. Further oncological follow-up and the long-term functional survey is mandatory, and should be conducted according to the recommendations for bilateral cases. (See Appendix 4).
5. Patients with stage I anaplastic tumours after pre-operative chemotherapy have a higher risk of relapse than those after immediate nephrectomy (29). Nephrogenic rests, 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 after partial nephrectomy with ultrasonography performed monthly for at least six months. Subsequently the standard follow-up is continued.
6. The decision for partial nephrectomy should be taken by all members of treating team and finally approved by the surgeon at operation.
9.8 RECOMMENDATIONS FOR 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 mediastium.

9.9 SURGERY-RELATED COMPLICATIONS

A joint NWTS-SIOP study on surgery-related complications is in progress. Previous SIOP reports demonstrated a marked reduction in surgery-related complications when pre-operative chemotherapy was compared with primary nephrectomy.

The aim of the study is to verify the retrospective results of the NWTS-3 (19.8% surgery-related complications rate after primary nephrectomy ignoring tumour rupture) and the SIOP-9 (8% surgery-related complication rate after post-chemotherapy nephrectomy including tumour rupture) prospectively (9,30). The forms and rules do not change: the “nephrectomy-related complications check list” should be consulted twice: at operation and 1 year later. Completed data sheets should be sent to the SIOP Nephroblastoma Trial and Study Office.

9.10 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 the pre-operative CT was not performed, please mark with titanium clips at least the upper and lower border of the tumour so as to facilitate the targetting of radiotherapy.

For Wilms tumour, a minimal invasive surgical technique does not offer any advantages over the classical open surgical approach. Laparotomy is always necessary to remove the primary tumour intact from the abdomen. For metastatectomy, endoscopic techniques do not allow palpation of the lungs or liver for small parenchymal nodules which may frequently be missed on imaging. However, this technical approach may be useful for diagnostic reasons in selected patients.

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 formaline 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 one "metastatectomy form" for each metastatectomy you performed even if it was performed during nephrectomy. One copy of the complete metastatectomy report should accompany the 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.

PROBLEMS, SUGGESTIONS, REQUESTS

We would welcome any opportunity to discuss problems, suggestions or requests and ask you to contact the SIOP Nephroblastoma Trial and Study Committee or a member of the Panel of Surgeons (see Appendix 1).

Surgeons-in-charge of writing this chapter were Dr Godzinski, Dr van Baren, Dr Bürger, Prof. Gauthier, Prof. Sawicz-Birkowska, Prof. Hoellwarth, Dr Cecchetto, Dr Holmes and Dr Walker. Co-authors, consultants and advisors were members of other panels of the SIOP Nephroblastoma Trial and Study Committee.
REFERENCES

SECTION 10
RADIOThERAPY

10.1 INDICATIONS FOR RADIOThERAPY (RT)

Indications for post-operative flank RT:
- Histologically intermediate risk, stage III (nodes positive N+, residual disease left after surgery, tumour rupture)
- High risk, stage II, except blastemal type
- High risk, stage III
- Stage IV and stage V according to local stage

Indications for post-operative whole abdominal RT:
Whole abdominal RT is indicated for DIFFUSE intra-abdominal tumour or GROSS pre-operative or peri-operative rupture.

Abdominal/flank RT will start as soon as possible within 2 weeks after abdominal surgery. If there is an expectation of surgery for lung metastases or lung RT, abdominal RT will be postponed. In case of lung surgery abdominal RT will start after this surgery. In case of no lung surgery abdominal RT starts after week 9 whether or not in combination with lung RT.

Indications for pulmonary RT:
Residual tumour tissue in the lungs is visible on a chest X-ray or CT scan after the commencement of pre-operative chemotherapy, and that this residual tumour is not completely excised and if post-operative chemotherapy according to the high risk protocol does not lead to a complete remission, by week 9. RT should not be given if a CR is achieved at week 9 of postoperative chemotherapy. Complete remission: no abnormalities seen on chest X-ray or chest CT-scan. RT is also indicated in case of a histological high risk primary tumour, regardless of metastatic response.

Indications for hepatic RT:
Liver metastases which do not respond completely to chemotherapy and which cannot be completely resected with negative margins.

Indications for RT to other metastatic sites:
Patients with haematogenous metastases to the brain (whole brain RT) and/or bone metastases (focal RT) at diagnosis, should be treated with the appropriate RT fields regardless of response to chemotherapy.
10.2 AIMS OF RADIOTHERAPY

To achieve control of abdominal disease in patients who have significant risk of intra-abdominal relapse.

To increase the control of pulmonary metastases in patients who do not achieve a complete remission.

To increase the control of hepatic metastases in patients who do not achieve complete remission after chemotherapy or surgery (R1 & R2 resections).

To increase the control of brain metastases.

To increase the control of bone metastases.

10.3 EQUIPMENT

Modality: photons from a linear accelerator. If not available one may use Cobalt-60. Energy usually 4-6 MV.

10.4 TARGET VOLUME

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

Localisation of primary tumour and kidney for flank/abdominal RT

For RT planning the pre-operative tumour extent should be localised according to the pre-operative contrast-enhanced CT scan.

The boundaries of the tumour and kidney during surgery must be marked with clips and in the case of areas suspicious of incompletely resected disease these should be marked with clips (material which does not interfere with CT or MR imaging) as well.

If the pre-operative contrast-enhanced CT scan is not available one should rely on these above mentioned markers for the delineating of the tumour and its extension.

Marking the boundaries of the tumour/kidney is probably the most important way of delineating the tumour and its extension, together with the surgical and histopathological reports.

A margin of one cm should be taken superior, lateral and inferior of these clips. The medial border always 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 CT abdomen may be performed to delineate the tumour.

SIMULATION

All patients will undergo a simulation procedure with a conventional simulator or CT-simulator. All patients will be treated in the supine position. Customized blocks are drawn on the simulator films and will be checked on the simulator. All critical organs will be blocked if this is possible.

CLINICAL TARGET VOLUME (CTV)

Flank RT
CTV: This encompasses the extent of post-chemotherapy and pre-operative macroscopic tumour and the kidney according to the surgical and histopathological reports and according to the extent on CT-scan/ultrasonography. The margin for CTV is 1 cm.

If there is no pre-operative CT-scan CTV is delineated by clips at the boundaries of the tumour and kidney placed by the surgeon during surgery. The margin for CTV is 1 cm beyond the clips.

The treated volume should extend across the midline to achieve homogeneous irradiation of the full width of the vertebral bodies.

Boosts for residual macroscopic disease
CTV: This should encompass the extent of macroscopic residual disease after surgery with a margin of 1 cm. 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 celiac axis arises from the aorta at the level of the pedicle of the 12th vertebral body (2). Again the full width of the vertebral bodies should receive a homogeneous dose.

Whole abdominal RT
CTV: This 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: This 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: This includes the extent of incompletely resected tumour with a margin of 2 cm.
RT for brain metastases
CTV: the whole brain is treated.

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:

Internal margin: 1 cm for breathing movements.

Especially for left sided tumours RT of the heart should be avoided if possible.

10.5 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). Patients with tumour positive lymphnodes should receive a boost to the paraaortic lymphnodes.
Stage II, stage III, high risk: 25.2 Gy
Boost to the macroscopic residual disease after surgery: 10.8 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). Dose per fraction should be lowered to 1.5 Gy. A milk and gluten-free diet should be considered for the duration of the abdominal radiotherapy.
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).

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 10-15 Gy should be considered for areas of gross residual disease after surgery.

10.6 **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 homogeneity 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 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.
DOSE UNIFORMITY AND REFERENCE POINTS (ICRU 50)

The dose variation within the target volume should not exceed -5% - +7% of the prescribed dose.

TREATMENT TECHNIQUE

Patients will generally be treated in the supine position.

NORMAL TISSUE SPARING

Critical organ dose
Remaining kidney: The dose to the remaining kidney should not exceed 12 Gy.

Liver: the dose to the whole liver should not exceed 20 Gy. A dose exceeding 20 Gy should not be received by more than half the liver.

Lung: the whole lung dose should not receive more than 15 Gy in 1.5 Gy fractions (with correction for inhomogeneity). A dose exceeding 15 Gy should not be received by more than 25% of the lung volume.

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

10.7 QUALITY ASSURANCE DOCUMENTATION

Copies of the following quality assurance information should be sent on request to the national clinical trials office or to the SIOP Secretariat along with copies of the radiotherapy trial forms:

Radiotherapy Data reporting forms
Diagnostic/Clinical Data
Simulator films (initial volume and boost)
Treatment machine verification films
Daily treatment chart
Copies of dose calculations
10.8 EXAMPLES FOR TYPICAL TARGET VOLUMES AND RADIATION PORTALS

Stage II high risk, stage III (related to anatomical landmarks) Fig. 1a, b, c

Cranial border:

- left sided tumours: 1-2 cm above the macroscopic tumour e.g. dome of diaphragm. If possible do not irradiate the heart.
- right sided tumours: if feasible 1-2 cm below the dome of diaphragm (sparring of liver)

Caudal border:

1-2 cm below the macroscopic tumour e.g. within the iliac fossa often including the iliac crest. watch the position of the ovaries (homo- and contra-lateral)

Lateral border:

including the abdominal wall

Medial border:

depending on tumour extension: including the vertebral bodies watch the contralateral kidney

Boost volume for macroscopic residual disease: extent of residual macroscopic disease at surgery with a 1-2 cm safety margin.

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

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

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

**Stage III intermediate and high risk:**
(if lymphnode involvement under the level of the renal artery, same instruction):

Target volume encompasses the whole paraaortic lymphnode chain including the homo-lateral pararenal lymphnodes and the macroscopic tumour extent at surgery plus a 1-2 cm safety margin. The safety margin may not be feasible towards the contra-lateral kidney.

Examples for typical Target volumes and radiation portals:
Stage III (related to anatomical landmarks) Fig. 2, a,b

**Cranial border:**

Left-sided tumours: 1-2 cm above the macroscopic tumour e.g. dome of diaphragm

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

Lymphnode chain: upper plate of TH XII

**Caudal border:**

1-2 cm below the macroscopic tumour e.g. within the iliac fossa often including the iliac crest.
Watch the position of the ovaries (homo-and contralateral)!

**Lymphnode chain:**
Lower plate of L IV (lymphnode chain) but for preventing inhomogeneous dose to the bone, the border is often the elongation of the caudal border

**Lateral border:** including the abdominal wall

**Medial border:** including the tranverse process of the vertebral column.

Boost volume for lymphnode chain in case of macroscopic residual disease in the lymphnodes (stage III):

**Cranial and caudal border:** see above

**Homo-lateral border:** including the tranverse processes of the vertebral column and the renal hilus

**Contra-lateral border:** including the transverse process of the vertebral column

**Examples for typical Target Volumes and Radiation Portals: Stage III macroscopic residual disease (continued)**

Fig. 2a: right-sided tumour with one homo-lateral pararenal lymphnode involved and removed (stage III). Radiation portal covering the tumour region (including the right dome of diaphragm and the iliac crest) and the whole paraaortic chain.
Fig. 2b:
Right-sided tumour with several paraaortic lymphnodes involved (stage III) and suspicious macroscopic residual disease in the lymphnode chain at surgery (stage III macroscopic residual disease). Radiation portal covering the tumour and the paraaortic lymphnode region. Boost volume in case of macroscopic residual disease refined to the lymphnode chain including the homo-lateral renal hilus.

Examples for typical target volumes and radiation portals: Stage III major intraperitoneal rupture (continued)

**Stage III (all histologies): major intraperitoneal rupture**

Target volume encompasses the whole intraperitoneal cavity.

Examples for typical target volumes and radiation portals: stage III major intraperitoneal rupture (related to anatomical landmarks) fig.3
Examples for typical target volumes and radiation portals: stage III major intraperitoneal rupture (related to anatomical landmarks) fig.3 (continued)

**Cranial border:** including both domes of the diaphragm

**Caudal border:** upper part of the symphysis

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

**Lateral border:** including abdominal wall. Watch shielding the remaining kidney (max dose 12 Gy) watch dose at the testes

**Boost Volume for macroscopic residual disease:** extent of residual macroscopic disease at surgery with a 1-2 cm safety margin.

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Fig. 3: Massive intraperitoneal rupture during surgery as right-sided tumour broke into many pieces and spread around the intraperitoneal cavity (stage III major rupture). Radiation portal covering the whole intraperitoneal cavity.

No boost indicated as no detectable macroscopic residual disease was seen at surgery.

Examples for typical target volumes and radiation portals: stage III major retroperitoneal rupture (related and anatomical landmarks) fig. 4.

Stage III (all histologies) major retroperitoneal rupture

**Target volume** encompasses the whole homo-lateral retroperitoneal space including the prevertebral space.
**Cranial border:** including the dome of the diaphragm

**Caudal border:** upper part of the symphysis

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

**Homo-lateral border:** including the abdominal wall

**Contra-lateral border:** including the vertebral bodies, line from edge of LV to symphysis (watch the location of the contralateral ovary! Watch the dose at the testes!).

**Boost volume** for macroscopic residual disease: extent of residual macroscopic disease at surgery with a 1-2 cm safety margin.

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**Fig. 4:**
Extensive retroperitoneal rupture in a huge tumour without contamination of the intraperitoneal cavity (stage III major retroperitoneal rupture). Radiation portal including the right retroperitoneal cavity and the retroperitoneal prevertebral space. Boost is indicated if there is macroscopic disease left in the retroperitoneal space during surgery.

**Keep in mind:** When defining the margins of the radiation field the following well known fact has to be taken into account: geometric field margins by definition represent in most megavoltequipments the 50 %-isodose curve and do not represent the adaequate dosimetric target coverage.
10.9 PULMONARY RADIOThERAPY

Stage IV: Lung

Target volume encompasses both lungs including the costodiaphragmatic recesses.

If local abdominal radiotherapy has to be performed, pulmonary and abdominal targets are defined on the same film. If the targets overlap, a decision has to be taken related to target matching of the two adjoining radiation fields. Special attention has to be paid to radiation related morbidity when treating a larger volume.

Examples for typical target volumes and radiation portals: stage IV lung (related to anatomical landmarks) Fig. 5

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

**Cranial and lateral border:** including the lung, shielding the shoulder region

**Caudal border:** including the bottom of the costodiaphragmatic recesses: e.g. 2-4 cm below the radiologically visible diaphragm, depending much on the phase of respiration which is to be seen at lateral recesses or on tranverse fluoroscopy

**Lateral borders:** including the thoracic walls

**Boost volume:** 5-10 Gy to tumour remnants visible at the start of radiotherapy. If very widespread, 5 Gy to the whole lung (up to 20 Gy). In very young children, protect as much lung tissue as possible.
Examples for typical target volumes and radiation portals: stage IV lung
(continued)

Fig. 5:
Pulmonary metastases at diagnosis (stage IV lung) with residual inoperable disease in the left
and central right lung after pre-operative chemotherapy. Indication for pulmonary
radiotherapy if there is disease after post-operative aggressive chemotherapy. Radiation portal
including both lungs with its recessses. Remember air-correction when calculating dose.
Lateral view needed to calculate dimension of lung tissue.

10.10 ORGANS AT RISK

Bone and soft tissue
It is not clear to what degree a radiation dose of 15 Gy in young children will impair bone and
soft tissue growth. It can be assumed that, if there is an impairment, this will only be small and
of no significant clinical relevance. The amount of impairment is certainly larger after a
radiation dose of 30 Gy.

The whole vertebral column should always be included within the radiation portal in order to
avoid dose inhomogeneity which is known to produce scoliosis. Nevertheless, the radiation
portal should not include major parts of the contralateral kidney (fig. 1,2)
The **iliac crest** contains the apophysis from which the growth of the iliac bone mainly takes place. In order to avoid asymmetric iliac bone growth radiation dose at this apophyseal line should not be more than 15 Gy (fig. 1, 2).

The epiphyseal lines of the acetabulum cannot be saved, if the whole intraperitoneal cavity is to be adequately irradiated ("abdominal bath") (fig. 3, 4). The femoral head should not be included in the treatment volume as it does not belong to the target volume and epiphyseal slipping is a possible consequence after radiatherapy in young children (fig 3,4).

The **shoulder** is not to be included within the treatment volume when pulmonary radiotherapy is indicated (fig. 5).

For technical reasons there is little chance to keep **soft tissue** out of the treatment volume. The skin is spared by the build-up effect of megavolt beams. Sparing of the underlying soft tissue increases with the megavoltage energy.

**Liver**

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

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

**Gastrointestinal tract**

Because of the radiosensitivity of the rapidly proliferating mucosa sparing from the irradiation volume is advisable but only possible by adequately tailoring the treatment portal.

**Kidney**

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

**Ovary**

At least one ovary should not receive a radiation dose (from scattered radiation, beneath a shielding block) of more than 10-15 % of the dose at the reference point (15 Gy) (fig. 1,2,4).

As the necessary distance between the field margin and the location of the ovary to achieve this dose can be estimated before treatment performance (in using e.g. 10 MV photoins the distance should be more than 2 cm), much attention should be paid to adequate localization in this regard. If the target dose is 30 Gy the ovarian dose should not exceed 5-10% of the reference dose.

Only in total abdominal radiotherapy both ovaries are irradiated up to 15 Gy.
Testes
Radiation dose to the testes from scattered radiation should be clearly below 5 % of the radiation dose at the reference point (15 Gy). Special attention is necessary in total abdominal radiotherapy because of the close relationship between the caudal border and the position of the testes, particularly in small boys (fig. 3,4).

Mammalian Bud
The mammalian bud is known to be very radiosensitive even in low dose radiotherapy and should be spared from radiotherapy whenever possible. Special attention has to be paid when treating tumours in the upper abdomen and including the dome of the diaphragm (fig. 1b, 3,4). In radiotherapy of both lungs some sparing of the mammalian bud may only be achieved by the build-up-effect in high megavoltage beams (fig.5).

10.11 TECHNICAL AND PHYSICAL TREATMENT PLANNING AND PERFORMANCE

Treatment planning is based on adequate tumour localization and target definition. It includes treatment simulation at a dedicated treatment simulator, production of individual, focussed shielding blocks, and calculation of dose.

Computed tomography within the planning procedure and computed assisted calculation of dose distribution based on transverse CT is recommended.

The most often chosen field arrangement is two parallel equally weighted opposed fields (from anterior and posterior).

Treatment simulation
At the treatment simulator the borders of the portals are precisely and reproducibly defined by fluoroscopic imaging, documented on a simulation film (X-ray-film) and drawn on the skin of the child. The child is in the same position (usually supine) as during the following treatment.

Tumour extension, target volume and shielding blocks are delineated on the simulation film based on the surgical and histopathological report (drawing) and pre-operative X-ray film and sectional imaging (CT). The position of the contralateral kidney is visualized on the simulation film by intravenous contrast medium.

In case of a CT assisted treatment planning tumour, target volume, and organs at risk are delineated on one or several CT slices taken with the child in treatment position.

Shielding blocks
The kidney block should preferably be placed in the posterior field only. The production is individual, focussed shielding blocks is based on the drawing on the simulation film and carried out by hand or computed assisted. The thickness of the blocks is dependent on the atomic number of the shielding material and the beam energy and should be at least 5 h.v.l. thick.

Radiation dose below the shielding block should preferably be below 10 % and should not exceed 15 % of the dose at the reference point. When shielding the ovaries by blocking, thicker blocks, 6 h.v.l., are advised.

10.12 CALCULATION AND REPORTING OF DOSE IN THE TARGET AND ORGANS AT RISK
Target volume dose
Target dose is calculated and reported according to the ICRU criteria (1). This reference point is in a central part of the target volume. For nephroblastoma treatment the reference point of target dose is specified as follows (1,3): for parallel opposed equally weighted beams (most usual) on the central axis midway between the beam entrances; for parallel opposed unequally weighted beams on the central axis at the centre of the target area; for any other arrangement of intersecting beams at the intersection of the central axis of the beams.
Dose inhomogeneity within the target volume should be in $\pm 5\%$ of the dose at the reference point and should not exceed $\pm 10\%$. CT based computed dose calculations have to follow the same rules for target dose specification. In pulmonary radiotherapy the dose at the reference point (central beam midway in the mediastinum) has to be corrected taking account of the minor radiation absorption in the air filled lungs which represent the target volume. It results in a reduction of dose at the reference point about 10-15 $\%$ in order to arrive at the prescribed dose in the lung.
The distance at which the 90%-isodose is reached from the 50%-isodose at the geometric field margin towards the centre of the portals depends on the beam sharpness. Megavoltage equipment, beam quality and energy, source size and source surface distance, field size, depth of reference point are all factors influencing the beam sharpness.

Dose in organs at risk
Dose in organs at risk is calculated and reported for each organ separately. It is recommended to add the (estimated) volume of the organ irradiated to the reported dose. Typical organs at risk in nephroblastoma treatment are the vertebral column, iliac bone, contralateral kidney, soft tissue of the irradiated flank, liver, ovaries, testes and heart (4).

Treatment Performance
Patients are treated on megavoltage equipment with modern technical refinements (e.g. gantry rotation, isocentre, beam collimation). Modern linear accelerators are very suitable machines for these treatments. Cobalt 60 units (SSD at least > 80 cm) may also be used regarding the physical and technical properties. Patients are treated in supine position through anterior and posterior portals (by gantry rotation) which are equally weighted. Both fields are treated every day. Divergent shielding blocks are positioned on the tray holder.
Verification films are taken at the megavoltage beam before the first treatment and at regular intervals at least once a week.
A photograph is taken with the contours of the treatment field and the shielding blocks drawn on the skin of the child. For megavoltage photon energy above 10 MV, bolus is needed because of the low dose in the first 1-2 cm.

Side effects
Significant acute haematologic side effects (neutropenia, thrombocytopenia) are observed when irradiating extensive volumes including a large amount of bone marrow together with chemotherapeutic agents that lead to significant haematological toxicity by itself (actinomycin D, epirubicin, doxorubicin, carboplatin). Therefore the dose of these chemotherapeutic agents has to be reduced, when a large volume is to be irradiated.

Hepatopathy (veno-occlusive-disease, VOD) can be caused by actinomycin D alone. If VOD developed during pre-operative chemotherapy, post-operative irradiation of large parts of the
liver should be avoided.
In irradiation of the liver (15-20 Gy) liver function and thrombocytes have to be monitored
(e.g. liver function tests), as an impairment may occur in the acute or chronic phase (5,6).

**Gastrointestinal side effects** like diarrhoea and vomiting may be observed during abdominal
radiotherapy in particular if large volumes are treated. Symptomatic treatment for vomiting and
for diarrhoea is necessary including intravenous fluids are required. A diet free of lactose and
saccharose and with low fat content is recommended for treatment of acute and late radiation
enteritis (7).

**Impairment of bone and soft tissue** growth mainly takes place years after radiotherapy and is
most pronounced during growth spurts. The amount of impairment is dependent on radiation
dose, irradiated volume, and age of the child and reveals as kyphoscoliosis. hypoplasia
(vertebral column, iliac bone, ribs, soft tissue of the flank) and osteochondroma (8,9). The
impairment is expected to be smaller after a low dose of radiotherapy (15 Gy).

**Impairment of renal function** induced by irradiation doses up to 12 Gy is not to be expected,
as this radiation dose is far beyond the dose level at which renal dysfunction ( e.g. as reduction
in creatinin clearance) becomes probable (10). In combination with carboplatin and ifosfamide
close follow-up for renal failure is advised.

**Ovarian insufficiency** is likely to occur after irradiation with doses about 15 Gy, if the true
pelvis had to be included into the irradiated volume (11). Nevertheless, little is known about
ovarian tolerance doses for young girls. Hormonal function and fertility can probably be
preserved if the ovarian dose can be kept below 2-3 Gy.

**Impairment of spermatogenesis** may occur even after scattered radiation doses above 50 to
100 cGy to the testes (12). Leydig cell function is much less radiosensitive and not influenced
by such low scatter radiation dose.

**Hypoplasia of the mamma** is known to occur after doses about 1-3 Gy in the young child
(13).

**Reduction of lung volume** and dynamic compliance can develop to some degree after
radiotherapy to both lungs, more so in young children, because of insufficient growth of the
rib-cage (14,15).

**Cardiomyopathy** in case of pulmonary irradiation, previous treatment with epirubicin or
radiotherapy followed by this drug may increase the chance of this complication. Echocardiography should be done at regular intervals to detect early toxicity.

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It is impossible to write a protocol that answers all the specific needs if applied in so many countries all over the world. This is to be kept in mind using the protocol.

**Diagnosis:** Section 4 specifies the minimum diagnostic observations required. It is up to the responsible physician to decide whether to use more evidence concerning the role of CT-scanning, MRI or biopsy. So besides the minimum required observations it is up to the responsible physician to decide on more sophisticated investigations.

**Major importance are the tridimensional measurements of the tumour at diagnosis and immediately prior to surgery.** (See 4.3)

Put a copy of the observations and their time schedule in your patients file.

**Pre-operative therapy:** Attention must be paid to the difference in case of localized disease or metastatic disease. In localized disease only 2 drugs are used for 4 weeks. In metastatic disease 3 drugs are used for 6 weeks. (See section 6 and 7).

**Surgery:** Remember the pre-operative tumour measurements. Planning of the date of surgery is important. There should be no more than 3 weeks between the last pre-operative chemo and the first post-operative chemotherapy.

See to it that, at the time of surgery, the surgeon, the pathologist and the cytogenetic laboratory are well informed.

**Post-operative points of attention:**
- clinical: The treatment of the patient now depends on a definitive stage and histology report. The clinician must stress this point to the pathologist.
- pathology: Correct handling of the specimen within a limited time scale is essential. Not only for a correct diagnosis, but also for national- and panel review. It is crucial to assess the percentage of necrotic tissue (see figure below) and to pay attention to the correct sampling of material for the biological study.

**POST-CHEMOTHERAPY SPECIMEN**

- Histological subtype
- Regressive type
- Completely necrotic type

- Blastic type
- Mixed type
- Epithelial type
- Stromal type

% of necrosis

- <60%
- 60% - 90%
- 100%
- biology: The laboratory should be aware of the operation in advance. At each institution the logistics should be ready to handle the material in close cooperation with the pathologist. The clinician is responsible for providing peripheral blood of the patient and the parents to the biology lab.

**Post-operative treatment:** This depends on *stage* and *histology* defined by the pathologist. (See Pathology Protocol)
In this study there is no clinical nor a surgical stage. There is only a *pathological stage*. Besides this there are three *histological risk groups*. The post-operative treatment depends on the combination of stage and risk group.

**STEP ONE: What stage is the tumour?**

**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) Intrarenal vessel involvement may be present

*Fine needle aspiration or percutaneous core needle biopsy (‘tru-cut’) does not upstage the tumour but the size of the needle gauge should be mentioned to the pathologist.*

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

**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 microscopical 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 a possibility that some viable tumour is left behind in the adjacent lymph node or beyond resection margins.)

Stage IV: Refer to section 7.

Stage V: Refer to appendix 4.

STEP TWO: In what risk group is the histology of the tumour?

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

**INTERMEDIATE RISK TUMOURS**
- Nephroblastoma - epithelial type
- Nephroblastoma - stromal type
- Nephroblastoma - mixed type
- Nephroblastoma - regressive type
- Nephroblastoma - focal anaplasia

**HIGH RISK TUMOURS**
- Nephroblastoma - blastemal type
- Nephroblastoma - diffuse anaplasia
- Clear cell sarcoma of the kidney
- Rhabdoid tumour of the kidney
STEP THREE: Combine these two for the correct treatment strategy

**THERAPY PROTOCOLS FOR LOCALISED DISEASE**

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LOW RISK</strong></td>
<td>NO FURTHER</td>
<td>AV-2</td>
<td>AV-2</td>
</tr>
<tr>
<td></td>
<td>TREATMENT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>INTERMEDIATE</strong></td>
<td>AV-1</td>
<td>DOX + R &lt; DOX -</td>
<td>RT / DOX + R &lt; RT / DOX -</td>
</tr>
<tr>
<td><strong>RISK</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIGH RISK</strong></td>
<td>AVD</td>
<td>HIGH RISK + RT</td>
<td>HIGH RISK + RT</td>
</tr>
</tbody>
</table>
SECTION 12

STATISTICAL CONSIDERATIONS

12.1 INTRODUCTION

As stated in Section 1 of the protocol, the SIOP 2001 Nephroblastoma clinical trial and study aims to:
- Collect prospectively detailed information on patient and tumour characteristics in relation to therapy and prognosis;
- Explore the possibilities of further reducing adjuvant treatment in Wilms tumours in order to minimise acute and late toxicity without jeopardising recurrence and survival.

Results and experiences from previous SIOP studies in nephroblastoma have been used to plan therapy and design new studies for specific risk groups.

The following schedule of risk group directed therapy will be applied:

<table>
<thead>
<tr>
<th>Risk</th>
<th>Stage</th>
<th>Treatment (Post-operative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>I</td>
<td>No further treatment</td>
</tr>
<tr>
<td></td>
<td>II, III</td>
<td>AV-2</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>I</td>
<td>Short arm SIOP 93-01 (AV-1)</td>
</tr>
<tr>
<td></td>
<td>II, III</td>
<td>Randomisation +/- DOX (III+RT)</td>
</tr>
<tr>
<td>High risk</td>
<td>I</td>
<td>Three drugs (AVD)</td>
</tr>
<tr>
<td></td>
<td>II, III</td>
<td>High risk protocol + RT</td>
</tr>
</tbody>
</table>

* GPOH protocol will treat patients with intermediate risk (excluding epithelial and stromal predominant) and pre-operative volume >500 ml as stage II with DOX.
* GPOH protocol will treat patients with intermediate risk (excluding epithelial and stromal predominant) and pre-operative volume >500 ml according to High Risk protocol.

**Intermediate risk, stage II/III**

The randomised study question in the SIOP 2001 study is about the post-operative treatment regimen in intermediate risk stage II and III patients.

The question is whether Doxorubicin can be excluded from the post-operative chemotherapy combination without deterioration of currently achievable event-free survival (EFS).

Stage II and stage III patients both receive the same chemotherapy regimen. In addition, stage III patients receive post-operative abdominal radiotherapy.

12.2 SAMPLE SIZE

The required sample size in this study is based on results from the SIOP 93-01 study and calculated using the methodology of establishing equivalence between treatments (1). The null
hypothesis of non-equivalence is to be tested (rejected): $H_0$: elimination of Doxorubicin treatment reduces the 2-year event-free survival to an unacceptable proportion ($\Delta \geq 10\%$) versus the alternative hypothesis ($H_a$) of equivalence.

The probability $\alpha$, of wrongly accepting the hypothesis that both treatment regimens are equally effective, will be limited to 5%. The probability of not recognising equivalence (wrongly accepting non-equivalence) is set at a level of 20% (power 80%). The estimated 2-year overall event-free survival in the SIOP 93-01 study was 86% (2/3 stage II (2-year EFS 88%), 1/3 stage III (2 year EFS 83%)). Thus, present considerations indicate 174 are patients needed in each treatment group at the final analysis: an overall sample size of 350 patients in total. Based on number from the SIOP 93-01 study it is estimated that it will take about 7 years to accrue this number of patients and another 2 years of follow-up are required for analyses at full power.

12.3 RANDOMISATION
Patients can only be randomised within three weeks after surgery. Form 5 should have been completed and submitted before randomising. Randomisation will be performed centrally by computer according to the minimisation technique. Patients will be stratified by country, institute and pathological stage.

12.4 INTERIM ANALYSES
During the period of accrual to the study, interim analysis of event-free survival will be supplied, in strict confidence, to an Independent Data Monitoring Committee (IDMC) (see Appendix 2), along with other analysis that the Committee may request. In the light of these interim analyses, the Data Monitoring Committee will advise the Executive Committee whether in their view the trial has provided enough evidence that for all, or some types of patients one particular treatment is indicated or contraindicated in terms of net difference in survival. A sequential analysis, applying O’Brien-Fleming boundaries with an overall significance level of 0.05 can be used to statistically guide the advice (2). The Executive Committee can then decide whether to modify the intake to the study. Unless this happens, the principal investigators and the collaborators will remain ignorant of the interim results.

12.5 MAIN STATISTICAL ANALYSES
The primary efficacy variable is ‘event-free survival’ (EFS). All randomised patients will be included in the analyses compared according to the treatment they were randomised to receive (‘intention-to-treat’ (ITT)). All patients who prematurely withdraw from the study for any reason will be actively followed up.

The two proportions of failures (recurrences or deaths) will be compared using the normal approximation test of Newcombe-Wilson (3).

If, at the final analyses, after a 2-year minimum follow-up of all patients, the observed confidence limit of the differences is less than 10%, the conclusion will be that the two treatment regimens are equivalent.

Analyses of the ‘per protocol population’ (all patients from the ITT population adhering to the protocol and analysed according to the treatment that they received) will be performed for the primary efficacy endpoint only in order to assess the robustness of the results.
Stage I, low risk
As with the SIOP 93-01 protocol, there will be no stopping rules included for patients with stage I, low risk disease. However, relapses, when they occur, have to be reported immediately to the secretariat in Amsterdam. The 95% confidence interval of the EFS rate will be estimated at the time of each event and provided to the Independent Data Monitoring Committee.

Stage I, intermediate risk
Patients with stage I, intermediate risk will receive the short chemotherapy regimen (4 weeks) that was suggested in the SIOP 93-01 trial. An interim analysis at the end of the accrual period in 2000 did not show any in-equivalence between the 4 weeks schedule compared to the 18 weeks schedule in terms of event-free survival. However, at the time of the preparation of the SIOP 2001 protocol the final analyses (requiring at least 2 year follow-up of all patients) of the trial in this patient group were not yet available. Therefore, in the SIOP 2001 protocol these patients will be followed up carefully and in 2002, when the final analyses of all SIOP 93-01 trial patients become available, the newly collected data will be analysed and evaluated against the 95% confidence intervals of the event-free survival of the corresponding patients of SIOP 93-01.

Other risk groups
In general all other risk groups (combinations of stage and histology) are small. EFS and overall survival with corresponding confidence intervals will be estimated for all of these groups. The results will be reported and considered in the light of previous studies and new developments.

REFERENCES


SECTION 13
BIOLOGICAL STUDIES

13.1 BACKGROUND

Prognostic factors in Wilms tumour

Two clinical factors are established as conferring adverse prognosis in Wilms tumour, namely, histological subtype (anaplasia) and advanced tumour stage. Although many molecular abnormalities have been proposed to be associated with adverse outcome in Wilms tumour, none is yet used to stratify treatment. These include allele loss at chromosomal regions within 16q, 1p and 22q, p53 mutation or overexpression, telomerase activity, gain of 1q, expression of TRKB and certain multidrug resistance genes etc. One of the aims of the current NWTS 5 study is to analyse, in a prospective fashion, the prognostic significance of allele loss on 16q, 1p and DNA ploidy in favourable histology Wilms tumour. This trial is planned to run into 2002 and so mature results will not be available until 2003 at the earliest.

The SIOP 2001 nephroblastoma trial and study has the unique opportunity to assess prognostic factors that relate to response to pre-operative treatment. Two factors that are being analysed in the current study are histological appearance and tumour volume following pre-operative chemotherapy. It is important that the relation of these to molecular markers is studied so that the results of SIOP 2001 can be compared with those of NWTS 5.

13.2 AIMS

A. Prospective testing of biological prognostic markers

1. To correlate allele loss at 16q, 1p and other chromosomal regions of interest with relapse-free and overall survival of children with Wilms tumour treated within the SIOP 2001 nephroblastoma trial and study.

2. To correlate the above allele losses with clinical risk factors defined following pre-operative chemotherapy (i.e. histological appearance and tumour volume).

3. To establish, on a national basis, a Wilms tumour biological samples bank containing frozen tumour and normal kidney and/or blood, that will be available to conduct further research into molecular prognostic factors and Wilms tumour biology.

B. Additional research projects using the SIOP-WT study structure

Further studies will be conducted on a national or international basis according to the research interests of participating institutions, subject to approval by the SIOP Wilms Tumour Biology Committee.
For example, studies on:

**Familial Wilms tumour**
All cases of familial Wilms tumour should be notified to the SIOP data centre. Further studies, including pedigree evaluation and blood sampling will be at the discretion of the local clinician, who is encouraged to contact one of the following interested laboratories (Drs. Pritchard-Jones & Rahman, UK; Dr Jeanpierre, France; Drs Gessler & Royer-Pokora, Germany).

**Overgrowth syndromes, particularly Beckwith-Wiedemann syndrome.**
High resolution molecular studies of genes on chromosome 11p15 are undertaken by Dr Marcel Mannens, Amsterdam, who is happy to receive diagnostic and research samples. Other researchers interested in receiving material for research studies are: Dr Rahman and Dr Maher (UK), Dr Jeanpierre (France).

**Denys-Drash syndrome and Wilms tumour with associated genitourinary malformation**
Drs. Jeanpierre and Fournet, Hopital Necker, France, are interested in receiving samples (constitutional DNA and tumour) on patients in this category. They maintain a WT1 mutational database at [http://www.umd.necker.fr](http://www.umd.necker.fr). Dr Schumacher, Germany, is interested in receiving samples of nephrotic kidney from patients with DDS.

**Bilateral Wilms tumour and nephrogenic rests**
Drs. Jeanpierre and Fournet, Hopital Necker, France, are interested in receiving samples of tumour, nephrogenic rests and normal kidney, to look for the molecular bases of this association.

**Diagnostic testing for molecular abnormalities in patients with aniridia or Beckwith-Wiedemann syndrome.**
Clinicians experiencing difficulties in obtaining relevant molecular analyses (e.g. detection of WT1 submicroscopic deletions by FISH, WT1 mutational analysis etc.) should contact their national reference laboratory for advice on where to send samples.

### 13.3 STRUCTURE

There is a biology subcommittee. All responsible persons of the National Reference Laboratory (NRL) are members of this committee. Representatives of participating centres are welcome to attend the meetings of this committee if they are interested.

The committee is chaired by one of the NRL representatives. The subcommittee chooses their own chairperson.

There is a central biological data base which will be maintained by Dr Richard Grundy, Birmingham.

Research laboratories performing specific studies (aim B) are welcome to discuss how cooperation and logistics can be facilitated or organised by the committee.
13.4 NATIONAL REFERENCE LABORATORIES

& contact details for other research groups with an interest in Wilms tumour biology

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**Dr Richard Grundy**
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University of Birmingham
Birmingham B4 6NH
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Germany

**Prof. Dr Manfred Gessler (National Reference Lab for Germany)**
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Fax: (49) 931 888 7038 (alt. 4150)
E-mail: gessler@biozentrum.uni-wuerzburg.de

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Fax: (33) 1 47 83 32 06
E-mail: jeanpierre@necker.fr

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Service d’anatomie pathologique,
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Fax: (31) 20 691 8626
E-mail: m.a.mannens@amc.uva.nl

Austria
13.5 SAMPLES REQUIRED

- **Tumour:** At least two pieces (0.5 - 1 cm$^3$ 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 cm$^3$) snap frozen in liquid nitrogen or at –70°C.
- If present, **nephrogenic rests** should be sampled as above.
- 10 ml 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.

Sample handling

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. Wilms tumours may contain extensive areas of necrosis following chemotherapy. Pathologists should ensure that samples for storage are taken from areas of grossly viable tumour. Adjacent samples should be studied for pathology/histology. These ‘mirror blocks’ should be marked as they may be requested for future biological studies allayed to the SIOP 2001 nephroblastoma trial.
13.6 STATISTICAL CONSIDERATIONS

The prognostic value of each biological marker must be assessed within the context of current known prognostic factors such as tumour stage and histology and, of course, treatment applied. Biological markers may be used to answer different questions, each of them requiring different statistical methodologies. The prevalence of and impact on survival of each putative biological marker are currently either unknown or only approximations. Despite these provisos, it is anticipated that a SIOP nephroblastoma biological study should yield clinically meaningful results and insights into the molecular basis of Wilms tumour biology. Therefore, one of the most important aspects of this study is to establish a comprehensive sample bank with as many tumours as possible across all tumour stages and histologies. It is anticipated that the tumour bank could grow by 75-100 samples per year, assuming approximately 50% of registered patients provide material.

The principal biological question is a prognostic factor analysis of specific regions of allele loss at 16q, 1p, 22q and possibly other regions that may be defined as of interest in the current NWTSG 5 study. It is not yet established if these regions of allele loss occur independently, although preliminary data suggest they may be interrelated and that their frequency increases somewhat with higher tumour stage.

Using preliminary data from the NWTSG, it is assumed that 15 – 20% of localised, favourable histology tumours will have allele loss for 16q. Based on previously published small series, the expected adverse effect on disease free survival is a reduction of ~20% for stage I and 25% for stage II/III tumours, respectively. An estimate of the number of tumour samples required for analysis follows:

The SIOP 9301 data show approximate 5 yr EFS probabilities of 87% for stage I, 85% for stage II and 74% for stage III. The assumptions made for calculation of sample size are: the ratio of the number of patients in each risk group (no allele loss to allele loss) is 5:1, 50% of patients entered on study provide a biological sample and 90% of these samples are informative for allele loss. For stage I tumours, then to demonstrate a 20% absolute difference in EFS (hazard ratio for allele loss 2.9), a total of 300 patients are required to enter the study (one-sided $\alpha=0.05$, 80% power). Similarly to show a 25% absolute difference in EFS in stage II patients (hazard ratio for allele loss 3.15), 225 are needed to enter study (one sided $\alpha = 0.05$, 80% power). Also, to show a 25% absolute difference in EFS in stage III (hazard ratio for allele loss 2.4), 250 are needed to enter study (one-sided $\alpha=0.05$ and 80% power).

Based on the accrual rate in the SIOP 9301 study, it would take approximately 7 years to recruit this number (n=300) of stage I patients, 10 years for stage II and 25 years for stage III.

For stage I patients, these accrual targets are realistic and should be shorter now that more countries (eg UK) and centres are joining SIOP 2001. For the higher stage patients, the sample set will only permit meaningful data to be generated if the relative number of patients with allele loss increases with higher stage or if other biological factors can be defined with greater adverse impact on event free survival. Since the latter factors are currently unknown, every effort should be made to accumulate a biological samples bank across all tumour stages and histology.
For the other analyses, namely correlation of regions of allele loss with pathological risk group and tumour volume reduction following pre-operative chemotherapy, the frequencies of the possible associations are unknown, making statistical predictions of sample size difficult. However, if a sample bank large enough to power the prognostic factor analysis is accumulated successfully, this should allow meaningful correlations of molecular markers with clinical parameters.

**METHODOLOGY**

Paired normal and Wilms tumour DNA samples will be investigated for allele loss (LOH) using a select panel of robust and highly polymorphic microsatellite markers by polymerase chain reaction (PCR). LOH for an individual allele will be defined as \( >50\% \) reduction in band intensity, as determined by densitometry. Tumour LOH for a specified chromosomal region will be defined by the loss of more than 1 adjacent marker. Allelic imbalance will also be further investigated. A set of common markers will be used by all participating laboratories, with blinded sharing of samples for quality control. An initial screen using 2 highly polymorphic markers for chromosomes 1p, 16q, 22q and 11q will identify tumours for further in-depth molecular investigation. The nature and number of markers to be used will be decided following preliminary studies across the chromosomal regions of interest and using data provided by the NWTSG.

**Patient outcome:** Molecular analysis will be ‘blind’ without knowledge of the status of the patient, other than diagnosis, by the researcher. Once the molecular analysis is complete, analysis of clinical correlations will be undertaken by the SIOP Nephroblastoma Trial Office and, where appropriate and agreed by the Biology Committee, national subsets may be analysed by their own national data centres.

Quality Assurance.
Reproducibility is critical as molecular analyses will be undertaken in several laboratories. Therefore 10\% of all samples will be exchanged between national reference laboratories for blinded analysis on an annual basis.

Database
A central database will be created and maintained by Dr Richard Grundy at the University of Birmingham.

**13.7 SPECIMEN ROUTING**

**Operating theatre**
- surgeon takes out the specimen
- surgeon fills in the surgical form
- surgeon sees to it that the intact nephrectomy specimen is taken promptly to the pathology laboratory (NB Do NOT cut into the specimen in the operating theatre as this makes it impossible for the pathologist to assign an accurate tumour stage.)
**Pathological laboratory**
-pathologist deals with the specimen with special care for staging!
- he/she sees to it that viable tumour tissue is sampled according to the protocol for biological study
- this tissue is snap frozen as soon as possible after resection (ideally within 30-60 mins) and stored at -70°C
- pathologist makes diagnosis and fills in pathology form
- pathologist decides whether short term central review is necessary

**Biology laboratory**
- snap frozen tissue is taken to tissue bank
- biologist arranges for registration
- also blood samples from patient and parents are sent to this lab by the clinician and is stored at this site
- material is sent to a National Reference Laboratory if relevant (see "Further routing").

"FURTHER ROUTING" OF TISSUE / BLOODSAMPLES

Local hospital

```
<table>
<thead>
<tr>
<th>National Reference Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>storage</td>
</tr>
<tr>
<td>tests</td>
</tr>
<tr>
<td>transport to additional research laboratory if indicated</td>
</tr>
<tr>
<td>results</td>
</tr>
<tr>
<td>send data to biological data base</td>
</tr>
</tbody>
</table>
```
13.8 CARDIAC TOXICITY

The median delay between cardiac injury by anthracyclins and severe abnormalities found (including congestive heart failure), is as long as 15 years. A pilot study of cardiac troponin I and T isoforms and Brain Natriuretic Peptide (BNP), after doxorubicin or not (control samples) is part of the study for those centers who are able and willing to participate.

Cardiac isoform of troponin I and T are 100% cardiac specific: their release in the blood stream is additionally the compulsory consequence of a myocyte membrane disruption (frequently myocyte death).

That is why, ultra sensitive dosage of cTnT and cTnI (in the range of picomole rather than in nanomole/mL as seen in myocardial infarction) are a good alternative to endocardial biopsy. BNP is secreted directly by the myocyte itself. It can increase sodium diuresis, in order to relieve the myocyte after anthracyclin injury. The search for early parameters for cardiac injury is therefore a major goal in paediatric oncology. Especially to validate or not the prolonged infusion (and the best duration of it) and the usefulness of some cardioprotectant agents (ICRF-187 for instance).

Informed consent by the parents will be required. The plasma collection (3 mL on citrate or EDTA, but not heparin) and storage must take place at –80°C at baseline, then at 24 H, 48 H and day 5 for troponins; baseline and day 21 for BNP will be mandatory for patient being given Doxorubicin. A simplified blood collection protocol will be proposed for pts in the arm without Doxorubicin, since they are collected as control.

Meanwhile troponins and BNP normal values in children of different age groups will be obtained in the labs of the French pediatric hospitals, in the vicinity of IGR. For every patient (children and adults) a Doxorubicin Cmax will be mandatory, at the end of Doxorubicin infusion, in order to establish, if any, a simple correlation between Cmax and Troponin release and BNP increase (relation between duration of infusion / Cmax and myocytes killing or suffering).

MONITORING CARDIAC TOXICITY

Methods
- Echocardiography (Mandatory)
  - Fractional shortening
  - Ejection fraction
  - End systolic wall stress
- Cardiac Troponin isoforms I and T (Voluntary)
  Brain Natriuretic Peptide (BNP)
- Doxorubicin Cmax
  2 ml of serum within 1 hour after the end of the doxorubicin infusion.
**Timing**

- Echocardiography: before the first administration of Doxorubicin and after every 200 mg/m².
- Cardiac Troponin isoforms: Baseline, 24 hours, 48 hours, 120 hours and day 7, 21.
- BNP: Baseline and day 21.
- Doxorubicin Cmax: within 1 hour after the end of doxorubicin infusion.

**Material**

At each point 3 ml plasma on citrate or EDTA kept deep frozen. Analysis can be done in the participating institution if possible. Otherwise the investigator should contact the Institut Gustav Roussy in Paris (Dr F. Pein).

*End Systolic Wall Stress (meridional) is calculated by the following formula, requiring Blood pressure measurement at time of Doppler US:

\[
\text{EsWS} = \left[ \frac{\text{MBPs} \times \text{LVDs} \times 1.35}{4 \times \text{LVPWs} \times (1 + \text{LVPWs}/\text{LVDs})} \right]
\]

- \(\text{EsWS}\) = end systolic wall stress in \(\text{gm/cm}^2\)
- \(\text{BP}\) = blood pressure in \(\text{mmHg}\)
- \(\text{MBPs}\) = mean systolic blood pressure = \(\text{BPs} - \left(\text{BPs} - \text{BPD}\right)/3\)
- \(\text{LVDs}\) = systolic left ventricular diameter in \(\text{mm}\)
- \(\text{LVPWs}\) = systolic left ventricular posterior wall in \(\text{mm}\)

Normal values of ESWs in children must be below 70 gm/cm²

More exactly, Colan formula for EsWS in children is:

\[
(\text{EsWS (meridional)} = 12.2 \times (\text{Age}^{0.31}) + 20.4 )
\]
APPENDIX 1

CONTACT DETAILS

The Secretariat is responsible for the coordination of the actual and previous studies. The participating centres should send their data to the following address.

**Secretariat The Netherlands**

SIOP Nephroblastoma Trial & Study Office  
Emma Kinderziekenhuis / AMC  
Meibergdreef 9, room A3-273  
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E-mail: DENIZOT@lyon.fnclcc.fr
Organising Committee

The following persons are involved in this trial and will be responsible for its organisation, for the information of participating centres and publication of the results.

Executive committee

Christophe Bergeron   (France)
Beatriz de Camargo   (Brazil)
Norbert Graf   (Germany)
Jan de Kraker   (The Netherlands)  (Study Chair)
Kathy Pritchard-Jones   (United Kingdom)

Statistics

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Würzburg  
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Amsterdam  
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APPENDIX 2

PRACTICAL ORGANISATION OF THE TRIAL AND STUDY

Centre Participation
To participate in the study each institution should have one responsible physician. A declaration form signed by a paediatric oncologist, paediatric surgeon, radiotherapist and pathologist must be available at the SIOP Study Office in Amsterdam, preferably before the first patient is entered into the study by that centre.

Ethical Considerations
The responsible physician in each country/centre will be responsible for ensuring that this study is conducted in agreement with the Declaration of Helsinki, and that national and/or local ethical committee approval is obtained as necessary. The study will be run in accordance with the requirements of Good Clinical Practice (ICH GCP). The outline of the randomized study will be explained to the patient/parent and written informed consent will be obtained. The study will have to be approved by the institutional or national review board according to the legal WHO guidelines.

Status of Study
This is an international study. The national childrens cancer study groups of France, Germany and the UK together with all other participating countries constitute the SIOP Nephroblastoma Trial and Study. The coordination is done by the SIOP office in Amsterdam.

Publication Policy
The SIOP-WT studies are multi-centre studies with participating centres from all over the world. The majority of patients however are from the national European groups SFOP / GPOH / UKCCSG and the other European countries.

Publications using data from the SIOP central data bank are considered to be official SIOP-WT papers and these should be agreed by the main author of the project with the full SIOP WT committee before starting the work, so that authorship can be discussed within this group prior to preparation of any publication.

All persons designated as authors should qualify for authorship. Every other author should have participated sufficiently in the work to take public responsibility for the content.

Since this is a multi-centre trial, all members who are named as authors should fully meet the above criteria for authorship.

All manuscripts will clearly state that the publication is offered on behalf of SIOP and should include in an appendix the names of the participating centres.
All manuscripts and abstracts (including abstracts for presentation at meetings) and other documents that contain data from the central SIOP-WT study data bank must be submitted to the executive committee at least 21 days prior to the deadline for conference submission. All abstracts must have written approval from the executive committee prior to final submission.

At an appropriate place in the article one or more statements should specify contributions that need acknowledging for general support, technical help, financial and material support, etc.

**Practical Administration**

**The Protocol**
- One common protocol will be used for the international study by all participating centres. The finalised master protocol in the English language will be held at the SIOP Nephroblastoma Trial and Study Office.

- Addenda may be added independently by any of the national groups to address local needs, provided they have no bearing on the essential aims of the international protocol.

- Subsequent to finalisation, any amendments to the protocol must be agreed by the SIOP Wilms Group. The SIOP Nephroblastoma Trial and Study Office will issue either amended pages or a revised version of the protocol.

**Study Forms**
- One common set of forms will be used by all participating centres.

- Additional forms may be produced independently by any national group/centre for the collection of data additional to that required for the international study.

**Data Collection**
- The international database for the study will be held by the SIOP Nephroblastoma Trial and Study Office in Amsterdam.
- For Germany, France and the United Kingdom, data collection will be carried out through the national data centre/study secretariat.
  a) The national groups will be responsible for data quality according to local practice.
  b) A complete dataset will be transferred electronically at least 6-monthly to the international database in Amsterdam.
  c) Forms returned from the treating institutions shall be stored at the national data centres.
  d) Any queries detected by the SIOP Nephroblastoma Trial and Study Office will be fed back to the national centres for resolution.
Confidentiality of patient data
- The use of names as patient identifiers on paper forms and national databases will be according to national practice. An abbreviated patient identifier will be used for data transfer and for the master database.

Access to data from SIOP Central Databank
Data from the SIOP central databank may be made available to individuals. Requests, to the SIOP Trial & Study Office, should include the following information:
- Reason(s) for data request, specifying question to be answered.
- What data are needed (item and in which form)
- Proposed method to be used when working with the data (define file specification)
- Whether there are any objections to involvement of the SIOP Statistician. (If so, please specify)
- Which other committees are informed/involved.
- If the data are going to be published, do you agree to name those people relevant to the question and study.

The request should be signed by the individual, giving also their institution.

Randomisation arrangements
Randomisation will take place in a period between the announcement of the definitive classification by the local pathologist and the start of treatment, thus allowing the patient and his or her parents sufficient time for discussion and to provide written informed consent. The post-operative treatment should start not later than 3 weeks post-surgery.

All randomisation procedures will be performed by the statistical office of this study, based at the comprehensive cancer centre in Amsterdam. For France, Germany and the UK randomisation will be conducted through the national centre. All other centres will contact the comprehensive cancer centre in Amsterdam direct.

Requests for randomisation will be accepted and issued only by the use of a randomisation form sent by fax or email (see form 5). After confirmation of the randomisation form, the randomisation treatment allocations will be confirmed in writing to the treatment centre. Randomisation can take place during office hours in Amsterdam (Monday to Friday from 9.00-17.00 hrs local time):

Comprehensive Cancer Centre Amsterdam
Plesmanlaan 125
1066 CX Amsterdam (The Netherlands)
Tel: 31 - 20 - 34 62 544
Fax: 31 - 20 - 34 62 525
Email: trialbureau@ikca.nl
IDMC (Independent Data Monitoring Committee)

The IDMC shall review the outcome data for the SIOP 2001 randomized trial when the protocol-specified number of events or patients has been reached.

The IDMC shall review the trial with consideration of the objectives, scientific impact of the findings, and patient safety.

The IDMC shall review all modifications of the trial protocol involving a change in the accrual goals or other major changes.

The IDMC shall make recommendations in a report to the SIOP 2001 Core Committee. Recommendations will be made based on a consensus of the Committee members. The report should be completed within one month of the IDMC meeting.

The Core Committee is responsible for dissemination of results. If the trial is stopped based on an IDMC recommendation at an interim analysis, the IDMC must review the paper prior to submission to assure proper reporting of the recommendation.

Unblinded results should be presented to the IDMC during accrual.

If the trial goes up to the planned accrual, the responsibility of the IDMC ends after the last patient enrolled has completed the planned therapy. At that time, the results are released to the Core Committee.

The IDMC will continue to monitor long-term outcome. The IDMC will also review interim efficacy reports of closed trials if requested to do so by the Core Committee.

The Core Committee should inform the Chair of the IDMC if any unusual patient side-effects are encountered. This contact should be made as soon as clarified and should not wait for the next scheduled report.

Members of the IDMC for this trial are:

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E-mail: dietmar.schmidt@dgn.de
CENTRE REGISTRATION FORM

SIOP 2001

Responsible doctor: ........................................................................................................

Centre: .........................................................................................................................

Address: ......................................................................................................................

Tel: ........................................ Fax: .................................................................

E-mail: .......................................................................................................................

- We want to participate in SIOP 2001.
- We will enter patients of all stages/ages with nephroblastoma and all renal tumours in children.
- We will undertake to respect the protocol of the trial, but our medical responsibility takes precedence over the protocol.
- We will provide all the necessary information and specimens.

Signature

Physician Name ........................................

Surgeon Name ........................................

Radiotherapist Name ........................................

Pathologist Name ........................................

The SIOP 2001 protocol has cleared the "Human experimentation committee" of our institution if there is one: yes / no / no committee.

Please return this form to:

Dr J. de Kraker
SIOP Nephroblastoma Trial & Study Office
Emma Kinderziekenhuis/AMC
Meibergdreef 9, room A3-273
1105 AZ AMSTERDAM.
The Netherlands.
APPENDIX 3

RECOMMENDED TREATMENT FOR CASES RECEIVING IMMEDIATE NEPHRECTOMY

CHEMOTHERAPY GUIDELINES

The following treatment recommendations are based on the United Kingdom experience in UKW1 & 2 studies) (1,2). Modifications to the length of therapy, total dose of anthracycline and treatment of focal anaplasia have been made in the light of published data from NWTS 4 study (3, 4). Note that 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, except for children receiving vincristine monotherapy (see infant dose modifications section 8).

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 pathological risk group B applies to tumours that have not received pre-operative chemotherapy. Note that the presence of large amounts of viable blastema is of no prognostic significance in immediate nephrectomy specimens.

B. FOR PRIMARY NEPHRECTOMY CASES

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 of the kidney
- Rhabdoid tumour of the kidney

Post-operative chemotherapy regimens for tumours having primary excision:

**Dose modifications for infants and children <12 kg.**
Children <12 kg receive 2/3 of the doses of all the drugs calculated either by surface area (vincristine and doxorubicin) or per kg (actinomycin D). There is no further dose modification for age. Children receiving vincristine monotherapy should also have this dose reduction. If they experience toxicity, the subsequent dose should be reduced by 50% followed by cautious increases if tolerated.

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

Vincristine 1.5 mg/m² (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.

*Note: infants and children < 12 kg should be given 2/3 of the dose of vincristine even when the drug is used alone. If there are signs of significant toxicity, the subsequent dose should be reduced by 50% followed by cautious increases if tolerated.*

Total duration of therapy: 10 weeks.

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

Vincristine 1.5 mg/m² (maximum dose 2 mg) weekly for 11 weeks and then three weekly, at weeks 14, 17, 20, 23 and 26 (16 doses in total), plus:

Actinomycin D 45ug/kg (maximum dose 2 mg) at weeks 2, 5, 8, 11, 14, 17, 20, 23 and 26 (9 doses in total).

*Note: infants and children < 12 kg receive lower doses of both drugs (see section 8).*

Total duration of therapy: 26 weeks.

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

Vincristine 1.5 mg/m² (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:

Actinomycin D 45ug/kg (maximum dose 2 mg), 50% dose at week 2* then full dose at weeks 10, 16, 22, 28 (5 doses in total).
Doxorubicin 50 mg/m² at weeks 7, 13, 19, 25 (4 doses (200 mg/m²) in total). Each dose to be infused over 4 hrs minimum (see page 79).

**Note: infants and children < 12 kg receive lower doses of both drugs (see section 8).**

Abdominal radiotherapy (15 Gy) to be given weeks 2 – 4.

Total duration of therapy: 28 weeks.

**Stage IV patients** having immediate nephrectomy should be few in number and confined to patients presenting as surgical emergencies with unrecognised lung or liver metastases. They should be treated with the three drug “preoperative” chemotherapy for stage IV tumours (see section 7). 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 - SIOP ‘high risk’ post operative chemotherapy. Abdominal radiotherapy is given to local abdominal stages II and III. Lung radiotherapy is given to all stage IV cases with lung metastases, regardless of metastatic response to chemotherapy/surgery.

**CCSK**

Stage I – IV – Give the three drug “preoperative” chemotherapy as for stage IV tumours followed on by the SIOP high risk post operative chemotherapy.

No radiotherapy for stage I, abdominal radiotherapy for all other stages.

**MRTK**

Treat on soft tissue sarcoma protocol, MMT 98 of SIOP.
Flow diagrams for recommended chemotherapy for 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 as a single agent.

<table>
<thead>
<tr>
<th>VCR 1.5 mg/m²</th>
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<tbody>
<tr>
<td>WEEKS</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
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<td>9</td>
</tr>
</tbody>
</table>

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.

| VCR 1.5 mg/m² | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
|---------------|---|---|---|---|---|---|---|---|---|
| ACT-D 45 μg/kg|   |   |   |   |   |   |   |   |   |   |
| WEEKS         | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|               | 14| 17| 20| 23| 26|   |   |   |   |   |   |
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| 22.5 µg/kg|   | ↓*|   |   |   |   |   |   |
| DOX  | 50 mg/m²  |   |   |   |   |   |   |   |   |
| weeks|          | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

| VCR  | 1.5 mg/m² | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ | ↓ |
| ACT-D| 45 µg/kg  |   |   |   |   |   |   |
| DOX  | 50 mg/m²  |   | ↓ |   |   |   |   |
| weeks|          | 10| 11| 12| 13| 14| 15| 16| 17| 18| 19|

*Note 50% dose because of closeness to radiotherapy.
RADIOTHERAPY GUIDELINES

INDICATIONS FOR RADIOTHERAPY (RT)

Indications for post-operative flank RT:
Histological risk group:

- Intermediate risk, stage III (i.e. N+, residual disease left after surgery, tumour rupture).
- High risk, stage II and stage III.
- Stage IV and V according to local abdominal stage and histological risk group.

Indications for post-operative whole abdominal RT:
Whole abdominal RT is accompanied by an increased risk of early and late morbidity and may be considered for DIFFUSE intra-abdominal tumour or GROSS pre-operative or peri-operative rupture.

Indications for pulmonary RT:
Intermediate risk histology:
RT is indicated when residual tumour in the lungs is visible on a chest X-ray six weeks after the commencement of chemotherapy with AVD as per the pre-operative schedule for metastatic tumours and this residual tumour is not completely excised.

High risk histology:
RT is indicated for all lung metastases of high risk tumours, regardless of speed of response to chemotherapy and stage of abdominal tumour.

Indications for hepatic RT:
Liver metastases which do not respond completely to chemotherapy and which cannot be completely resected with negative margins.

Indications for RT to other metastatic sites:
Haematogenous metastases brain (whole brain RT) and/or bone metastases (focal RT) at diagnosis.

AIMS OF RT:
To achieve control of abdominal disease in patients who have a significant risk of intra-abdominal relapse.

To increase the control of pulmonary or hepatic metastases in patients who do not achieve a complete response to chemotherapy alone.

For equipment, target volume, treatment dose, time dose considerations, etc. see section 10.
REFERENCES


APPENDIX 4

MANAGEMENT OF BILATERAL WILMS TUMOUR

Patients with bilateral tumours account for 5% of all nephroblastoma patients. The overall survival is approximately 80% at 4 years and complete nephrectomy can be avoided in 70% of them (1). The aim of the treatment is to cure, and at the same time use a parenchyme-sparing procedure to preserve as much functional renal tissue as possible. The SIOP and NWTS experience converge on the same strategy: chemotherapy first to decrease tumour volume and preserve the maximum amount of renal tissue during surgery (1,2,3,4,5).

1) General remarks
To obtain the best results the patients with bilateral Wilms tumour should benefit from:
1) a complete radiological examination designed to establish the number, size, aspects and extension of the tumours at diagnosis and during follow up
2) a co-operation between oncologist, radiologist and surgeon to choose the best time to operate
3) an experienced surgeon in renal parenchymal-sparing procedures. Each case of bilateral Wilms tumour needs an individual approach according to the recommendations of the SIOP protocol and should only be treated in centres specialised in the treatment of this disease.

2) Strategy in simultaneous bilateral disease
- Accurate imaging strategy for the diagnosis of bilateral disease
- Chemotherapy first
- Delayed surgery
- Post-operative chemotherapy according to stage and histology grading
- Secure follow up imaging with short intervals

2.1) Accurate imaging in case of bilateral Wilms tumour
One should:
- establish the number, size, aspects and extension of the tumours in both kidneys
- establish the functionality of the kidneys
- establish the difficulties in sparing surgery
The most useful techniques are high quality Doppler assisted sonography and computed tomography scan. The most important information is just before surgery. Sonography should be performed preferably in the presence of the surgeon.

2.2) Pre-operative chemotherapy
The recommended chemotherapy to be administrated following the accurate imaging procedure is the standard pre-operative chemotherapy (VCR / Actinomycin D). The results of SIOP 9 (randomisation of duration of chemotherapy before surgery) did not show an increase in number of low stage disease after 2 months of chemotherapy. However, tumour volume decreased further after 8 weeks (62% instead of 48%) (Lemerle, 1993). This chemotherapy should be performed as long as the tumours show signs of regression and up to the time of kidney sparing surgery if possible. To decrease the irradiation dose using CT-scan the evaluation can be performed with sonography.
The response to this therapy should be evaluated for the first time at week 5 (after 2 VCR/ActinoD and 2 VCR).

In the event of a good response, another 4 weeks of chemotherapy will be administered and the next evaluation with sonography will be performed at week 9. In the event of continuous response, chemotherapy will be continued with VCR/ActinoD without intermediate VCR and the evaluation will be performed every four weeks. The duration of chemotherapy has to be geared to its effectiveness as checked by imaging procedures (see flow sheet at the end of this appendix).

2.3) Surgical recommendations (see also Section 9)
Stage V cases should be treated individually. The aim is to perform bilateral partial nephrectomy or wedge resections to preserve functional renal tissue. Surgery is planned after optimal tumour reduction by pre-operative chemotherapy. CT scan prior to surgery is mandatory to assess the feasibility of partial resection. The less involved kidney should be operated on first. Complete nephrectomy on one side with partial nephrectomy on the opposite side can be a good solution, providing enough functional renal tissue can be preserved (6,7). It should be remembered that the possibility of radiotherapy in the treatment of bilateral WT is limited. Sometimes partial nephrectomy with safe margins is not possible, even after long duration chemotherapy. There are however examples from the SIOP-9 Study indicating that incomplete surgery followed by low-dose (10 Gy) radiotherapy and chemotherapy may result in a long-term remission (8). This option should be taken into account, when bilateral nephrectomy seems to be the only way out. Sometimes the bilateral nature of the tumour is discovered only at surgery. Ultrasonography and CT-scan make this event rare. A tru-cut biopsy on both kidneys should be performed, abdomen closed, adequate imaging completed and chemotherapy started before the surgery according to the above protocol is undertaken. In case of small lesion, the biopsy may be excisional.

The strategy for the metachronous stage V
A. Metachronous stage V Wilms’ tumour is that arising in the remaining kidney after a complete remission of the unilateral (first) tumour.
B. Chemotherapy is the first treatment in such cases and it aims to reduce the tumour size so as to allow for the nephron-sparing surgery on the only remaining kidney.

2.4) Post-operative chemotherapy
Chemotherapy will be adapted according to the lesion with the highest stage and the highest grade histology. The dose of Doxorubicin will be adapted according to the preoperative chemotherapy given, and should not exceed a total dose of 300 mg/m².

2.5) Follow-up
For bilateral tumours the following follow-up is recommended: every 2 months for the first year and second year with chest X-ray and US every time; every 3 months for the third and fourth year with sonography every time; Renal function should be checked at 3 months, 1 year and 3 years after surgery. According to the results, the follow-up will be planned by the paediatric nephrologist.
A. Thereafter it is up to the responsible physician to decide on frequency of investigations. Some patients with unilateral WT have a high risk of developing a contralateral WT: age < 1 year with PLNRS (9). The patients have to be followed very carefully with regular abdominal ultrasonography.

B. The duration of chemotherapy depends on its effectiveness. One should continue as long as there is a measurable response. Partial nephrectomy or wedge excision of the tumour should be done only if it will not compromise tumour resection and clean margins can be obtained. The chemotherapy after surgery will depend on the stage, histology and the previous chemotherapy.

4) Radiotherapy
In the case of local stage III disease the dose must not exceed 12 Gy to the remaining kidney.

5) Bilateral nephrectomy
This procedure is rarely indicated and only for patients in whom all conservative measures have failed or in Denys-Drash syndrome when a life threatening blood pressure makes a bilateral nephrectomy inevitable. Renal transplantation may be considered according to the national policy, usually after 2 years of disease free follow up.
Bilateral Wilms tumour at diagnosis

\[
\begin{array}{cccc}
\text{V} & \text{V} & \text{V} & \text{V} \\
\text{AD} & \text{AD} \\
\end{array}
\]

\begin{align*}
\text{V} & = \text{Vincristine} & 1.5 \text{ mg/m}^2 \\
\text{AD} & = \text{Actinomycin D} & 45 \mu\text{g/kg} \\
\text{DOX} & = \text{Doxorubicin} & 50 \text{ mg/m}^2
\end{align*}

weeks 1 2 3 4

First assessment after week 4 (sonography)

Decrease of tumour volume

\[
\begin{array}{cccc}
\text{V} & \text{V} & \text{V} & \text{V} \\
\text{AD} & \text{AD} \\
\end{array}
\]

weeks 5 6 7 8

Stable or progressive disease

\[
\begin{array}{cccc}
\text{V} & \text{V} & \text{V} & \text{V} \\
\text{AD} & \text{AD} \\
\text{DOX} \\
\end{array}
\]

weeks 5 6 7 8

Second assessment after week 8 (Sonography or CT scan)

Decrease of the tumour volume

Stable and sparing surgery not possible

Surgery (start with the less involved kidney and later for the contra-lateral kidney)

Increase the chemotherapy

Chemotherapy

Surgical or sparing surgery is possible

Chemotherapy according to higher stage and histology (Doxorubicin not more than 300 mg/m²). If stage I low risk or intermediate risk treat as stage II low risk.

If stable disease and sparing surgery possible: surgery.

If decrease of tumour volume: chemotherapy.

If stable disease and sparing surgery not possible: discussion with the board.

Third assessment (CT scan)
REFERENCES


APPENDIX 5

MANAGEMENT OF NEPHROBLASTOMATOSIS (NBM)

The presence of multifocal or diffuse Nephrogenic Rests (NRs) in one or both kidneys is termed nephroblastomatosis (NBM) (1). Beckwith proposed a dynamic histological classification of NRs: dormant, sclerosing, hyperplastic and neoplastic (2). In clinical practice, two different settings are encountered:

1) Microscopic multifocal NRs associated with a Wilms tumour. In such cases, there is an increased risk of metachronous contralateral Wilms tumour formation (14)

2) Macroscopic lesions discovered on imaging of the kidney corresponding to hyperplastic NRs of focal or diffuse type. The former presents as one or more nodules which can be mistaken for Wilms tumour from which it is differentiated by its shape (see below). The histology is identical and so biopsy is of no value. The diffuse hyperplastic NR typically follows the renal outline.

Special imaging characteristics allow recognition of the macroscopic nephrogenic rests. Focal hyperplastic NRs preserve the lenticular or ovoid shape of the original lesion in contrast to the round shape of the neoplastic lesion, though examples of large and spherical NRs are reported (5, 6). The multifocal type of NBM is markedly hypodense on CT and hypo-intense on MR images. The diffuse type of NBM shows a thick, uniform and homogeneous rind of abnormal tissue surrounding the renal periphery, which is non-enhancing on CT and MRI and hypo-echogenic on US. The most characteristic feature of NBM is their overall homogeneity with all three imaging modalities before and after contrast medium. In comparison WT is generally heterogeneous, which increases after contrast medium administration (3,4).

In order to obtain a better understanding of NBM and its management, the SIOP WT 2001 trial and study recommends the following consistent treatment plan for these patients. They will be registered and treatment and its outcome documented on the appropriate data forms.

1) Background

Vincristine and actinomycin D are effective agents against nephroblastomatosis in children (8,9,10).

Few series, all with limited numbers of children, have been published, so there is only limited information on the treatment of NBM. Chadarevian reported 4 cases with massive nephroblastomatosis, one newborn, the others aged 10, 13 and 22 months (11). Therapy included vincristine and actinomycin D up to 2 years in 3 cases and for 8 weeks in one, plus adriamycin in one case. Two patients received irradiation. Surgery was performed in only 1 case. The authors attributed the prompt and dramatic regression to the combination of actinomycin D and vincristine. All three patients treated without surgery achieved complete remission and remained in complete remission at 10, 30 and 44 months follow up.

Haddy reported a case of bilateral diffuse nephroblastomatosis in a child of 14 months of age who had been treated with vincristine and actinomycin D for 15 months (12). She achieved complete remission with no other treatment and was in CR 10 months later. Telander reported a similar experience for a child with NBM treated with actinomycin D and vincristine for 6
months followed by irradiation. Ten months after stopping therapy open renal biopsies were performed and normal kidneys were found (13).

Coppes reviewed the metachronous stage V nephroblastomas in the NWTSG experience (14). He concluded that there was some evidence that patients less than 1 year of age with an initial stage I tumour had a higher incidence of developing contralateral tumours than children with more advanced disease at diagnosis. Further analysis suggested that this could be due to the initial treatment regimen and by the association with NRs. Univariate analysis suggests that chemotherapy with three drugs, ActD, VCR and Doxo, is more effective in inhibiting the transformation of a NR into a Wilms tumour than with two drugs, VCR and ActD. Single chemotherapy as VCR or ActD is even less effective (14).

The report of Prasil on three patients with NBM emphasises the importance of the duration of chemotherapy and the risk of leaving a lesion in the kidney (15).

2) Recommendations

- **Chemotherapy first:**
  Nephroblastomatosis should be treated with a combination of vincristine-actinomycin D as in stage I WT. The duration of chemotherapy has to be geared to the response documented by imaging. As long as the NBM shrinks, the treatment should be continued.

- **Surgery has to be performed:**
  - if there is stabilisation or progression of lesions in spite of chemotherapy
  - if a nodular spherical lesion appears within the initial lesion
  - if the lesion becomes heterogeneous

Partial nephrectomy or wedge excision of the lesion should be done as in the case of bilateral Wilms tumour.

- **Treatment after complete remission:**
  When the lesions have disappeared with chemotherapy or chemotherapy plus surgery (sometimes sclerotic lesions show persistent abnormalities on imaging) maintenance therapy should be continued to a total of 1 year (see chart on following page).
Nephroblastomatosis
US, CT scan

V  V  V  V  V
AD  AD

weeks 1 2 3 4

First assessment after week 4 (US)
Decrease of lesion size

Stable or nodular or heterogeneous
disease

V  V  V  V  V
AD  AD

weeks 5 6 7 8

Next assessment after week 8 (US +/- CT scan)
Decrease of lesion size

protocol

V  V  V  V  V

AD  AD  AD  AD

weeks 9 10 11 12

Assessment (US +/- CT scan)
Decrease of the lesion

V-AD every 14 days x 2 courses

Assessment (US +/- CT scan)
Decrease of the lesion

V-AD every 21 days until disappearance of the lesions

NBM  WT

Kidney sparing surgery

SIOP protocol according to stage and histology.

If stage I and if the weeks 9 10 11 12 or histology is low intermediate risk, treat with AV-2.

V = Vincristine 1.5 mg/m²
AD = Actinomycin D 45 µg/kg
If the lesions increase, revert to V-AD every 14 days. Otherwise, give V-AD every 28 days for total treatment duration of 1 year.

At complete remission of the lesions (with surgery or chemo or both), continue maintenance therapy for 1 year, giving V-AD every 28 days.

REFERENCES


APPENDIX 6

SUGGESTIONS FOR THE TREATMENT OF CLEAR CELL SARCOMA OF THE KIDNEY (CCSK), RHABDOID TUMOUR OF THE KIDNEY AND RECURRENT DISEASE

- CCSK
If diagnosed after surgery these patients have to be treated as high risk tumours.
AVD no RT for stage I and HR + RT for stage II and III.
If diagnosed before any treatment (biopsy or immediate surgery) see appendix 3.

- RTK
For correctly pretreated patients and for primary nephrectomy patients, the treatment should be according to the soft tissue protocol MMT95 of SIOP.

- RECURRENT DISEASE
1. **Treatment strategy** depends on the nature of the initial treatment and on prognostic factors:
   - site and extension of the relapse, histology, timing of the relapse.

2. **A complete investigation**, with thoracic CT scan and whole abdominal CT scan including the anatomical study of the remaining kidney, and a precise GFR evaluation (scintigraphy or EDTA clearance). Other investigations may sometimes be necessary such as bone scintigraphy in CCSK or in patients with bone pain; more rarely in RTK, highly disseminated diseases or in case of special symptoms, like seizures, a brain CT scan is recommended.

3. **Two broad categories** of relapses should be considered:
   a. **Patients with standard risk relapse.**
      - first relapse
      - with low or intermediate grade histology,
      - occurring at least 6 months after the end of initial treatment
      - occurring in one organ, likely lungs, liver (or bone if unique)
      - or in the abdomen in a non irradiated area,
      - and without distant lymph-nodes.

* **Immediate surgery** should be considered only in case of a **solitary metastasis** in one lung, one lobe of the liver or an operable local relapse. Completely excision with safe margins is necessary. If exploration during surgery fails to reveal any other metastases and if the excision is histologically complete, there is no need for post-operative radiotherapy. Otherwise irradiation will be given to the recurrent site.

In both situations, maintenance multidrug chemotherapy with the previously non-administered drugs should be given: in case of a previous stage I intermediate risk tumour primarily treated shortly with VCR and ACD (4 weeks post-operative) and relapsing very late (> 12 months), a three drug combination (VCR+ACD+DOXO) remains a very good option.

In contrast,
- for those patients (initial stage II), being treated post-operatively with a longer duration (27 weeks), with or without Doxorubicin,
- or relapsing within 6 months after the end of initial treatment,
the four drugs used in SIOP 2001 “high-risk protocol” as adjuvant therapy, will have a higher probability of activity than a three drug combination. The problem of cumulative doses of anthracycline must be emphasized in cases initially treated in DOXO arm. In the “High-Risk protocol” with a four drugs combination, Doxorubicin could be replaced by two VCR (one week interval) combined with Cyclo, alternated with Etoposide + Carboplatin.

* Multiple metastases in a single organ, even if resectable or obviously inoperable metastases (requiring for instance a pneumonectomy or radical right hepatectomy), will receive chemotherapy first, in order to reduce the tumours before surgery and, more importantly to assess the chemotherapy-sensitivity of (all) the recurrent site(s).

- After reduction, in chemosensitive cases, surgery should then be considered when radical surgery seems possible or when it is useful to evaluate histological tumour control (stable disease).
- Radiotherapy should be given only on minimal residual disease, i.e., after a maximum reduction through chemotherapy and, after as complete as possible surgery.
- Maintenance chemotherapy, since proven to be active, should be continued, taking into account cumulative doses of anthracyclines, combined radiation dose and possible cumulative tubular damage on the remaining kidney, when carboplatin, and ifosfamide have been given.

The choice of retrieval chemotherapy proposed should be as before:
- Either a three drug for late relapse (> 12 months) and/or in shortly treated (post-operatively) stage 1 intermediate grade patients,
- Or in initial stage II treated during 27 weeks, with or without Doxorubicin,
- Or relapsing between 6 and 12 months after nephrectomy,
A similar schedule as in initial “high grade” SIOP 2001 protocol will be proposed, provided these recurrent patients are never being given etoposide, carboplatin and cyclo- or ifosfamide.

b. Patients with high risk relapse
Poor prognostic factors in recurrences of Wilms tumour depends on several indicators:
- advanced initial stage of the disease: stage III and IV
- number of drugs used, 3 drugs (arm Doxo+ or High Risk protocol)
- unfavorable histology (anaplasia, blastemal predominant) and CCSK
- relapse site, especially unusual sites (brain, bones, liver)
- early timing of relapse (< 6 months)
- multi-organ metastases or multiple (5 at least in each lung) in both lungs
- relapse involving lymph-nodes (especially distant, mediastinum, groin)
- relapse in previously irradiated-field

Radiotherapy is limited in previous irradiated areas. Chemotherapy should be different from that previously used.
Surgery, when possible can be very useful either to radically excise secondary lesions or to evaluate tumour control after chemotherapy and to identify areas to be irradiated.

Until a separate protocol for this category of patients is available, the following strategy is recommended:
Induction will consist of (2+2) cycles of “CCE” or “ICE” chemotherapy. All cycles should begin on Day 21 of the previous cycle or thereafter when peripheral counts recover with an ANC > 1,000/mm³ and platelet count ≥ 100,000/mm³. Chemotherapy should start at least 48 hours after discontinuation of G-CSF.

- **Carboplatin (CARBO)**
  200 mg/m² as an IV infusion over 1 hour on days 1, 2 and 3.
  Total dose per cycle = 600 mg/m²

- **Etoposide (VP-16)**
  100 mg/m²/day as an IV infusion over 1 hour on days 1, 2 and 3.
  Total dose per cycle = 300 mg/m²

- **either, Cyclophosphamide (CYCLO)**
  1000 mg/m²/day as an IV infusion over 1 hour on days 1, 2 and 3.
  Total dose per cycle = 3000 mg/m² and **Mesna** 120% of that given dose per day

- **or, Ifosfamide (IFO)**
  3000 mg/m²/day as an IV infusion over 3 hours on days 1, 2 and 3.
  Total dose per cycle = 9000 mg/m² and **Mesna** 120% of that given dose per day

- **G-CSF**
  5 micrograms/kg/day subcutaneously on days 5-15. G-CSF is to be stopped after 48 hours with ANC above 500/mm³

The choice of “CCE” or “ICE”, will probably be the occasion of an International randomization, with a toxicity endpoint, since in the international experiences (SIOP, NWTSG), the Ifo-based phase-II protocol are equivalent to the cyclo-based protocol, provide a dose ratio of 3:1 of Ifo:Cyclo is used.
Until the time when a separate protocol for this category of patients will be available, the following treatment is recommended.

**Recurrence as a single lesion**

- **Operable**
- **Inoperable**

**Preoperative chemotherapy**

- **Response**
- **Stable disease or progression**

**Surgery**

- **CR**
- **No CR**

**Initial stage I**

- **Stage II**

**Previous treatment without DOX**

- **Previous treatment with DOX**

- **Primary surgery**

**AVD**

**CCED**

**CCEV**

**CCED**

**CCEV**

**Evaluation after 8 weeks**

- **Response**
- **Nonresponse or progression**

**Surgery**

- **CR**
- **No CR**

**CCED / CCEV continue**

**ICE**

**No irradiation**

**Irradiation 15 Gy +/- Boost postoperative**
## APPENDIX 7

### RECOMMENDATIONS FOR LONGTERM FOLLOW-UP OF CHILDREN WITH RENAL NEOPLASMS

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Frequency after stopping therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with non metastatic disease at diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>chest X-ray</td>
<td>1st year: every 3 months</td>
</tr>
<tr>
<td></td>
<td>2nd year: every 3 months</td>
</tr>
<tr>
<td></td>
<td>3rd year: every 6 months</td>
</tr>
<tr>
<td>serum creatinin</td>
<td>6 months x 8</td>
</tr>
<tr>
<td>abd. ultrasonography</td>
<td>end of treatment</td>
</tr>
<tr>
<td></td>
<td>one and 5 years after stopping therapy</td>
</tr>
<tr>
<td>blood pressure</td>
<td>every visit</td>
</tr>
<tr>
<td>echocardiography</td>
<td>according to protocol</td>
</tr>
<tr>
<td></td>
<td>in all other circumstances to institutional policy</td>
</tr>
</tbody>
</table>

| **Patients with nephrogenic rests (any stages)** | abd. ultrasonography | 3 months x 8 |
| see also appendix 5                  | 6 months x 6         |
|                                       | yearly x 5           |

| **Metastatic patients in CR after stopping therapy** | chest X-ray | 1st year: 2 months |
|                                                   |            | 2nd year: 2 months |
|                                                   |            | 3rd year: every 6 months |
| serum creatinin                                | 6 months x 8 |
| abd. ultrasonography                          | end of treatment one and five years after end of therapy |

| **Irradiated patients**                      | X-ray bony structures, spine +/- pelvis | yearly to full growth, then every 5 years |
### Bilateral tumours

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>chest X-ray</td>
<td>1st + 2nd year every 2 months</td>
</tr>
<tr>
<td>abd. ultrasound</td>
<td>3rd + 4th year every 3 months</td>
</tr>
<tr>
<td></td>
<td>5th – 10th year every 4 months</td>
</tr>
<tr>
<td>serum creatinin</td>
<td>every 6 months</td>
</tr>
<tr>
<td>proteinuria</td>
<td>every 6 months</td>
</tr>
</tbody>
</table>

### Partial nephrectomy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>abd. ultrasonography</td>
<td>3 months x 8</td>
</tr>
<tr>
<td></td>
<td>6 months x 6</td>
</tr>
<tr>
<td></td>
<td>yearly x 5</td>
</tr>
</tbody>
</table>
## APPENDIX 8

### TOXICITY CRITERIA AND REPORTING SERIOUS ADVERSE EVENTS

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>GRADE 0</th>
<th>GRADE I</th>
<th>GRADE II</th>
<th>GRADE III</th>
<th>GRADE IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HEMATOLOGIC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>WNL</td>
<td>&gt; 100 g/l</td>
<td>80 to 100 g/l</td>
<td>65 to 79 g/l</td>
<td>&lt; 65 g/l</td>
</tr>
<tr>
<td>Leukocytes: $x10^9$/l</td>
<td>&gt; 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Granulocytes: $x10^9$/l</td>
<td>&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>Platelets: $x10^9$/l</td>
<td>WNL</td>
<td>&gt; 75</td>
<td>50 to 74.9</td>
<td>25 to 49.9</td>
<td>&lt; 2.5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>None</td>
<td>Mild, no Transfusion</td>
<td>Gross, 1 - 2 units Transf./episode</td>
<td>Gross, 3 – 4 units Transf./episode</td>
<td>Massive &gt; 4units Transf./episode</td>
</tr>
<tr>
<td><strong>SKIN AND EPIDERMAL INFECTIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INFECTION</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Life Threatening</td>
</tr>
<tr>
<td>FEVER in absence Of infection</td>
<td>None</td>
<td>37.1 to 38°C</td>
<td>38.1 to 40°C</td>
<td>&gt; 40°C for &lt; 24 hours</td>
<td>&gt; 40°C for 24 h or with hypotension</td>
</tr>
<tr>
<td>SKIN</td>
<td>None or no change</td>
<td>Scattered macular or papular eruption or erythema: asymptomatic</td>
<td>Scattered macular or papular eruption with pruritus or other assoc. Symptoms</td>
<td>Generalized Symptomatic macular, papular or vesicular eruption</td>
<td>Exfoliative Dermatitis</td>
</tr>
<tr>
<td><strong>DIGESTIVE BIOLOGY</strong></td>
<td>WNL</td>
<td>--</td>
<td>&lt; 1.5 x N</td>
<td>1.5 to 3 x N</td>
<td>&gt; 3.0 x N</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>WNL</td>
<td>≤ 2.5 x N</td>
<td>2.6 to 5.0 x N</td>
<td>5.1 to 20.0 x N</td>
<td>&gt; 20.0 x N</td>
</tr>
<tr>
<td>SGOT / SGPT</td>
<td>WNL</td>
<td>≤ 2.5 x N</td>
<td>2.6 to 5.0 x N</td>
<td>5.1 to 20.0 x N</td>
<td>&gt; 20.0 x N</td>
</tr>
<tr>
<td>Alk. Phosph. or 5 Nj</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STOMATITIS</strong></td>
<td>None</td>
<td>Painless ulcers, erythema, mild soreness</td>
<td>Painful, erythema, Edema or ulcers, but can eat</td>
<td>Painful, erythema, edema or ulcers, but cannot eat</td>
<td>Requires parenteral or enteral support</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Normal (see Colan formula for children SF)</td>
<td>Asymptomatic decline of resting SF or EF of &gt;10% but &lt;20% of baseline value. Wait 1 week and re evaluate</td>
<td>Asymptomatic decline of resting SF or EF ≥ 20% but &lt;25% of baseline value. Omit next anthracycline</td>
<td>Responsive CHF or decline of resting SF or EF ≥ 25%, requiring therapy and definitely stop anthracyclines</td>
<td>Severe CHF requiring intensive care</td>
</tr>
<tr>
<td>Doppler US: left Ventricular function: SF =shortening Fraction ; EF =ejection fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RENA L</strong></td>
<td>≥ 90</td>
<td>60 – 89</td>
<td>40 – 59</td>
<td>20 – 39</td>
<td>≥ 19</td>
</tr>
<tr>
<td>CREATININE CLEARANCE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TUBULAR TOXICITY</strong></td>
<td>None</td>
<td>Increase of β 2 Microglobulin and or Lysozyme in urine. Mild hyperamino-aciduria (HAA)</td>
<td>Decrease of phosphate reabsorption (TRT 75-85 %) glucosuria &lt; 10 mmol/l. Moderate HAA</td>
<td>Debre de Toni-Franconi Syndrom Hypophosphataemia rickets, tetany Hyperchloreaemia metabolic, acidosis polyuria, dehydration</td>
<td>Prolonged (≥ 5 years) or definitive substitution required, or progressive renal failure</td>
</tr>
<tr>
<td><strong>NEUROLOGICAL NEUROCORTICAL</strong></td>
<td>None</td>
<td>Mild somnolence or agitation</td>
<td>Moderate somnolence or agitation</td>
<td>Severe somnolence, agitation, confusion, disorientation or hallucinations</td>
<td>Coma, seizures toxic psychosis</td>
</tr>
<tr>
<td><strong>NEURO CONSTIPATION</strong></td>
<td>None or no change</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
<td>Ileus &gt; 96 hrs</td>
</tr>
<tr>
<td><strong>NEURO-SENSORY</strong></td>
<td>None or no change</td>
<td>Mild paresthesias loss of deep tendon reflexes</td>
<td>Mild or moderate Objective sensory loss; moderate paresthesias</td>
<td>Severe objective sensory loss or paresthesias interfering with functioning</td>
<td>-</td>
</tr>
<tr>
<td><strong>NEURO MOTOR</strong></td>
<td>None or no change</td>
<td>Subjective weakness; no objec-tive findings</td>
<td>Mild objective weakness without significant</td>
<td>Objective weakness with impairment of function</td>
<td>Paralysis</td>
</tr>
</tbody>
</table>

Taken from NCI Version 2.0
REPORTING SERIOUS ADVERSE EVENTS

An Adverse Event (AE) is any untoward medical occurrence or experience in a patient which occurs during or following treatment regardless of the causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment, and which is unexpected. Adverse events which are considered as serious are those which result in:
- death
- a life-threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization
- severe/permanent disability
- a congenital anomaly

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

During protocol treatment all deaths, all SAE’s that are life-threatening and any unexpected SAE must be reported to the SIOP Nephroblastoma Trial & Study Office in Amsterdam by fax within 48 hours of the initial observation of the event. All details should be documented on the Serious Adverse Event and Death Report. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the SIOP Nephroblastoma Trial & Study Office. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the completion of protocol treatment, unexpected Serious Adverse Events that are considered to be possibly related to protocol treatment and ANY death (regardless of the cause) must also be reported to the SIOP Nephroblastoma Trial & Study Office using the same procedure, within 48 hours after the SAE or death was known to the investigator.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following:
<table>
<thead>
<tr>
<th>RELATIONSHIP</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNRELATED</td>
<td>There is no evidence of any causal relationship</td>
</tr>
<tr>
<td>UNLIKELY</td>
<td>There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient’s clinical condition, other concomitant treatments)</td>
</tr>
<tr>
<td>POSSIBLE</td>
<td>There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient’s clinical condition, other concomitant treatments).</td>
</tr>
<tr>
<td>PROBABLE</td>
<td>There is evidence to suggest a causal relationship and the influence of other factors is unlikely.</td>
</tr>
<tr>
<td>DEFINITELY</td>
<td>There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.</td>
</tr>
<tr>
<td>NOT ASSESSABLE</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.</td>
</tr>
</tbody>
</table>

The SIOP Nephroblastoma Trial & Study Office will forward all reports within 24 hours of receipt to the study coordinator. It is of utmost importance that all SAE’s (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicitly considered alive without SAE. This information will be used in monitoring the incidence of SAE’s, the estimation of overall survival and monitoring of overall protocol safety. The SIOP Nephroblastoma Trial & Study Office will be responsible for reporting of SAEs to regulatory authorities, as appropriate.
APPENDIX 9

Parent information sheet

SIOP Wilms’ Tumour Study

This is only one example of such a patient information sheet. It can be adapted for local circumstances.

Your child has been diagnosed as having a Wilms’ tumour or nephroblastoma. We would like to invite you to take part in an international clinical study which aims to maintain or improve the already excellent success rates of treating Wilms’ tumour while reducing the overall side effects. The study is called SIOP Wilms’ tumour 2001 (SIOP is the International Society of Paediatric Oncologists or childhood cancer specialists).

What is Wilms’ tumour?

Wilms’ tumour is an uncommon kidney cancer of childhood. Approximately one in ten thousand children get Wilms’ tumour, usually in only one kidney (unilateral), although occasionally there may be tumours in both kidneys (bilateral disease).

In most cases we do not know what causes Wilms’ tumour, although a small number of children with Wilms’ tumour have a heritable or genetic tendency. This is usually obvious, either because other members of the family have had Wilms’ tumour or because the child has certain growth or development problems that have been present from birth. If this is the case for your child, your doctor will discuss it with you. However, please note that for the majority of children with Wilms’ tumour, there is no such hereditary tendency, nor is there any increased risk in their brothers or sisters.

What is the best treatment for Wilms’ tumour?

Wilms’ tumour can be treated very successfully using a combination of chemotherapy, surgery and sometimes radiotherapy. Overall, approximately 85% of children can be cured of their disease using relatively simple treatment without much risk of long-term side effects. The length of treatment and its intensity depends on something called tumour ‘stage’ – this is a measure of how far the tumour has spread beyond the kidney and can only be measured accurately after surgery to remove the affected kidney.

- **Stage I** is when the tumour is confined within the kidney and is completely removed.
- **Stage II** is when the tumour has breached through the kidney lining but is still completely removed.
- **Stage III** is when some of the tumour is left behind, either because the tumour ruptures or because complete surgical removal is not possible.
- **Stage IV** is when the tumour has spread to other parts of the body, usually the lungs or glands.
- **Stage V** is the special case of tumours in both kidneys (bilateral disease).
There are two main approaches to the timing of surgery that have been in use around the world for over 30 years. The approach taken by the International Society of Paediatric Oncology (SIOP), which is followed by many countries in Europe and elsewhere, is to give pre-operative chemotherapy to shrink the tumour and perform the surgery after 4 – 8 weeks. This treatment aims to shrink the tumour and make the surgery easier. The alternative approach, widely used in North America and previously in the UK, is to perform an immediate operation to remove the tumour. We now prefer the SIOP approach of starting chemotherapy before surgery, as it leads to more tumours being of low stage, requiring the least treatment, and reduces the need for radiotherapy (this sentence only necessary in UK).

Previous SIOP studies have shown that stage I tumours require only minimal post-operative chemotherapy of 5 weeks duration, with two drugs (Vincristine and Actinomycin D). Tumours of stages II, III or IV are treated with three chemotherapy drugs (Vincristine, Actinomycin D and Doxorubicin) and a longer duration of chemotherapy (approximately 6 months). Stage III and some stage IV tumours require treatment with radiotherapy as well as chemotherapy.

What questions is this study asking?

The main question that is being asked in this study is whether stage II and stage III tumours need treatment with two or three drugs. The standard treatment is with three drugs. However, one of the uncommon side effects of Doxorubicin is weakening of the heart muscle, which may not happen until many years after treatment. Therefore, it is a drug we would like to reduce or avoid using in the treatment of Wilms’ tumour if at all possible. The aim of this study is to randomly allocate children with stage II and III disease to receive either the standard post-operative treatment with three drugs or the new reduced treatment with only two drugs (i.e. with or without Doxorubicin). The duration of chemotherapy will be the same for both groups.

Previous SIOP studies have identified certain appearances of the tumour under the microscope (we call this ‘histology’) that are associated with more resistant tumours. These are called ‘high risk’ tumours and will receive more intensive treatment. A few tumours have the opposite appearance and are called ‘low risk’. They receive reduced treatment. The majority of Wilms tumours fall into the ‘intermediate risk’ histology group and are eligible for the randomised study.

Another question being asked in this study is about the importance of changes in the genetic material (DNA) of Wilms tumours and how this affects their response to treatment. To answer these biological questions, we would like to store a small sample of your child’s blood and tumour for use in laboratory research. Each sample is stored with a coded number so that the researcher is not given any personal identifiable information about your child.

What will happen if I agree to take part?

If your child has a stage II or stage III Wilms’ tumour with intermediate risk histology, you will be asked if you would be prepared to take part in this study. This means that there is a 50/50 chance your child will receive either the standard post-operative chemotherapy, with three drugs, or the reduced treatment being tested in the study, with only two drugs. For all other tumour stages and for high and low risk histology tumours, the study is not asking questions about alternative treatment but has recommended a standard treatment for each
tumour stage. For all patients, limited clinical information on tumour stage and response to treatment will be kept at your national data centre and at the SIOP Wilms’ tumour study office in Amsterdam, in accordance with normal standards of medical confidentiality and data protection.

Are there any benefits to taking part?

Whether or not you decide to take part, your child will receive the best possible medical care. By taking part in this study, we hope that some children with Wilms’ tumour will be able to safely avoid having the chemotherapy drug Doxorubicin without reducing their chance of being cured of their Wilms’ tumour. We also hope that children who currently have a slightly lower chance of being cured, will have this chance improved by receiving more intensive treatment. Finally, by allowing scientists to study the genetic changes that have occurred in your child’s tumour, we hope to learn more about why some tumours do well, whereas others do less well and to improve treatment for children with Wilms’ tumour in the future.

What will happen if I decide not to take part?

Whether your child continues in the study or withdraws, your child will continue to receive the best treatment available. In this case, your child will be given the standard treatment which we know is best for their particular tumour stage. You may take part in the clinical study without agreeing to have your child’s blood and tumour stored for the biological study.

Participation in this study is entirely voluntary. If you do not wish your child to take part in the study, your decision will not influence your child’s treatment options, which your doctor will discuss with you. You may withdraw your child from the study at any time without having to give a reason. Your child’s doctor may wish to withdraw your child from the study if it is felt to be in your child’s best interest. If you choose to let your child take part in the study you will be asked to sign a consent form.

If you have any problems, concerns or you require further information regarding this study please contact Dr Kathy Pritchard-Jones on extension 3496 at the Royal Marsden Hospital on 020 8661 + Ext. If you have any complaints about the way the investigator has carried out the study, you should contact the Royal Marsden NHS Trust Complaints Department on 020 8642 6011.

Needs a specific consent form, including written consent for blood and tumour storage.
APPENDIX 10

SUGGESTIONS FOR TREATMENT OF CHILDREN LESS THAN 6 MONTHS

As their prognosis is better, a less aggressive treatment is required:

1. For the majority surgery first is indicated for the following reasons:
   a. Small or medium sized tumours easily removable are most frequent, most of them are stage I and need no further therapy than nephrectomy.
   b. It often concerns a mesoblastic nephroma diagnosed in young babies. This is a benign tumour that needs no further therapy than nephrectomy. In children with a very cellular mesoblastic nephroma and for children older than 12 months a careful follow up is necessary.

2. In case of a huge tumour, reduction of the tumour size with vincristine alone, given before nephrectomy, can be useful, make nephrectomy easier and avoid high stage tumours.

3. Babies with stage II or III tumours present the same problems as those found in tumours of this stage in older children. Theoretically, chemotherapy should be the same as for older children but these drugs can cause severe side effects in the newborn or young babies and doses should be reduced. For stage I and II, post-operative treatment according to stage I is recommended. In case of stage III, AV protocol with dose reduction is recommended but abdominal irradiation is poorly tolerated by babies and sequelae are severe and practically effective irradiation of the whole abdomen cannot be given. In any case, doses over 15 Gy are unadvisable and feeding by gastric tube and appropriate diet is recommended.
# APPENDIX 11

## SCHEDULE OF FORM RETURN

<table>
<thead>
<tr>
<th>Form Name</th>
<th>Form number</th>
<th>Date of Return</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration Form</td>
<td>Form 1</td>
<td>Within 1 month of diagnosis</td>
</tr>
<tr>
<td>Pre-op. CT Form, localised disease</td>
<td>Form 2A</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Pre-op. CT Form, metastatic disease</td>
<td>Form 2B</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Operative findings Form</td>
<td>Form 3A</td>
<td>1 month after surgery</td>
</tr>
<tr>
<td>Surgery related complications Form</td>
<td>Form 3B</td>
<td>1 year after surgery</td>
</tr>
<tr>
<td>Metastectomy Form</td>
<td>Form 3C</td>
<td>1 month after surgery</td>
</tr>
<tr>
<td>Pathology Form</td>
<td>Form 4</td>
<td>Immediately after the operation</td>
</tr>
<tr>
<td>Randomisation Form</td>
<td>Form 5</td>
<td>Within 3 weeks post surgery</td>
</tr>
<tr>
<td>Post-op. Chemotherapy Form, AV-1</td>
<td>Form 6A</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Post-op. Chemotherapy Form, AVD + AV-2</td>
<td>Form 6B</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Post-op. Chemotherapy Form, High risk</td>
<td>Form 6C</td>
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</tr>
<tr>
<td>Additional Chemotherapy Form</td>
<td>Form 6D</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Radiotherapy Form</td>
<td>Form 7</td>
<td>1 month after end of treatment</td>
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<td>Serious Adverse Event Form</td>
<td>Form 8</td>
<td>Fax within 24 hrs of event</td>
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<tr>
<td>Relapse Form</td>
<td>Form 9</td>
<td>Within 1 week</td>
</tr>
<tr>
<td>Death Form</td>
<td>Form 10</td>
<td>Within 1 week</td>
</tr>
<tr>
<td>Cardiotoxicity Monitoring Form</td>
<td>Form 11</td>
<td>Within 1 week</td>
</tr>
<tr>
<td>Bilateral Wilms / Nephroblastomatis DIagnosis Form</td>
<td>Form 12A</td>
<td>Within 1 month of diagnosis</td>
</tr>
<tr>
<td>Bilateral Wilms / Nephroblastomatis Treatment Form</td>
<td>Form 12B</td>
<td>1 month after end of treatment</td>
</tr>
<tr>
<td>Follow-up Form</td>
<td>Form 14</td>
<td>Once a year</td>
</tr>
</tbody>
</table>
IMPORTANT INFORMATION

The Scientific Committee of SIOP has reviewed this protocol for scientific validity and has deemed the hypotheses being addressed are scientifically valid. However, SIOP is not the sponsor, as defined by the ICH Harmonized Tripartite Guidelines, of this study and accepts no legal responsibility for the conduct of this study. In addition, neither the Board nor the Scientific Committee of SIOP accepts responsibility for the overall conduct of this study and has specifically pointed out that implementation of this study requires the approval of the Research Ethics Committee / Institutional Review Board of each participating institution. The responsibility for the management of any individual patient treated with this protocol rests with the treating physician.