Radiotherapy for WILMS TUMOR

SIOP Approach

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Disclaimer

• Nothing to disclose
CONTENTS

• Introduction
• SIOP studies
• SIOP approach
• Indications of RT
• Treatment Volume
• Dose / OAR
• Updates
• Conclusion
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>

**Higher risk of recurrence after rupture: 52% vs 27%**

**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.

Outline of the study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>9 months</th>
<th>DFS/S equal</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCR added, to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Act-D postop</td>
<td>15 months</td>
<td></td>
</tr>
<tr>
<td>Preop. RT</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Ruptures</td>
<td></td>
<td>(p=0.0025)</td>
</tr>
<tr>
<td>Primary surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Various reasons:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e.g. small tumours</td>
<td></td>
<td>20%</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>Diagnosis</th>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Chemotherapy</td>
<td>No difference between the two gps for tumour rupture or stage distrib.</td>
</tr>
<tr>
<td></td>
<td>(VCR/ActD x 4wks)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<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).

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.

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (4 weeks)</td>
<td>R</td>
</tr>
<tr>
<td>S</td>
<td></td>
</tr>
<tr>
<td>CT 4 weeks - S</td>
<td>No advantage in favour of prolonged preoperative treatment</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).

**4 weeks of preoperative chemotherapy established as standard**

July 1993 – Aug 1999: 1104 patients
Randomization → Stage I, Intermediate Risk Histology:
Duration of Post op Chemo

There was no difference in 2-year EFS between the no further therapy group (91%) compared to those who received additional chemotherapy (89%)

SIOP APPROACH

UPFRONT CHEMOTHERAPY

↓

SURGERY

↓

POST OP TREATMENT

RISK STRATIFICATION
Radiotherapy in SIOP Studies

• SIOP 1: 90%
• SIOP 2: 90%
• SIOP 5: 72%
• SIOP 6: 34%
• SIOP 9: 24%
NEPHROBLASTOMA
(Wilms tumour)

CLINICAL TRIAL AND STUDY

SIOP WT 2001

UKCCSG PROTOCOL NO: WT 2002 01
SIOP Classification
Postop Histopathology

• LOW RISK TUMORS
  • Mesoplastic nephroma
  • Cystic partially differentiated nephroblastoma
  • Completely necrotic nephroblastoma

• INTERMEDIATE RISK TUMORS
  • Epithelial type - nephroblastoma
  • Stromal type - nephroblastoma
  • Mixed type - nephroblastoma
  • Regressive type - nephroblastoma
  • Focal anaplasia – nephroblastoma

• HIGH RISK
  • Blastemal type - nephroblastoma
  • Diffuse anaplasia - nephroblastoma
  • Clear cell sarcoma of kidney
  • Rhabdoid tumor of kidney
STAGING
STAGE I

• Tumor limited to kidney
• Extension beyond kidney contour + fibrous pseudocapsule
  • Renal capsule / Pseudocapsule Infiltration
    • Outer surface negative
    • Clear resection margin

• Tumor protruding / bulging into renal pelvis or Dipping into ureter but walls not infiltrated

• Renal sinus vessels: not involved
• Intrarenal vessels maybe involved
Stage II

• Completely resected – **Margins Clear**
  • Extension beyond kidney
  • Renal capsule penetrated
  • Fibrous pseudocapsule infiltrated
  • Infiltration of blood or lymphatic vessels outside renal parenchyma

• Vena Cava or adjacent organ infiltration **completely resected**
Stage III

- Gross or microscopic residual
- Involved abdominal lymph nodes
- Pre or intra operative tumor rupture
- Peritoneal surface penetrated
- Peritoneal surface implants
- Tumor thrombi at vessel or ureteric margin
  - Piecemeal resection
- Surgical (WEDGE) biopsy:
  - Preoperative Chemo
  - Surgery
Stage IV

- Hematogeneous Metastases
  - Lung
  - Liver
  - Bone
  - Brain etc

- Lymph node metastases outside abdominopelvic region
Stage V

• Bilateral Renal Tumors at Diagnosis

• Each side should be sub-staged accordingly
AIMS OF RADIOTHERAPY

• To achieve control of abdominal disease
  • significant risk of intra-abdominal relapse.
• To increase the control of pulmonary metastases
  • incomplete remission after chemo
• To increase the control of hepatic metastases
  • incomplete remission after chemotherapy or
  • surgery (R1 & R2 resections)
• To increase the control of brain metastases.
• To increase the control of bone metastases.
INDICATIONS
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
Whole Abdomen RT

• Diffuse Intra Abdominal Tumor
  or
• GROSS pre or perioperative rupture

TIMING: within 2 weeks after abdominal surgery

Exception: Lung Mets
  • Abdominal RT to start after Lung Surgery
  • At 9 weeks +/- Lung RT
Pulmonary RT

• POST CHEMO: Residual tumour tissue on a chest X-ray or CT scan

• Doubtful pulmonary nodule
  • Consider excision

• Complete remission: no abnormalities on
  • chest X-ray or
  • chest CT-scan.
Hepatic RT

• Liver metastases which do not respond completely to chemotherapy

• Liver metastases cannot be completely resected with negative margins.
RT to other metastatic sites

- Brain (whole brain RT)
- Bone metastases (focal RT)

regardless of response to chemotherapy
TARGET VOLUME
CLINICAL TARGET VOLUME (CTV)

Flank RT - CTV:

• A margin of 1 cm is given to
  • post-chemotherapy and
  • pre-operative macroscopic tumour and
  • kidney according to surgical / histopathological reports &
  • extent on CT-scan/ ultrasonography

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
• macroscopic residual disease + 1 cm

paraaortic lymphnodes
• T-10-TV-11 till L4-L5

*full width of the vertebral bodies should receive a homogeneous dose
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.
Examples for typical Target Volumes and Radiation Portals: Stage III macroscopic residual disease (continued)

Fig. 2a: right-sided tumour with one homolateral 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.
**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.
Whole abdominal RT

• Entire abdominal contents
• Peritoneum extending from
  • Superior: dome of the diaphragm
  • Inferior: pelvic floor
    (lower border of obturator foramen)
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.
Pulmonary RT

• Both lungs including
  • Apices and
  • Costa-diaphragmatic recesses

*abdominal radiotherapy also has to be given, both fields should be matched in order to avoid any gap or overlap
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.
Liver RT

• Incompletely resected tumour + 2 cm
Bone Mets

• Obvious disease visible on imaging + margin (not <3cm)
Brain Metastases

• Whole Brain
PLANNING TARGET VOLUME (PTV)

• Individual departmental policy:
  • Internal margin: 1 cm for breathing movements.

• left sided tumours RT of the heart should be avoided if possible.
TREATMENT DOSE
Flank RT

- **Stage III intermediate risk**: 14.4 Gy
  - Boost to the macroscopic residual disease after surgery: **10.8 Gy**
  - Positive lymph nodes: 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.

*dose per fraction is 1.8 Gy*

Maybe lowered for larger volumes
Whole abdominal RT

• Entire peritoneal: maximum of **21 Gy**
  • Boost: as for flank RT

• <1 year of age: total dose 10-12 Gy

*dose per fraction is 1.5 Gy

**toxicity / very young children (< 2 years): 1.25 Gy**
Brain RT:
• Whole brain : 25.5 Gy
• Boost : 4.5 Gy

Liver RT:
• Area of R1 resection: 20 Gy

Bone RT:
• Metastatic site: 30 Gy

*dose per fraction is 1.5 Gy*
Pulmonary RT

• b/l Lungs: 15 Gy for both lungs
  • Correction of tissue heterogeneity
  • Dose per fraction: 1.5 Gy
  • Boost of 10-15 Gy: gross residual disease after surgery.
Treatment Interruptions

• **Rests/ Interruptions**
  • must be kept to an absolute minimum
  • Avoid holidays

• **Interruptions for myelotoxicity**
  • **neutrophil** count falls below 0.5 x 10^9/l
  • Resume after at least 1.0 x 10^9/l.

  • **platelet** count falls below 25 x 10^9/l
  • Resume after at least 50 x 10^9/l

  • **Haemoglobin:** maintained at a minimum of 10 g/dl

*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.*
NORMAL TISSUE SPARING
Critical organ dose

- Remaining kidney: <12 Gy.

- Liver
  - whole <20 Gy
  - >20 Gy should not be received by more than half the liver

- Lung: < 15 Gy in 1.5 Gy fractions (with correction for inhomogeneity).
  - > 15 Gy should not be received by more than 25 % of the lung volume

- Shielding:
  - Joints
  - Lung RT : shoulder joints
  - Whole abdominal RT : hips
CONSENSUS STATEMENT

OPEN

POSITION PAPER

Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP–RTSG 2016 protocol

Marry M. van den Heuvel-Eibrink¹, Janna A. Hol¹, Kathy Pritchard-Jones², Harm van Tinteren³, Rhoikos Furtwängler⁴, Arnauld C. Verschuur⁵, Gordan M. Vujanic⁶, Ivo Leuschner⁷, Jesper Brok², Christian Rübe⁸, Anne M. Smets⁹, Geert O. Janssens¹,¹⁰, Jan Godzinski¹¹,¹², Gema L. Ramírez-Villar¹³, Beatriz de Camargo¹⁴, Heidi Segers¹⁵, Paola Collini¹⁶, Manfred Gessler¹⁷, Christophe Bergeron¹⁸, Filippo Sprefico¹⁶ & Norbert Graf⁴ on behalf of the International Society of Paediatric Oncology — Renal Tumour Study Group (SIOP–RTSG)
Table 4 Radiotherapy guidelines in UMBRELLA SIOP–RTSG 2016 for locoregional disease

<table>
<thead>
<tr>
<th></th>
<th>Stage I (total/fraction dose)</th>
<th>Stage II (total/fraction dose)</th>
<th>Stage III (total/fraction dose)</th>
<th>Stage III (major rupture) ($) (total/fraction dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>no</td>
<td>no</td>
<td>14.41.8 Gy (± 10.8/1.8 Gy)*</td>
<td>15.0/1.5 Gy (± 10.8/1.8 Gy)$</td>
</tr>
<tr>
<td>High-risk blastema-</td>
<td>no</td>
<td>no</td>
<td>25.2/1.8 Gy (± 10.8/1.8 Gy)*</td>
<td>19.5/1.5 Gy (± 10.8/1.8 Gy)*</td>
</tr>
<tr>
<td>type Wilms tumour</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk diffuse</td>
<td>no</td>
<td>25.2/1.8 Gy (± 10.8/1.8 Gy)*</td>
<td>25.2/1.8 Gy (± 10.8/1.8 Gy)*</td>
<td>19.5/1.5 Gy (± 10.8/1.8 Gy)*</td>
</tr>
<tr>
<td>anaplasia</td>
<td></td>
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</tr>
</tbody>
</table>

*Boost dose indicated for localized residual tumour at the time of radiotherapy only. Radiotherapy to the whole abdomen. §Boost only indicated for multiple residual peritoneal deposits (± 4.5/1.5 Gy)

Table 5 | Radiotherapy guidelines in UMBRELLA SIOP–RTSG 2016 for metastatic disease

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Lung (whole ± boost) (total/fraction dose)</th>
<th>Liver (whole ± boost) (total/fraction dose)</th>
<th>Brain (whole ± boost) (total/fraction dose)</th>
<th>Bone (total/fraction dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Intermediate-risk</td>
<td>12.0/1.5 Gy (± 10–13 Gy)*</td>
<td>14.4/1.8 Gy (± 10.8/1.8 Gy)*</td>
<td>15.0/1.5 Gy (± 10.8/1.8 Gy)*</td>
<td>30.6/1.8 Gy</td>
</tr>
<tr>
<td>High-risk</td>
<td>15.0/1.5 Gy (± 15–20 Gy)*</td>
<td>19.8/1.8 Gy (± 16.2/1.8 Gy)*</td>
<td>25.2/1.8 Gy (± 10.8/1.8 Gy)*</td>
<td>30.6/1.8 Gy</td>
</tr>
</tbody>
</table>

*Boost dose indicated for residual tumour at the time of radiotherapy only.
Evaluation of boost irradiation in patients with intermediate-risk stage III Wilms tumour with positive lymph nodes only: Results from the SIOP-WT-2001 Registry

- June 2001-May 2015: 2,569 patient
- Stage III: 523 (20%) patients
  - 113 due to positive LN
- 101 (89%) received radiotherapy
  - 36 (36%): flank RT + LN boost
  - Four (4%) no adjuvant RT
  - 8 patients: RT information mission
Evaluation of boost irradiation in patients with intermediate-risk stage III Wilms tumour with positive lymph nodes only: Results from the SIOP-WT-2001 Registry

- No difference in (boost vs no boost):
  - 5-year EFS (84% vs 83%, P=0.77)
  - LRC (96% vs 97%, P=0.91)
  - 5-year OS (97% vs 95%, P=0.58)
WHOLE LUNG RADIOTHERAPY (bilateral)

• Favorable Histology
  • 15 Gy → 12 Gy
• Lung lacking complete response at 10 weeks of chemo

• Poor Survival: <40%
  • Viable metastases at surgery or
  • high-risk histology

D'Angio GJ et al. Cancer. 1989 Jul 15;64(2) Treatment of Wilms' tumor. Results of the Third National Wilms' Tumor Study
Warmann SW et al, Ann Surg. 2011 Jul;254(1) Tumor biology influences the prognosis of nephroblastoma patients with primary pulmonary metastases: results from SIOP 93-01/GPOH and SIOP 2001/GPOH.
CONCLUSION

• Close collaboration with colleagues
• Pre Op Chemo
• Adequate surgery
• Histopathology Reporting
• Treatment as per protocol

• Multidisciplinary Discussion & Management