### EVIDENCE BASED MANAGEMENT FOR Wilms’ Tumour

Wilm’s tumor is the second most common abdominal tumor and constitutes 6% of all childhood cancers. Wilm’s tumor is the paradigms for multidisciplinary treatment of Pediatric malignant solid tumor.

Wilm’s tumor develops as a result of abnormalities in development of metanephric blastema. Wilm’s tumor has been reported to be associated with various anomalies. Genitourinary anomalies are the most common and account for incidence of 4 to 8%. The anomalies include fused kidney, renal dysplasia, cryptorchidism, hypospadias, duplications of collecting system, WAGR Syndrome (WT, aniridia, Genitourinary abnormalities and mental retardation) wilm’s tumor is also featured in many disorders of overgrowth including Beckwith-Weidmann Syndrome, Perlmann Syndrome, isolated hemihypertrophy. Although most patients with Wilms tumor are Karytypically normal, genomic studies have led to the localization and subsequent cloning of WT genes in two regions - 11p13 & 11p15. The former is WT1 gene and is associated with WAGR Syndrome & latter is WT2 gene which is associated with Beckwith Wiedemann Syndrome.

### Evaluation

1. **History & physical Examination**
   - Detection of an asymptomatic abdominal mass bulging in the flank.
   - Non specific symptons like abdominal pain, fatigue
   - Haematuria (in <10%)
   - Hypertension (V. rare)
   - Associated Urogenital anomalies, Aniridia, overgrowth Syndrome.

### Investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Purpose</th>
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<tr>
<td>1. Abdominal USG</td>
<td>Organ of origin, Identify contralateral Kidney, Presence/absence of tumor, thrombus in IVC</td>
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<tr>
<td>2. CT Scan</td>
<td>Further evaluation of extent of tumor, Extension into adjoining structures such as Liver spleen &amp; colon, Visualisation and function of contralateral Kidney</td>
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<td>3. X-ray chest PA</td>
<td>Pulmonary Metastases</td>
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<td>4. Bone scan &amp; X-ray Skelatal survey</td>
<td>Bone mets in clear cell Sarcoma of Kidney (CCSK)</td>
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<tr>
<td>5. Brain imaging (MRI / CT-Scan)</td>
<td>Intracranial mets in Rhabdoid Tumor (RT) &amp; CCSK</td>
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<td>6. Fine needle aspiration cytology of mass</td>
<td>Cytological confirmation of diagnosis prior to prenephrectomy Chemotherapy.</td>
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</table>
**Surgical staging includes**
1. Through examination of the contralateral Kidney after opening Gerota’s facia.
2. Retroperitoneal node sampling
3. Palpation of Liver.

**IDEAL PATHOLOGY REPORT**
1. Clinical details age, sex, etc.
2. Topography
3. Gross*
   - Specimen type - partial or radical nephrectomy
   - Tissues included
   - Laterality
   - Kidney size & weight
   - Tumor site
   - Tumor characteristics - number of tumor nodules, Give greatest dimensions of all nodules if multiple, Location of these nodules
   - State of cortex and hilum - Gerota’s fascia intact or disrupted, renal vein invasion present & adrenal involvement if any
4. Microscopy
   a) Type -
      - Wilms tumor favorable histology
      - Wilms tumor with anaplasia (unfavorable)-focal / diffuse **
   b) Nephrogenic rests - type(intralobar, perilobar, unclassified)
   c) Margins
      - Cannot be assessed/ uninvolved - Distance of all margins Involved margins
      - Gerota’s fascia
      - Renal vessels
      - Ureter
   d) Renal sinus involvement***
   e) Regional lymph nodes
5. National Wilms tumor registry Stage

**Comments**

*Submit all specimens intact to the pathologist for grossing. Take at least 1 microscopic section per centimeter, majority sections should be from periphery in order to record nephroblastomatosis & invasiveness of tumor. One or more sections from adjacent kidney are must to evaluate nephroblastomatosis

**Anaplasia - Focal Anaplasia is confined to one sharply localized region - Hence to delineate anaplasia while taking sections draw a figure as to where sections have been given from as subsequently it may be difficult to trace anaplasia.

***Renal sinus is an area in the hilum of kidney occupied by renal pelvis hilar vessels and fat. In this area there is no renal capsule. Papers in recent times have shown that renal sinus involvement has poor prognosis in-patients with otherwise low stage disease.

**National Wilms Tumor Study (NWTS) staging**

**Stage I** : Tumor confined to the kidney & completely excised
**Stage II** : Tumor outside the kidney but completely excised
   - Local tumor spillage during surgery
   - Lymph nodes negative
Stage III: Non hematogenous disease confined to the abdomen
   - Perioperative rupture of renal capsule
   - Diffuse tumor spillage during surgery
   - Peritoneal implants
   - Positive lymph nodes

Stage IV: Hematogenous metastases to lungs or liver

Stage V: Bilateral Wilms’ tumor

NWTS Algorithm based on NWTS 4
   SIOP Algorithm based on SIOP 93 - 01.
   Carbo = carboplatin; CPM = cyclophosphamide; DAM = dactinomycin; DOX = doxorubicin;
   EPI = epirubicin; Ifos = ifosfamide; VCR = vincristine; RT = radiotherapy; FH = favourable histology;
   UH = unfavourable histology; wk = week; PI = pulse intensive.

Prenephrectomy Chemotherapy
   To decrease the need for post op abdominal radiation therapy in event of tumor rupture during nephrectomy, International Society of Pediatric Oncology (SIOP) conducted series of trials in which all patients received Chemotherapy before nephrectomy. National Wilm’s Tumor Study Group (NWTSG) recommend immediate nephrectomy to avoid several risks.

Risks of Prenephrectomy Chemotherapy
   1) Chemotherapy to a patient with benign disease as in SIOP trials Prechemotherapy confirmation of diagnosis is not mandatory. This risk is 7.6 % to 9.9%
   2) Modification of tumor histology
      Data suggest that chemotherapy did not modify tumor histology to such an extent that diagnostic features of anaplasia could not be identified.
   3) Loss of staging information.
      This concern is exemplified in SIOP. 6 trial in which Postchemotherapy stg. II Lymphnode -ve patients randomised not to receive radiotherapy had high intra-abdominal recurrence suggesting that pre-op chemotherapy produced sufficient tumor response to destroy pheinephric tumor extension and deposits in Lymph
nodes.
Stage distribution of patients entered on NWTS - 3 & SIOP 6 are comparable. However 50% more European Stg. I - III FH. Patients will receive anthracycline, whereas 50% more North American patients will be treated with abdominal irradiation. Thus risk of anthracycline exposure with associated risk of cardiotoxicity should be weighed against tumor rupture leading to abdominal irradiation and risk of carcinogenesis.

**Absolute Indications for Prenephrectomy Chemotherapy**
1. Large tumor technically difficult to deliver at surgery.
2. Presence of major tumor thrombus in the inferior venacava.
3. Bilateral Wilm’s tumor
4. Wilm’s tumor in a solitary Kidney or horse shoe Kidney.

**RADIOThERAPY FOR WILMS’ TUMOR**
**Indications :**
- Stage II unfavorable histology.
- Stage III & IV favorable & unfavorable histology.
- Local recurrence.
- Palliative radiotherapy for metastatic disease.

**Principles of Radiation Therapy :**
Radiotherapy should be planned starting within 10 day of surgery.
No change of radiotherapy dose for favorable & unfavorable histology.
Rhabdoid tumors to be treated as a separate entity.

**Target volume :**
Volume should encompass tumor bed + site of excised kidney with 2-3cm margin.
Entire vertebral body to be encompassed.
Stage II - Tumor bed only

**Stage III & IV disease**

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Radiotherapy volume</th>
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<tbody>
<tr>
<td>Positive hilar nodes</td>
<td>Flank (operative bed)</td>
</tr>
<tr>
<td>Positive paraaortic nodes</td>
<td>crossing midline to include bilateral paraaortic nodes</td>
</tr>
<tr>
<td>Gross or microscopic residuum</td>
<td></td>
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<tr>
<td>Confined to flank</td>
<td></td>
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<tr>
<td>Peritoneal seeding</td>
<td>Whole abdomen</td>
</tr>
<tr>
<td>Gross residual abdominal disease</td>
<td>Boost tumor &gt;3cm</td>
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<tr>
<td>Diffuse spillage at surgery</td>
<td>Shield acetabulum</td>
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<tr>
<td>Preoperative intraperitoneal rupture</td>
<td>&amp; femoral heads</td>
</tr>
<tr>
<td>Lung Metastases</td>
<td>Whole lung (bilateral)</td>
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**Total Dose:**
Recommended radiation therapy doses in NWTS – 5

<table>
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<tr>
<th>Characteristics</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Stage I &amp; II FH, Stage I anaplastic</td>
<td>No radiation therapy</td>
</tr>
</tbody>
</table>
Stage III FH, Stage IV FH with abdominal
Stage III, Stage II-IV anaplastic, Stage I-IV
Clear Cell Sarcoma/ Rhabdoid tumor of
Kidney
Stage IV (Lung metastases)
Stage IV (Liver metastases)
Stage IV (Brain metastases)
Stage IV (Bone metastases)
Stage IV (Bone metastases)
Relapsed Wilms’ Tumour

10Gy to flanka + 10Gy
boost to gross residual disease
(>3cm)

12-Gy Whole-Lung
irradiation
19.8Gy to Liver
30.6Gy to Whole Brain
30.6Gy to tumor with
3cm margin
12.6-18Gy
(<12 months of age)
and 21.6Gy in older
children if previous
radiation dose is
£ 10.8Gy. Boost of
upto 9Gy to gross
residual disease after
surgery. Total dose
including previous
radiation not to exceed
30.6Gy (<1yr age)
& 39.5Gy (³ 2yr age)

FH : Favorable Histology
a Whole-Abdomen Irradiation for : Diffuse Peritoneal Implants
Preoperative Anterior Rupture of Renal Capsule
Diffuse Abdominal Operative Spillage
b In patients with FH disease, if pulmonary nodules are visible on CT scans but not
detected on chest radiographs, then whole lung irradiation is not mandatory.
Follow-up 1) Chest x-ray/ CT-scan chest (if pulmonary mets) and abdominal USG
Once in 3 months X 2years
Once in 6 months X until 5 years since diagnosis.

Evaluation in Late effect Clinic
2. Evaluation of Renal Functions on annual basis
4. Evaluation of Anthcycline related cardiotoxicity with 2 DEcho on annual/biennial
basis
4. Assessment of growth and Sexual development.
5. Assessment of musculoskeletal development in irradiated patients.
6. Assessment of fertility
7. Watch out for second Malignant Neoplasia.

Wilm’s Tumour -
Management

Pendergrass TW.
From 68 hospitals in the National Wilms’ Tumor Study, records of 547 patients showed six patients with aniridia, 16 with hemihypertrophy, and 24 with genitourinary abnormalities. Multiple cases of Wilms’ tumor occurred in three families. The results confirm high frequencies of aniridia and genitourinary anomalies in patients with Wilms’ tumor, and show that concurrence with hemihypertrophy may be more often recognized or recorded now than it was ten years ago. The results demonstrate the desirability of developing checklists for other childhood neoplasms some of which have their own constellation of anomalies.

**Germline WT1 mutations in Wilms’ tumor patients: preliminary results.**
Li FP, Breslow NE, Morgan JM et al.

We conducted a comparative study of the prevalence of germline WT1 mutations in patients with Wilms’ tumor. Patients in Group 1 have familial Wilms’ tumor, bilateral disease, associated urogenital anomalies, and/or second cancers. Those in Group 2 are unilateral, sporadic Wilms’ patients without other associated conditions. Patients with aniridia or Denys-Drash syndrome are known to have WT1 alterations, and are excluded from this study. Preliminary results on 96 subjects show that the overall germline WT1 mutation frequency is low (< 5%). The work to date establishes the feasibility of identifying patients with germline WT1 mutations and, in the future, offering genetic predisposition testing to at-risk relatives. However, genetic predisposition testing of children for WT1 mutations raises many ethical, legal, and psychosocial issues; research is needed to evaluate risks and benefits.

**The surgical treatment of Wilms’ tumor: results of the National Wilms’ Tumor Study.**
Leape LL, Breslow NE, Bishop HC

Surgical data derived from the 606 patients in the National Wilms’ Tumor Study have been analyzed to determine the effect of surgical technique on results of treatment. In addition to surgical excision of the tumor, patients were treated with chemotherapy and radiation therapy according to the study protocol. Under these controlled conditions, certain aspects of surgical technique, which have traditionally been thought to be important for success, appear to be irrelevant. Physical characteristics of the tumor, preoperative rupture and vascular invasion by tumor were not associated with higher relapse rates. Large tumors, those with capsular infiltrations, and tumors with spread to lymph nodes higher recurrence rate. Operative spill increased the chance of abdominal recurrence. There was no evidence that early ligation of the renal vein was of value in prevention of recurrence, nor was incomplete removal of tumor associated with an increase in relapse rate. Although several critical factors of surgical technique were not studied, it is clear that others are not significant and need not be continued.

**Is contralateral exploration of the kidney necessary in patients with Wilms tumor?**
Kessler O, Franco I, Jayabose S et al.

PURPOSE : Surgical exploration of the contralateral kidney in patients with Wilms tumor is standard practice. The introduction of modern imaging techniques
(ultrasound, computerized tomography and magnetic resonance imaging) in place of excretory urography has led to a more accurate definition of intrarenal pathology. Is contralateral kidney exploration still necessary in patients with Wilms tumor?

MATERIALS AND METHODS: We reviewed the records of 75 patients from 3 medical centers who were evaluated and treated for Wilms tumor in the last 14 years. All children underwent preoperative excretory urography, computerized tomography, ultrasound and/or magnetic resonance imaging. RESULTS: Seven bilateral Wilms tumors were diagnosed preoperatively and confirmed surgically, whereas extensive operative exploration of the contralateral kidney in the other 69 patients revealed no additional pathological condition. This concurred with preoperative radiological findings with 100% sensitivity and specificity. Furthermore, 1 month to 12 years of followup (mean 4.3 years) revealed no tumor in the contralateral kidney. The major postoperative complication was small bowel obstruction in 5 patients 15 to 180 days (mean 77.2) after explorative laparotomy. CONCLUSIONS: In all patients preoperative radiological investigation was accurate in excluding bilaterality. With modern imaging techniques and effective chemotherapy extensive contralateral renal exploration may no longer be mandatory for managing Wilms tumor.

Protocol for the Examination of Specimens From Patients With Wilms Tumor or Other Renal Tumors of Childhood
Stephen J. Qualman, Jay Bowen, Mahul B. Amin et al.

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations. The College regards the reporting elements in the “Surgical Pathology Cancer Case Summary” section of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice. The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that hospitals, attorneys, payers, and others might use the protocols. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons has mandated the use of the checklist elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with the document. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations those are beyond the scope of this document.

Prognosis for Wilms’ tumor patients with nonmetastatic disease at diagnosis—results of the second National Wilms’ Tumor Study.
Breslow N, Churchill G, Beckwith JB et al.

Multivariate statistical methods were used to study prognosis for 632 patients entered on the second National Wilms’ Tumor Study who had nonmetastatic, unilateral disease at diagnosis. Separate analyses were conducted for each of four endpoints: abdominal recurrence, distant metastasis, relapses without regard to site,
and death. The two most important predictors for metastasis and general relapse were an unfavorable (anaplastic or sarcomatous) histology and the presence of microscopically confirmed disease in the regional lymph nodes. Operative spillage of tumor increased the rates of abdominal recurrence and death, even after accounting for histology and lymph node effects. The presence of a tumor thrombus in the renal vein or IVC increased the risk of metastasis, and intrarenal vascular invasion was associated with general relapse after accounting for histology, lymph nodes, and spillage. However, these latter associations were weaker, and some uncertainty remains regarding the true prognostic import of such findings due to a high degree of collinearity among variables. By contrast to the results of a similar data analysis for the first National Wilms’ Tumor Study, specimen weight had no bearing on outcome, and the effects of age at diagnosis were entirely explained by the association of age with other more critical factors.

**Focal versus diffuse anaplasia in Wilms tumor–new definitions with prognostic significance: a report from the National Wilms Tumor Study Group.**
Faria P, Beckwith JB, Mishra K et al.

Anaplasia, defined by the presence of extreme nuclear and mitotic atypia, is a potent marker of adverse prognosis in Wilms tumor (WT). Anaplastic WT cells apparently have increased resistance to therapy rather than increased aggressiveness. The distribution of anaplasia should therefore have critical prognostic relevance. The original definitions for focal anaplasia (FA) and diffuse anaplasia (DA) were based on quantitative rather than topographical criteria and lacked prognostic significance. A new definition was developed based on the distribution of anaplastic changes within the tumor: FA applies only to tumors with anaplasia confined to one or a few discrete loci within the primary tumor, with no anaplasia or marked nuclear atypia elsewhere. This revised definition was evaluated in 165 cases with anaplastic WT entered on the third and fourth National Wilms Tumor Study. Only three relapses and one death occurred among 39 cases with FA, regardless of tumor stage, a result comparable to that for nonanaplastic WT. Eight children with metastases at diagnosis and FA in the primary tumor were alive and free of relapse; 22 of 23 children with stage IV DA WT died of tumor. This new definition reinforces the importance of carefully documenting the exact site from which each tumor section is obtained.

**The treatment of Wilms’ tumor: results of the Second National Wilms’ Tumor Study.**
D’Angio GJ, Evans A, Breslow N et al.

One-hundred-eighty-eight children up to 16 years of age were randomized in the second National Wilms’ Tumor Study (NWTS) with tumors that were confined to the kidney and that had been totally excised (Group I). Most fared well whether treated for six or for 15 months with both actinomycin D (AMD) and vincristine (VCR). No postoperative radiation therapy (RT) was given. The two-year relapse-free survival (RFS) and two-year survival rates were 88 and 95%, respectively. Two-hundred-sixty-eight randomized patients with more advanced local lesions (Groups II and III) and 57 with distant metastases (Group IV) had postoperative RT and were scheduled for 15 months treatment with either AMD and VCR (Reg. C) or AMD plus VCR plus Adriamycin (Reg. D). The 77% two-year RFS rate for Reg. D was significantly
different from the 63% with Reg. C. As in the first NWTS, patients with tumors of unfavorable histology (UH) had a significantly worse prognosis than those with favorable histology (FH), as did those with positive nodes. Survival rates at two years were 54% for UH vs. 90% for FH, and 54% vs. 82% for those with and without lymph node involvement.

Treatment of Wilms’ tumor. Results of the Third National Wilms’ Tumor Study.
D’Angio GJ, Breslow N, Beckwith JB et al.

The Third National Wilms’ Tumor Study sought to reduce treatment for low-risk patients and find better chemotherapy for those at high risk for relapse. Eligible patients (1439) were randomized according to stage (I-IV) and histology (favorable [FH] or unfavorable [UH]), and contributed data to survival and relapse-free survival (RFS) analyses. Four-year (postnephrectomy) survival percentages and randomized treatment regimens for low-risk patients were 96.5% for 607 Stage I/FH patients who received dactinomycin (Actinomycin D [AMD], Merck Sharp & Dohme, West Point, PA) and vincristine (VCR) for 10 weeks versus 6 months; 92.2% for 278 Stage II/FH patients; and 86.9% for 275 Stage III/FH patients who received AMD + VCR +/- Adriamycin (ADR, Adria Laboratories, Columbus, OH) for 15 months. Stage II/FH patients also had either zero or 2000 cGy irradiation (RT) postoperatively and Stage III/FH patients either 1000 or 2000 cGy. Four-year survival was 73.0% for 279 high-risk patients (any Stage IV, all UH) who received postoperative radiation therapy (RT) and AMD + VCR + ADR +/- cyclophosphamide (CPM). Statistical analysis of survival and RFS experience shows that the less intensive therapy does not worsen results for low-risk patients and CPM does not benefit those at high risk.

Prognostic factors in nonmetastatic, favorable histology Wilms’ tumor. Results of the Third National Wilms’ Tumor Study.
Breslow N, Sharples K, Beckwith JB et al.

A comprehensive statistical analysis of relapses to lung and abdomen and of deaths due to tumor that occurred among 1466 patients with nonmetastatic, favorable histology (FH) Wilms’ tumor entered on the Third National Wilms’ Tumor Study (NWTS-3) was undertaken. In addition to lymph node involvement, ages at diagnosis and tumor size as measured by the weight of the excised specimen were the most important determinants of outcome. The effects of tumor size were most apparent for patients with localized (Stage I) disease; age effects were found for patients with regional (Stage II or III) disease. The presence of microscopic tumor in the margin of surgical resection was an independent predictor of abdominal recurrence and death in the latter group. Although the report of the surgeon of diffuse soilage of the peritoneal cavity from tumor spilled or cut across in the course of nephrectomy was highly correlated with outcome, it was not possible to establish an independent prognostic role for such a finding after adjustment for the aforementioned factors. Patients with intralobar nephrogenic rests (ILNR) had a favorable survival outlook even after accounting for their generally younger ages and lower stages.

Comparison between single-dose and divided-dose administration of dactinomycin and doxorubicin for patients with Wilms’ tumor: a report from the National Wilms’ Tumor Study Group.
PURPOSE: The National Wilms’ Tumor Study (NWTS)-4 was designed to evaluate the efficacy, toxicity, and cost of administration of different regimens for the treatment of Wilms’ tumor (WT). PATIENTS AND METHODS: Between August 6, 1986 and September 1, 1994, 1,687 previously untreated children less than 16 years of age with stages I to II/favorable histology (FH) or stage I/anaplastic histology WT (low-risk [LR] group) or stages III to IV/FH WT or stages I to IV/clear cell sarcoma of the kidney (high-risk [HR] group) were randomized to treatment that included vincristine and either divided-dose (standard [STD]) courses (5 days) or single-dose (pulse-intensive [PI]) treatment with dactinomycin. HR patients also received either STD courses (3 days) or PI treatment with doxorubicin. RESULTS: The 2-year relapse-free survival (RFS) rates for LR patients were 91.3% for 544 randomized to treatment with PI and 91.4% for 556 randomized to treatment with STD chemotherapy (P=.988). The 2-year RFS rates for HR patients were 87.3% for 299 randomized to treatment with PI and 90.0% for 288 randomized to treatment with STD chemotherapy (P=.865). CONCLUSION: We conclude that patients treated with PI combination chemotherapy for LR or HR WT or clear cell sarcomas of the kidney have equivalent 2-year RFS to those treated with STD regimens. PI drug administration is recommended as the new standard based on demonstrated efficacy, greater administered dose-intensity, less severe hematologic toxicity, and the requirement for fewer physician and hospital encounters.

Effect of duration of treatment on treatment outcome and cost of treatment for Wilms’ tumor: a report from the National Wilms’ Tumor Study Group.

PURPOSE: National Wilms’ Tumor Study (NWTS)-4 was designed to evaluate the efficacy, toxicity, and cost of the administration of different regimens for the treatment of Wilms’ tumor (WT). PATIENTS AND METHODS: Between August 6, 1986 and September 1, 1994, 905 previously untreated children aged younger than 16 years with stage II favorable histology (FH) WT (low-risk [LR]), stages III to IV FH WT, or stages I to IV clear-cell sarcoma of the kidney (high-risk [HR]) were randomized after the completion of 6 months of chemotherapy to discontinue (short) or continue for 9 additional months (long) treatment with chemotherapy regimens that included vincristine and either divided-dose (standard [STD]) courses (5 days) or single-dose (pulse-intensive [PI]) treatment with dactinomycin. HR patients also received either divided-dose (STD) courses (3 days) or single-dose (PI) treatment with doxorubicin. RESULTS: The 4-year relapse-free survival (RFS) rates after the second randomization for LR patients were 83.7% for the 190 patients treated with short and 88.2% for the 187 patients treated with long chemotherapy (P=.11). The 4-year RFS rates after the second randomization for HR FH patients were 89.7% for the 256 patients treated with short and 88.8% for the 246 patients treated with long chemotherapy (P=.87). The charge for treatment with the short PI treatment regimens for all children with stages I through IV FH WT was approximately one half of that with the long STD treatment regimens. CONCLUSION: The short administration schedule for the treatment of children with WT is no less effective than the long administration schedule and can be administered at a substantially lower total treatment cost.
The effect of chemotherapy dose intensity on the hematological toxicity of the treatment for Wilms’ tumor. A report from the National Wilms’ Tumor Study.
Green DM, Breslow NE, Evans I et al.

PURPOSE: To determine the relationship between hematological toxicity and actual dose intensity of treatment of patients randomized to therapy during the first 28 months of the National Wilms’ Tumor Study-4. METHODS: The mean minimum white blood cell count (WBC), platelet count (PLT), hemoglobin, and absolute neutrophil count (ANC) during the first two courses of chemotherapy and the mean number of days of hospitalization for toxicity were compared between standard and “pulse-intensive” regimens for all randomized patients entered on National Wilms’ Tumor Study-4 between August 6, 1986 and December 31, 1988. The mean dose intensity of dactinomycin, vincristine, and doxorubicin received during the first two courses and the entire course of treatment was compared between standard and “pulse-intensive” regimens. RESULTS: The mean minimum WBC, PLT, and ANC were all significantly lower during the first two courses of chemotherapy for stage I patients treated with the standard regimen, compared with the “pulse-intensive” regimen. The mean dose intensity of dactinomycin and doxorubicin was significantly higher for patients treated with the “pulse-intensive” regimens, compared with the appropriate standard regimen. CONCLUSIONS: The “pulse-intensive” administration schedule for the treatment of children with Wilms’ tumor permits administration of chemotherapy at higher dose intensity without an increase in hematological toxicity.

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 (S.I.O.P.).
Lemerle J, Voute PA, Tournade MF et al.

The preliminary results of a controlled clinical trial organized by the S.I.O.P. of radiotherapy and chemotherapy in patients with nephroblastoma are presented. Forty-two centers have participated. Between September 1971 and October 1974, 398 patients were registered; 195 were eligible for the trial and were randomized. The remaining 203 patients were excluded from the trial, but were followed in the same way as the patients in the trial. The results were evaluated in terms of recurrence-free survival rate and survival rate. Results in patients who received preoperative and postoperative radiotherapy (group A, 73 patients) were compared with the results in patients who received only postoperative radiotherapy (group B, 64 patients). The tumor ruptured at surgery in three patients of group A, and in 20 patients of group B, a difference that is statistically significant. No significant difference in survival and recurrence-free survival between groups A and B is observed at present. Results in patients treated with a single course of actinomycin D (group I, 80 patients) were compared with the results in patients treated with multiple courses (group II, 80 patients). At present, no significant difference is found between the two groups.

Effectiveness of preoperative chemotherapy in Wilms’ tumor: results of an International Society of Paediatric Oncology (SIOP) clinical trial.
Lemerle J, Voute PA, Tournade MF et al.
The results of a controlled clinical trial of preoperative radiotherapy compared to chemotherapy in patients with nephroblastoma are presented. Of 397 histologically proven cases of Wilms’ tumor registered at 34 centers between January 1977 and July 1979, 164 were eligible for the trial and were randomized to receive preoperative radiotherapy and chemotherapy (group R, 76 patients) or preoperative chemotherapy (group C, 88 patients). The results were evaluated in terms of the number of surgical tumor ruptures and of local tumor extent at pathologic examination, reflecting the effectiveness of the preoperative treatment. Survival and recurrence-free survival in the two treatment groups were also taken into account. The stage distribution was comparable in the two groups, with 52% stage I tumors in group R, and 43% in group C. Significant changes in the pathologic pattern were more frequent in group R than in group C (53% versus 17%). From these data it is concluded that preoperative chemotherapy is as good as preoperative radiotherapy in terms of prevention of tumor rupture. In addition, it was shown that 43% of an unselected population of patients with Wilms’ tumor could be treated without any radiotherapy when chemotherapy had been given preoperatively.

Results of the Sixth International Society of Pediatric Oncology Wilms’ Tumor Trial and Study: a risk-adapted therapeutic approach in Wilms’ tumor.
Tournade MF, Com-Nougue C, Voute PA et al.

PURPOSE: The Sixth International Society of Pediatric Oncology study (SIOP6) concerned Wilms' tumor with favorable histology, preoperatively treated to obtain a high rate of stage I patients, and sought to reduce treatment for patients with stage I and stage II negative nodes (IIN0) tumors and to find better therapy to prevent relapses in stage II positive nodes (IIN1) and stage III patients. PATIENTS AND METHODS: Eligible patients (N=509) had received four weekly doses of vincristine (VCR) and two courses of dactinomycin (AMD) preoperatively and were assigned after surgery, according to stage and lymph node involvement, to three different prognostic groups, which were to be randomized. Stage I patients (n=303) received VCR and AMD either for 17 weeks (S) or 38 weeks (L). Stage IIN0 patients (n=123) received either 20 Gy irradiation (R+) or no irradiation (R-) and received VCR and AMD for 38 weeks. Stage IIN1 and III patients (n=83) received intensified VCR and AMD (INTVCR) versus VCR, AMD, and Adriamycin (ADRIA; Doxorubicin Farmitalia Carbo Erba, Rueil, Malmaison, France; doxorubicin). Assessment criteria were 2-year disease-free survival (DFS) and 5-year survival (SURV) percentages. A stopping rule was added that took into account abdominal recurrences for the stage IIN0 trial. RESULT: A 52% rate of stage I tumors was obtained, with a low rate of ruptures (7%). The 2-year DFS and 5-year SURV rates according to the different therapeutic groups were stage I, 92% versus 88% (equivalent) and 95% versus 92% for S and L, respectively; stage IIN0, 72% versus 78% (stage equivalent) and 88% versus 85% for R+ and R-, respectively; and stage IIN1 and stage III, 49% versus 74% (P < .029) and 77% versus 80% for INTVCR and ADRIA, respectively, which results in an 82% DFS and 89% SURV rate for the entire trial population. However, six abdominal metastases observed during the first year of follow-up (FU) in the R- group versus none in the R+ group resulted in discontinuation of the stage IIN0 trial. CONCLUSION: Risk-adapted therapy to limit risk of sequelae is possible. More intensive chemotherapy is necessary to prevent abdominal recurrences in
nonirradiated stage IIN0 patients treated preoperatively. A three-drug protocol is necessary in stage IIN1 and stage III patients.

**Treatment of children with clear-cell sarcoma of the kidney: a report from the National Wilms’ Tumor Study Group.**
Green DM, Breslow NE, Beckwith JB et al.

PURPOSE: To evaluate the effect of the sequential addition of doxorubicin (DOX) and cyclophosphamide (CTX) to the combination of vincristine (VCR) and dactinomycin (AMD) on the relapse-free survival of children with clear-cell sarcoma of the kidney (CCSK). PATIENTS AND METHODS: We determined the 6-year relapse-free survival rate for patients with CCSK treated on National Wilms’ Tumor Study (NWTS)-1, NWTS-2, or NWTS-3 with the combination of VCR and AMD, with or without DOX, and for patients treated on NWTS-3 with the combination of VCR, AMD, and DOX with (regimen J) or without (regimen DD-RT) CTX. RESULTS: The 6-year relapse-free survival rate for the eight children with CCSK treated with VCR, AMD, and radiation therapy was 25.0%, compared with 63.5% for the 58 children treated with VCR, AMD, DOX, and radiation therapy (P=.09). The 6-year relapse-free survival rate for children with CCSK treated on regimen DD-RT was 64.6%, compared with 58.2% for those treated on regimen J (P=.79). CONCLUSION: We conclude that the addition of DOX to the combination of VCR plus AMD appeared to improve the 6-year relapse-free survival rate of children with CCSK. The addition of CTX in the dose and schedule used in NWTS-3 did not improve the 6-year relapse-free survival rate of children with CCSK. Because 30% of relapses occurred more than 2 years after diagnosis, prolonged follow-up evaluation of patients with CCSK is necessary.

Wilms tumor: the problem of diagnostic accuracy in children undergoing preoperative chemotherapy without histological tumor verification.
Zoeller G, Pekrun A, Lakomek M et al.

From 1989 to 1992, 9 consecutive children with a tentative diagnosis of Wilms tumor underwent therapy planned according to the International Society of Pediatric Oncology (SIOP)-9 Wilms tumor protocol, including preoperative chemotherapy. Because tumor biopsy is not recommended in this SIOP-9 protocol due to a possible tumor spread from open or needle biopsy, diagnostic accuracy is mandatory. We present our problems in diagnostic accuracy resulting in withdrawal of 2 children from preoperative chemotherapy, understaging the tumor in 2 and missing exact tumor histology due to complete tumor necrosis in 2. In addition, preoperative chemotherapy was applied in 1 child who later was found to have renal cell carcinoma. Although the SIOP-9 protocol of Wilms tumor treatment may be effective with regard to reducing the intensity of therapy, staging problems may be a major drawback in this therapeutic strategy based on preoperative chemotherapy.

Wilms’ tumor—model of a curable pediatric malignant solid tumor.
Green DM, Jaffe N

Wilms’ tumor is the model of the treatment of a pediatric solid tumor. Initially it appeared that multi-modality therapy, consisting of transabdominal nephrectomy, post-operative radiation therapy to the tumor bed and adjuvant, single agent
chemotherapy provided the highest likelihood of disease-free survival. The identification of important prognostic factors, such as histology, tumor weight, lymph node involvement and age at diagnosis has led to a re-examination of the treatment of Wilms’ tumor. Future therapeutic developments will include the administration of less therapy to some well defined groups of patients, and the exploration of new programs for patients who have been demonstrated to have a poor prognosis using currently accepted treatment techniques.

### Wilms’ Tumour - Radiotherapy

**A) TIMING OF POST-OPEATIVE RADIOThERAPY**

Abdominal relapses in irradiated second National Wilms’ Tumor Study patients.

**Thomas PR, Tefft M, Farewell VT et al.**


Ten of 259 (3.8%) irradiated patients with group 2 and 3 tumors in the second National Wilms’ Tumor Study experienced initial clinical relapse either in the operative site or elsewhere in the abdomen, excluding the liver and opposite kidney. Analysis of factors associated with abdominal recurrences has shown the independent significance of unfavorable histology, field size of the radiotherapy portals, and a postoperative delay of ten or more days before starting irradiation.

Influence of radiation therapy delay on abdominal tumor recurrence in patients with favorable histology Wilms’ tumor treated on NWTS-3 and NWTS-4: a report from the National Wilms’ Tumor Study Group.

**Kalapurakal JA, Li SM, Breslow NE et al.**


PURPOSE: This study was undertaken to determine whether radiation therapy (RT) delay of >or=10 days had an adverse impact on abdominal tumor recurrence among children with favorable histology (FH) Wilms’ tumor enrolled in National Wilms’ Tumor Study (NWTS) 3 and 4. METHODS AND MATERIALS: A total of 1226 patients with Stage II-IV FH tumors who received flank or abdominal RT in NWTS-3 and NWTS-4 were included in this analysis. Recurrent disease in the operative bed was classified as flank recurrence. Abdominal recurrence included all infradiaphragmatic tumor recurrences, including flank recurrences. This analysis included all flank/abdominal tumor recurrences, regardless of whether they might have been the initial or subsequent site of relapse. Based on the NWTS-1 results, RT delay was analyzed in two categories: 0-9 days and >or=10 days. RESULTS: The mean RT delay was 10.9 days; median delay was 9 days (range: 1-277 days). The RT delay was concentrated in a relatively narrow range of 8 to 12 days after nephrectomy in the majority of patients (59%). Univariate and multivariate analysis did not reveal RT delay of >or=10 days to significantly influence flank and abdominal tumor recurrence rates in NWTS-3 or NWTS-4. The 8-year flank tumor recurrence rates for 0-9 days and 10+ days RT delay were 1.9% and 1.2%, respectively (p value = 0.3). The 8-year abdominal tumor recurrence rates for 0-9 days and 10+ days RT delay were 4.8% and 5.3%, respectively (p value = 0.7). CONCLUSIONS: RT delay of >or=10 days did not significantly influence flank or abdominal tumor recurrence rates among children with FH tumors treated on NWTS-3 and NWTS-4. However, we were unable to test for a meaningful difference, because of the concentration of RT
delay close to 10 days.

B) RADIOTHERAPY TARGET VOLUME & DOSE:
Treatment of Wilms’ tumor. Results of the Third National Wilms’ Tumor Study.
D’Angio GJ, Breslow N, Beckwith JB et al.

The Third National Wilms’ Tumor Study sought to reduce treatment for low-risk patients and find better chemotherapy for those at high risk for relapse. Eligible patients (1439) were randomized according to stage (I-IV) and histology (favorable [FH] or unfavorable [UH]), and contributed data to survival and relapse-free survival (RFS) analyses. Four-year (postnephrectomy) survival percentages and randomized treatment regimens for low-risk patients were 96.5% for 607 Stage I/FH patients who received dactinomycin (Actinomycin D [AMD], Merck Sharp & Dohme, West Point, PA) and vincristine (VCR) for 10 weeks versus 6 months; 92.2% for 278 Stage II/FH patients; and 86.9% for 275 Stage III/FH patients who received AMD + VCR +/- Adriamycin (ADR, Adria Laboratories, Columbus, OH) for 15 months. Stage II/FH patients also had either zero or 2000 cGy irradiation (RT) postoperatively and Stage III/FH patients either 1000 or 2000 cGy. Four-year survival was 73.0% for 279 high-risk patients (any Stage IV, all UH) who received postoperative radiation therapy (RT) and AMD + VCR + ADR +/- cyclophosphamide (CPM). Statistical analysis of survival and RFS experience shows that the less intensive therapy does not worsen results for low-risk patients and CPM does not benefit those at high risk.

Wilms’ Tumor: Changing Role of Radiation Therapy.
Thomas PR.
Semin Radiat Oncol. 1997 Jul;7(3):204-211.

Wilms’ tumor is a highly curable neoplasm. Greater that 90% of all children with this disease can be expected to become long-term survivors. Although radiation therapy (RT) was once the mainstay of nonsurgical treatment, its use has been reduced both in indications and in dosage because of the chemoresponsiveness of the tumor. In the Third National Wilms’ Tumor Study (NWTS 3), patients with stage II tumors were shown not to require postoperative RT, and in patients with stage III tumors, 10 Gy was sufficient. In NWTS 5, patients with stage III favorable histology (FH), stage IV FH (with abdominal stage III), and stage II-IV anaplastic and all patients with clear cell sarcoma receive 10 Gy to the abdomen (usually given as 1.8 Gy x 6—total dose 10.8Gy). Results from the International Society of Paediatric Oncology, in which downstaged patients had a higher incidence of abdominal relapse, and the United Kingdom Children’s Cancer Study Group first Wilms’ Tumor Study, in which omission of whole-lung RT led to lowered survival in stage IV patients, suggest caution in further modifications of RT at this time.

Treatment of children with stages II to IV anaplastic Wilms’ tumor: a report from the National Wilms’ Tumor Study Group.
Green DM, Beckwith JB, Breslow NE et al.

PURPOSE: To evaluate the effect of the combination of vincristine, dactinomycin, and doxorubicin with (regimen J) or without (regimen DD-RT) cyclophosphamide on the relapse-free survival of children with stages II to IV Wilms’ tumor and focal or
diffuse anaplasia. PATIENTS AND METHODS: We reviewed the clinical courses of all randomized patients from National Wilms’ Tumor Study (NWTS)-3 and NWTS-4 with stages II to IV anaplastic Wilms’ tumor, and determined the 4-year relapse-free survival rate separately for those with focal or diffuse anaplasia. Anaplasia was evaluated using newly developed topographic definitions for focal and diffuse anaplasia. RESULTS: The 4-year relapse-free survival rate for five children with focal anaplasia who received regimen DD-RT was 80.0%, compared with 100.0% for eight children who received regimen J (P=.68). The 4-year relapse-free survival rate for 29 children with diffuse anaplasia treated with regimen DD-RT was 27.2%, compared with 54.8% for 30 children treated with regimen J (P=.02). CONCLUSION: We conclude that children with focal anaplasia have an excellent prognosis when treated with vincristine, doxorubicin, and dactinomycin. The addition of cyclophosphamide to the three-drug treatment regimen improved the 4-year relapse-free survival rate of children with stage II to IV diffuse anaplasia. This result suggests that further intensification of the treatment regimen for children with diffuse anaplasia may result in an additional improvement in prognosis.