Multidisciplinary Approach to Wilms’ Tumor: 
A Retrospective Analytical Study of 53 Patients

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ABSTRACT

Aim of the Work: The aim of this work was to assess the epidemiologic aspects, clinico-pathological features and the results of multidisciplinary treatment of Wilms’ tumor (WT) in pediatric patients treated at the National Cancer Institute (NCI), Cairo University, between January 2002 and December 2004.

Patients and Methods: This study included 53 patients, all under the age of 16 years, with previously untreated WT. Initial evaluation of all patients comprised laboratory investigations and radiological assessment which included chest X-ray and CT, abdomino-pelvic ultrasonography and CT. Doppler study of the renal vein and vena cava and bone scan were done when needed. Neoadjuvant chemotherapy was given to patients suffering from poor general condition, extensive tumor thrombus in the renal vein, irresectable and bilateral (stage V) nephroblastoma. Otherwise, up-front nephrectomy was the standard therapeutic approach in this study.

Results: The age of the patients ranged from 2 to 108 months with a mean of 39.9 months (±22.56). Males and females were almost equal in number (50.9% and 49.1% respectively). Tumors were located in the left kidney in 52.8%, right kidney in 41.5% and bilaterally in only 5.7% of the cases. An abdominal mass was the most common clinical presentation (77.4%). Favorable histology was found in 86.3% while unfavorable histology was elicited in 13.7% of the cases. Congenital anomalies were recorded in 4 patients. Stage I and III were the most common clinical presentation (77.4%). Favorable histology was found in 86.3% while unfavorable histology was elicited in 13.7% of the cases. Congenital anomalies were recorded in 4 patients. Stage I and III were the most common (29.4% each), followed by stage II and IV (17.7% each), and finally by stage V (5.9%). Neoadjuvant chemotherapy was given to 27 cases while up-front nephrectomy was undertaken in 26 cases. Intra-operative spillage occurred in 12% of patients who had preoperative chemotherapy and 31% of those who had up-front nephrectomy. Postoperative abdominal radiotherapy was given to 32 patients. Twenty five patients underwent renal bed irradiation only, while in the other 7 whole abdominal irradiation was used. Additional chest bath (1200 cGy) was given to 7 patients.

Complete remission (CR) was achieved in 74%, while death during neoadjuvant therapy took place in 4% of the cases. Disease progression during treatment was noticed in 8%. These patients were all treated with radio- and chemotherapy. Fatal outcome supervened in 75% of these, whereas in 25%, CR could be accomplished. Relapse after remission occurred in 14%. A 2nd CR could be achieved in 28.5% with a survival rate of 21.4%. Patients who relapsed >12 months after 1st CR had a 14 month-survival rate of 37.5% compared to 0% in those who relapsed <12 months after 1st CR. Disease-free survival (DFS) at 2 years was 82.4%, while overall survival (OAS) at 2 years was 78.9%. Therapy-related complications were mainly related to chemotherapy in 49% of patients and surgery in 5.9%.

Conclusion: Tight communication between the surgical, the medical and the radiation oncologists, together with the pathologist, is indispensable for better management of WT patients. Regional lymph node biopsy and accurate marking of residual disease are essential components of surgical treatment and heroic surgical attempts are unnecessary. Neoadjuvant chemotherapy, which is still a fertile source of debate, could possibly help to avoid excessive post-operative radiotherapy and its potential complications. Tumor stage and age of patient were found to affect the results of treatment of Wilms’ tumor; but the only statistically significant determinant of prognosis was histologic differentiation. Finally, further studies including molecular markers are needed to augment therapy for the blastemal predominance subtype or for favorable histology associated with loss of heterozygosity (LOH) at chromosomes 1p and 16q aiming at improved survival.

Key Words: Wilms’ tumor – Nephroblastoma.

INTRODUCTION

Nephroblastoma or Wilms’ tumor (WT) is an embryonal tumor arising from remnants of immature renal tissue. It accounts for 6% of all
pediatric tumors and typically affects children below the age of 6 years [1]. Initial survival rates in the early years of the 20th century were only 30%. Today, due to improvement in surgical techniques and the rapid development of active chemotherapeutic agents, long-term survival rates in both North American and European trials are approaching 85-90%. Moreover, new treatment protocols are now proceeding towards "risk-based management" based not only on stage and histology, but also incorporating genetic markers with the ultimate objective of maximizing cure together with minimal treatment-related toxicities [1,2].

The main prognostic indicators for WT are stage, histology, age and biological factors.

Stage: Two major staging systems have proven to be valuable in predicting outcome of treatment and are currently used: A pre–chemotherapy (up-front) surgery-based system developed by the National Wilms' Tumor Study Group (NWTSG) [3] and a post-chemotherapy-based system developed by the International Society of Pediatric Oncology (SIOP) [4].

Histology: Focal anaplasia portends an intermediate prognosis between that of tumors without anaplasia (also called "favorable" histologic feature) and that of tumors with diffuse anaplasia [5-7]. Clear-cell sarcoma (CCSK) and malignant rhabdoid tumor of the kidney are now considered as distinct tumor types [8]. Whereas the NWTSG classifies Wilms' tumors according to the presence or absence of anaplasia, the revised SIOP histologic classification divides Wilms' tumors into three risk groups: Low, intermediate and high risk groups [4,9].

Patient ages: Contrary to two previous group studies [10,11], other studies [12,13] have pointed out that the survival rate for adult patients is similar to that for pediatric WT, although toxicity of treatment is greater in the former group.

Biological prognostic factors: In the 1990s, several studies showed that children with loss of heterozygosity (LOH) at chromosomes 1p and 16q had greater risks of relapse and mortality; and future Children’s Oncology Group (COG) clinical studies will augment therapy for patients with favorable histology (FH) and LOH at 1p and 16q [14]. Other promising prognostic markers are an increase in gene copy number or expression at chromosome 1q [15] and telomerase expression level [16]. It is hoped that gene expression profiling will identify new prognostic factors in the future [17].

The role of chemotherapy according to the NWTSG and SIOP experience:

Today, the efficacy of actinomycin D (AMD), vincristine (VCR) and doxorubicin in treating WT is undisputed [18,19]. Several cooperative groups have made important contributions to the optimization of WT therapy, namely the National Wilm’s Tumor Study Group (NWTSG) in North America, the International Society of Pediatric Oncology (SIOP), the United Kingdom Children Cancer Study Group (UKCCSG) in Europe and others. The NWTSG and SIOP studies have included the largest number of patients and hence seem to be the most significant [2]. The NWTSG and its successor, the Children Oncology Group (COG), advocate up-front resection of the primary tumor. In contrast, SIOP recommends the administration of chemotherapy for 4 weeks before surgery. Both treatment approaches yield excellent clinical outcomes, yet a fertile debate continues about the relative merits of each approach [20].

The primary strength of the NWTSG approach is that up-front resection allows an accurate histologic diagnosis and assessment of tumor extent, while patients treated in SIOP nephroblastoma studies do not undergo tumor biopsy before starting therapy. In SIOP 93-01, approximately 5% of lesions treated with chemotherapy were ultimately shown not to be WT and 1.8% of these were benign [9]. Another benefit of removing the tumor before chemotherapy is that it enables the collection of untreated tumor tissue allowing an unadulterated analysis of the tumor’s molecular biology [2].

The primary strength of the SIOP approach is reduction of tumor volume, thereby "down-staging" the tumor and decreasing the likelihood of spillage [21]. As a result, fewer patients received local irradiation on SIOP-9 than on NWTS-5, although slightly more of the SIOP-9 patients received anthracycline [20]. A second advantage of preoperative chemotherapy is that response to treatment may provide a valuable prognostic indicator [22]. In the absence of a clear choice between up-front nephrectomy and
preoperative chemotherapy, it is reasonable to base the timing of resection on factors such as tumor size, the patient’s clinical condition, and the experience of the surgeon [2].

The role of surgery:

Most authors recommend a trans-abdominal, trans-peritoneal approach to permit meticulous exploration of sites of involvement and biopsy of suspicious lesions [23]. Gentle handling of the tumor and, in selected cases using preoperative chemotherapy, can greatly reduce the risk of intra-operative tumor rupture which occurs in 15 to 30% of cases. Tumor spillage increases the risk of local abdominal relapse by six folds resulting in subsequent poor outcome [24].

Shamberger et al. [24] emphasized the importance of lymph node sampling for pathologic confirmation of nodal involvement; since the rates of false positive and false negative lymph nodes, depending on clinical and radiological evaluation, were found to be 54% and 11%, respectively [25]. Analysis of NWTS-1,2,3 showed no significant reduction in survival rates with direct extension or contiguous involvement of the liver in comparison to other stage III presentations. Nevertheless, survival was affected with hematogenous intra-parenchymal liver spread [26].

Wilms’ tumor extends into the inferior vena cava in approximately 6% of cases. In these cases, cavotomy after proximal and distal vascular control can be used and if the thrombus is adherent it can be delivered by a Fogarty’s or a Foley’s catheter. With meticulous surgery, renal vein involvement does not adversely affect prognosis [27].

Surgical complications observed in the fourth National Wilms’ Tumor Study (NWTS-4) were bowel obstruction (5.1%), extensive hemorrhage and wound infection (1.9% each), extensive vascular injuries (1.4%), and injuries to other visceral organs (1%) [28]. Risk factors for surgical complications included intravascular extension into the inferior vena cava, the atrium, or both; a flank or paramedian approach; and a tumor diameter greater than 10cm. Interestingly, nephrectomy performed by a general surgeon carried a higher risk of complications (odds ratio: 9.0) than that performed by a pediatric surgeon (odds ratio: 1.0) or a pediatric urologist (odds ratio: 0.7) [2].

Kidney-sparing resection is not generally recommended and only 4.7% of patients are eligible for partial nephrectomy [29,30]. These include patients with a tumor involving one pole and less than one third of the kidney, if that kidney is functioning, if the collecting system and renal vein are both free of tumor involvement, and if clear margins can be obtained around the tumor [2].

Stage V, or bilateral Wilms’ tumor, is found in 4 to 8% of patients and the majority of these present by simultaneous involvement of both kidneys. Radical nephrectomy should never be performed at the initial surgical procedure. Rather, the initial procedure should aim at defining the extent of tumor in each kidney, obtaining bilateral biopsies for histological confirmation and taking biopsies from suspicious lymph nodes. Subsequently, the child should be treated with chemotherapy appropriate to the stage and histology of the tumor. Re-evaluation is performed at approximately week 5 to determine whether there has been sufficient response allowing partial resection with preservation of a substantial amount of renal tissue. A second look laparotomy is recommended when serial imaging studies show no further reduction in the tumor bulk. At the time of second look, partial nephrectomy should be considered, but only if complete tumor resection with negative margins is possible and part of either or both kidneys can be salvaged. When the extent of the tumor precludes salvage, radical nephrectomy is required [31].

The role of radiotherapy:

The NWTS-5 [32] has recommended the use of radiation therapy in specific indications according to tumor stage and histology. No irradiation is needed in FH with stage I-II or anaplastic tumors with stage I. On the other hand, postoperative radiotherapy should be given to all stages of clear cell sarcoma (CCSK) and rhabdoid tumors, to all but stage I anaplastic tumors, and to stage III-IV with FH. Irradiation is limited to the flank when the tumor involves only the renal hilar or the para-aortic nodes, or when residual disease is confined to the flank. Whole abdominal irradiation is needed in cases of intra-peritoneal tumor rupture, diffuse tumor spill or gross residual abdominal disease. A dose of 10.8Gy over 6 fractions is usually given.
Whole lung irradiation to 12Gy is also given to lung metastases and, when persistent, either a boost (to 19.5Gy) of radiation or surgical resection may be tried.

The SIOP-2001 [33] recommended flank irradiation for stage III with intermediate risk histology and stages II-III with high risk histology. Whole abdomen irradiation is indicated for all risk groups in cases of diffuse spillage or peritoneal metastases. Whole lung irradiation is given if lung metastases persist at week 9 after chemotherapy or surgery, or in cases of secondary metastases.

The timing of postoperative irradiation is important and the NWTS-5 recommends that it begins no later than the ninth postoperative day [32].

Aim of the work:

The aim of this work was to review the epidemiologic aspects, clinico-pathological features and clinical presentations of Wilms' tumor (WT) and to appraise the results and complications of different components of multidisciplinary treatment of this disease in pediatric patients treated at the National Cancer Institute (NCI), Cairo University, between January 2002 and December 2004. Timing and site of relapse together with salvage treatment and its final outcome were also assessed.

PATIENTS AND METHODS

This retrospective analytical study was carried out in the Departments of Pediatric Oncology, Surgery and Radiotherapy of the National Cancer Institute (NCI), Cairo University. Previously untreated pediatric patients with Wilms’ Tumor who presented to the NCI during the period from January 2002 to December 2004 were recruited and their number reached 53 patients. Eligibility criteria included: Age ≤16 years, pathologically or radiologically proven WT and no previous treatment by radio- or chemotherapy.

Initial evaluation of all patients consisted of complete history taking including family history of cancer, especially WT. Physical examination included weight and height, site and size of the tumor, blood pressure and congenital anomalies (like aniridia, genitourinary malformations or hemi-hypertrophy). Laboratory investigations comprised complete blood picture, liver and kidney function tests and urine analysis. Radiological assessment included chest X-ray and CT, abdomino-pelvic ultrasonography and CT (Fig. 1), Doppler study of the renal vein and vena cava when needed, bone scan in cases of clear cell sarcoma and brain CT in clear cell sarcoma and rhabdoid tumor of the kidney.

Treatment policy:

Surgery: When feasible, up-front nephrectomy was the standard therapeutic approach in this study. However, there were specific indications for pre-operative chemotherapy, namely poor general condition rendering the child unfit for surgery, extensive tumor thrombus in the renal vein extending to the supra-hepatic vena cava or right atrium, irresectable tumor at laparotomy and bilateral (stage V) nephroblastoma.

Laparotomy was carried out following the NWTSG V recommendations [28] through a transabdominal transperitoneal approach using a generous bucket-handle incision. To start, the contralateral kidney was exposed and palpated to exclude bilateral WT. Before mobilization of the primary tumor, an attempt was made to dissect, expose and ligate the renal vessels. The adrenal gland was removed with the tumor only if adherent, or if the tumor was in the upper pole. Radical en-bloc resection of contiguous structures (such as the colon, stomach, spleen or diaphragm) was only undertaken if the surgeon was sure that all gross disease would be removed. If residual tumor was to be left behind, only a biopsy was taken and the site identified with metal clips.

The peritoneum was considered soiled if an incisional or needle biopsy was taken or if the tumor was spilled or ruptured. The presence of hemorrhagic peritoneal fluid was also considered as major spillage regardless of microscopic identification of tumor cells in the fluid.

After tumor resection, routine sampling from the para-aortic, celiac and iliac nodes was carried out and involved or suspicious glands were excised and accurately labeled. All surgical specimens were immediately sent to the pathologist, fresh or in saline, rather than fixed in formalin (Fig. 2).
Chemotherapy: The day of nephrectomy was considered as day 0 for those who underwent up-front nephrectomy. Babies <12 months of age were given 1/2 the recommended dose based on body weight.

Stage I/FH or anaplastic histology and stage II/FH were given actinomycin D (AMD) and vincristine (VCR).

Stage III and IV/FH received AMD, VCR, doxorubicin and cardioxan in addition to radiotherapy, which was started not later than day 9 and in fractions of 180cGy.

Stage II-IV/anaplastic histology and stage I-IV clear cell sarcoma were treated with the same former combination in addition to cyclophosphamide (CTX) and mesna.

Stage I-IV rhabdoid tumor of the kidney, relapsing and resistant cases were treated with carboplatin and etoposide. This combination was given at w1+4 followed by cyclophosphamide and mesna.

Patients who were scheduled for preoperative chemotherapy received 6 weeks of weekly VCR together with AMD and doxorubicin. These patients were considered as stage III locally and radiological evaluation was carried out at w6 before referral to surgery.

Radiotherapy: Radiation was given in a dose of 180cGy/fraction. It was initiated only when the patient was stable postoperatively, with normal intestinal motility, absolute neutrophil count >1000/ul and hemoglobin level >10.0g/dl.

Stage I and II were not irradiated, while all stage III patients were given postoperative abdominal irradiation. Stage IV patients were also given postoperative abdominal irradiation if their primary tumor was stage III.

In case of residual flank disease, hilar nodes or para-aortic nodes, the field of radiation encompassed the tumor bed in the flank, crossing the midline to include bilateral aortic nodes. In cases with peritoneal seeding, gross residual abdominal disease or tumor rupture, radiation field encompassed the whole abdomen. Booster doses of 1080cGy were given to areas of gross residual disease =or >3cm.

The irradiation field was determined by the preoperative CT scan and was defined as the outline of the kidney and any associated tumor, plus a 1cm margin all around. Opposing anterior and posterior fields were used. When whole abdominal irradiation was needed, portals extended from the diaphragmatic domes down to the levels of the lower border of obturator foramina excluding the femoral heads.

Follow-up:

All, except three patients, were followed-up for a period ranging from 2 to 48 months with a median duration of 24 months. They were submitted to regular physical examinations; while chest X-ray or CT were undertaken every 6 weeks till complete remission then every 3 months for 2 years to be repeated every 6 months for 2 more years. Patients with nephrogenic rests were scheduled for abdominal U/S 6 weeks postoperatively, then every 3 months until the age of 8 years. Patients without nephrogenic rests were scheduled for abdominal U/S 6 weeks postoperatively, then every 3 months for 2 years to be repeated every 6 months for 2 more years. Those who presented with hematogenous metastases (liver, lung, brain or bone) required evaluation of the affected sites at intervals similar to those recommended for chest and abdomen cases.

Statistical analysis:

Data were analyzed using the SPSS statistical package version 12. Numerical data were expressed as mean ± standard deviation (SD), median, maximum and minimum. Qualitative data were expressed as frequency and percentage. The chi-square test was used to examine the relation between qualitative variables. Survival analysis was carried out using the Kaplan-Meier method and presented as cumulative survival rates. Comparison between two survival curves was done using the log-rank test. Probability (p-value) equal or less than 0.05 was considered significant, and if less than 0.001, highly significant. Disease-free-survival (DFS) was calculated only for patients who achieved complete remission (CR).

RESULTS

Patient characteristics:

This study included 53 patients, all under the age of 16 years with previously untreated WT. Their ages ranged from 2 to 108 months with a mean of 39.9 months (±22.56); and 71.7%
were <60 months. Males and females were almost equal in number (50.9% and 49.1%, respectively). Tumors were located in the left kidney in 52.8%, right kidney in 41.5% and bilaterally in only 5.7% of the cases. The most common clinical presentation, and by far, was an abdominal mass (77.4%). Abdominal pain and hematuria were encountered in 17% and 13.2% of the cases, respectively.

Favorable histology (FH) was found in 86.3% of the cases (75% of these had blastemal component and 25% were without), while unfavorable histology was elicited in 13.7% where anaplastic tumors and clear cell sarcoma each accounted for 5.9% and rhabdoid tumor for 1.9%. Congenital anomalies were found in 4 patients in this study. They were in the form of isolated hemi-hypertrophy, horse-shoe kidney, aniridia with cryptorchidism, and hydrocephalus with psychomotor delay and cryptorchidism, each of which was elicited in 1 patient (1.9%).

Patient management:

Neoadjuvant chemotherapy was given to 27 cases (51%), while up-front nephrectomy was undertaken in 26 cases (49%). Stage I and III were the most common (29.4% each) followed by stage II and IV (17.7% each) and finally by stage V (5.9%). Intra-operative spillage occurred in 11/51 patients (21.5%). Among those who had undergone upfront nephrectomy, 8/26 (31%) experienced spillage while only 3/25 (12%) did so among those who had preoperative chemotherapy (Table 1). Postoperative abdominal irradiation was given to 32 patients (60.4%), in 25/32 (78.1%) only to the renal bed while in 7/32 (21.9%) whole abdominal irradiation was used. Additional chest bath (1200cGy) was given to 7/32 (21.9%) patients.

Patient outcome:

Among the 53 patients in this study, 3 patients were non-evaluable as they were lost to follow-up after nephrectomy. Complete remission (CR) was achieved in 74%, while death during neoadjuvant therapy took place in 4% (2 patients). Disease progression during treatment was documented in 8% of the cases (4 patients). One occurred locally, one in the chest and two both locally and in the chest. They were all treated with postoperative radio- and chemotherapy. Disease progression ended with a fatal outcome in 3/4 patients, whereas CR could be achieved in only one patient.

Relapse after remission occurred in 14% of the cases (7 patients). One of them relapsed only locally, three developed hematogenous metastases (chest and/or bone), while the remaining three had both local and hematogenous metastases (chest and/or liver). Table (2) illustrates the time and type of relapse as well as the treatment given and final outcome. From this table it appears that 2/7 patients (28.5%) achieved a 2nd CR with a survival rate of 21.4%. It is also evident that the time of relapse bares some value since patients who relapsed at or >12 months after 1st CR (4/7) had a 14 month-survival rate of 37.5% compared to 0% in those who relapsed <12 months after 1st CR. Nevertheless, this was statistically insignificant ($p=0.113$) mostly due to the small number of patients.

Disease-free survival (DFS) at 2 years was 82.4% while overall survival (OAS) at 2 years was 78.9%. The effect of age, time of surgery, surgical stage, pathology, blastemal element (within the favorable histology) and time of postoperative radiotherapy on DFS and OAS is shown in Tables (3,4) respectively. It appears that blastemal predominance ($p=0.07$), age ($p=0.09$), timing of postoperative radiotherapy ($p=0.15$) and surgical stage ($p=0.28$) affected DFS, nevertheless their effect was found statistically insignificant (Figs. 3-6). On the other hand, blastemal predominance ($p=0.015$), surgical stage ($p=0.071$), neoadjuvant chemotherapy ($p=0.083$) and timing of postoperative radiotherapy ($p=0.312$) also appeared to affect OAS; nonetheless, blastemal differentiation was the only statistically significant factor (Figs. 7-10).

Therapy-related complications were mainly related to chemotherapy and surgery. Etoposide/carboplatin caused grade 4 myelosuppression in 15 cases. Vincristine neurotoxicity (ptosis, jaw pain, ileus) was recorded in 8 patients. Cyclophosphamide related hemorrhagic cystitis occurred in 2 patients. Hepatitis supervened in 7 patients. It was due to virus C infection in 6 patients and to actinomycin D toxicity in 1 patient. Surgical complications were confined to post-operative adhesive intestinal obstruction which occurred in 3 patients (5.9%).
Table (1): Surgical stage distribution and operative spillage (No = 51)*.

<table>
<thead>
<tr>
<th>Surgical stage</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>Total</th>
<th>Spillage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upfront nephrectomy:</td>
<td>%</td>
<td>No of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>53.3%</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>4</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>Neo-adjuvant chemotherapy:</td>
<td>%</td>
<td>No of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>46.7%</td>
<td>6</td>
<td>2</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

Total | 15 | 9 | 15 | 9 | 3 | 51* | 11 |

* Total number of patients are 51 as 2 patients died early during neo-adjuvant chemotherapy.

Table (2): Relapsed patients: Time and site of relapse, treatment and final outcome.

<table>
<thead>
<tr>
<th>Serial</th>
<th>Stage</th>
<th>Pathology</th>
<th>Management</th>
<th>Time of relapse in months (post-CR)</th>
<th>Site</th>
<th>Treatment of relapsed children</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td></td>
<td></td>
<td>2 year DFS</td>
<td>Cth</td>
<td>Surg</td>
<td>RT</td>
</tr>
<tr>
<td>1</td>
<td>V</td>
<td>FH</td>
<td>Cth</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>IV</td>
<td>FH</td>
<td>Cth + RT</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>III</td>
<td>FH</td>
<td>Cth + RT</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>III</td>
<td>UH</td>
<td>Cth + RT</td>
<td>12</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>III</td>
<td>FH</td>
<td>Cth + RT</td>
<td>14</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>7</td>
<td>I</td>
<td>FH</td>
<td>Cth</td>
<td>19</td>
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</tbody>
</table>


Table (3): Disease-free survival in relation to different variables.

| Variable | No* | 2 year DFS | p value | | | |
|----------|-----|------------|---------| | | |
| Age:     |     |            |         | | | |
| <60 months | 32  | 76.1%      | 0.094   | | | |
| ≥60 months | 12  | 100.0%     |          | | | |
| Time of surgery: |     |            |         | | | |
| Upfront nephrectomy | 22  | 84.4%      | 0.696   | | | |
| Post neo-adjuvant chemotherapy | 22  | 81.0%      |          | | | |
| Surgical stage: |     |            |         | | | |
| I | 12 | 90% | | | |
| II | 9 | 100% | | | |
| III | 13 | 72.2% | 0.284 | | |
| IV | 7 | 71.4% | | | |
| V | 3 | 66.7% | | | |
| Pathology: |     |            |         | | | |
| Favorable | 39 | 83.4% | 0.586 | | | |
| Unfavorable | 5 | 66.7% | | | | |
| Favorable histology: |     |            |         | | | |
| Without blastemal predominance | 30 | 89.1% | 0.077 | | | |
| With blastemal predominance | 9 | 66.7% | | | | |
| Time of post-operative RT: |     |            |         | | | |
| <19 days | 14 | 68.1% | 0.149 | | | |
| ≥19 days | 14 | 92.3% | | | | |

* Total No of patients is 44 because 6 patients were not evaluated for DFS. 2 of them died early during pre-operative chemotherapy and 4 patients showed disease progression.

Table (4): Overall survival in relation to different variables.

| Variable | No* | 2 year OAS | p value | | | |
|----------|-----|------------|---------| | | |
| Age:     |     |            |         | | | |
| <60 months | 36  | 78.5%      | 0.605   | | | |
| ≥60 months | 14  | 77.4%      |          | | | |
| Time of surgery: |     |            |         | | | |
| Upfront nephrectomy | 23  | 95.2%      | 0.083   | | | |
| Post neo-adjuvant chemotherapy | 27  | 66.5%      |          | | | |
| Surgical stage*: |     |            |         | | | |
| I | 12 | 100% | | | |
| II | 9 | 100% | | | |
| III | 15 | 61.2% | 0.071 | | |
| IV | 9 | 77.8% | | | |
| V | 3 | 100% | | | | |
| Pathology*: |     |            |         | | | |
| Favorable | 43 | 80.6% | 0.726 | | | |
| Unfavorable | 5 | 66.7% | | | | |
| Favorable histology: |     |            |         | | | |
| Without blastemal predominance | 32 | 90.5% | 0.015 | | | |
| With blastemal predominance | 11 | 27.3% | | | | |
| Time of post-operative RT: |     |            |         | | | |
| <19 days | 16 | 68.1% | 0.312 | | | |
| ≥19 days | 16 | 86.7% | | | | |

* Total No of patients are 48 as 2 patients died during pre-operative chemotherapy.
Multidisciplinary Approach to Wilms’ Tumor

Fig. (1): CT of a 4-year old child with left Wilms’ tumor involving middle and lower segments of the kidney.

Fig. (2): Surgical specimen of the previous case after nephrectomy.

Fig. (3): Disease free survival in relation to blastemal element within favorable histology ($p=0.077$).

Fig. (4): Disease free survival in relation to age groups ($p=0.094$).

Fig. (5): Disease-free survival in relation to time of post-operative RT ($p=0.149$).

Fig. (6): Disease-free survival in relation to surgical stage ($p=0.284$).
This work is a retrospective analysis of clinico-pathological features and treatment results of 53 previously untreated pediatric patients with Wilm's tumor who presented to the National Cancer Institute (NCI) during the period from January 2002 to December 2004.

Worldwide, Wilm's tumor is known to be the most common renal malignancy of childhood accounting for 6% of all pediatric tumors [1]. In Egypt, the frequency of WT in relation to other malignant cases referred to the NCI was 2.3% [34]. The M/F ratio in the present study was 1.0.96 showing the same slight male predominance that was reported by other Egyptian, Taiwani and Turkish studies [34-37]. In Europe and USA, a female predominance was reported where M/F ratio was: 0.92:1 rising to 0.6:1 in bilateral cases [38].

The median age at diagnosis in our study was 36 months, which is comparable to other Turkish and Egyptian studies [37,39]. Higher median ages were found in NWTS and SIOP studies which were 41.5 months for boys and 46.9 months for girls. Patients with bilateral
cases were younger, with a median of 29.5 months for boys and 32.6 for girls [40]. The younger median age in our study may be due to male predominance and the 3 bilateral cases that were not analyzed separately. Two age peaks, 36 and 60 months, were recorded in our study. This was reported by no other study.

In the present study, the left kidney was affected more frequently than the right, (52.8% and 41.5%, respectively). This was comparable to the findings of Yildiz et al. [37] but contrary to those of other Egyptian studies [39-41].

Abdominal swelling was the most common presenting symptom in our patients, accounting for 77.4% which is slightly lower than that reported by other Egyptian, Turkish and Italian studies [34,37,39,40,42] but slightly higher than that of the UKCCS2 held in Britain, which was 74% [43]. On the other hand, abdominal pain and gross hematuria were the presenting symptoms in 17% and 13.2% of the cases, respectively, which is comparable to other Egyptian and Italian studies [35,42].

In our series, congenital anomalies were found in 7.5% of cases. This is similar to the findings of Green [44] and the NWTS-3 [45] (4-8% and 7.35%, respectively). A higher incidence (17.3%) was reported by Hung et al. [36], while lower incidences (1.4% and 2.8%) were found by other Egyptian and Turkish studies [37,39].

In our study, stage I was found in only 29.4% and stage IV in 17.6%. Earlier stages were reported by the NEMROCK study [35] where stage I accounted for 35.5% and stage IV for only 6.5%. Similarly, less advanced stages were also reported by other Western and Asian studies. In the 2nd UKCCS [43], NWTS [26] and SIOP [13], stage I accounted for 34%, 47% and 61% respectively. In the Taiwanese [36], Turkish [37] and 3rd NWTS [45], stage IV accounted for only 6.8%, 9% and 10%, respectively. This may reflect lack of awareness among the mothers of our patients and their reluctance to seek expert medical advice.

Surgical spillage occurred in 21.5% of our patients, which is close to the 5th NWTS [46] that reported a rate of 19.3%. Spillage took place in 8/26 patients (31%) with upfront nephrectomy, whereas it occurred in only 3/25 patients (12%) with preoperative chemotherapy (Table 3). This reflects the influence of neoadjuvant chemotherapy in reducing spillage. Nevertheless, the difference was not statistically significant ($p=0.1$), probably due to the small number of cases. The final outcome was not affected probably because all cases experiencing spillage were given post-operative radiotherapy.

In the present study, 86.3% of the patients had favorable histology (FH), while 13.7% had unfavorable histology (UH). These findings are close to those of the 3rd NWTS (89% FH and 11% UH) [45], the 2nd UKCCS (90% FH and 10% UH) [48] and the Turkish study (88.2% FH and 11.8% UH) [37].

The percentage of our patients who received radiotherapy (renal bed and/or metastatic sites) was 62.7%, which is higher than that reported in other studies using neoadjuvant chemotherapy like the 9th SIOP study [47], where only 24% of the patients required irradiation. This large difference could be due to the late presentation of our patients. Also, patients who underwent upfront nephrectomy in our study showed a higher incidence of surgical spillage requiring post-operative radiotherapy while those who received neoadjuvant chemotherapy in this study were advanced and considered as stage III, so according to the NWTSG recommendations they were all candidates for post-operative radiotherapy.

The median time to postoperative radiotherapy in our study was 19.5 days compared to 9 days in both the 3rd and 4th NWTS. Both these studies found no difference in the rate of abdominal relapse among patients receiving radiotherapy 0-9 days postoperatively and those who were irradiated >10 days postoperatively [48]. In contrast, our patients showed better disease-free (DFS) and over-all survival (OAS) when they received radiotherapy >19.5 days postoperatively. DFS was 92.3% versus 68.1% and OAS was 86.7% versus 68.1%. These results were not statistically significant ($p>0.1$), probably due to the small number of patients in our study.

The relapse rate among our patients was 18.4% which lies between the rates of 17.9% and 24.2% reported by other Egyptian studies [35,39]. These are all higher than those demonstrated by the 4th NWTS and the 9th SIOP which were 11% and 10% respectively [44,49]. This
can be explained by the advanced stage at presentation in our patients.

The most frequent site of relapse in our series was the lung (85.5%) which is in accordance with Green[38] and the NEMROCK study[39]. The latter reported distant metastases in >60% of their relapsed cases, where 70% of these were in the lungs[38]. In contrast, two other Egyptian studies described the abdomen as the most frequent site of relapse[39,40]. This finding reflects improved local control in our series due to more vigilant surgery and improved radiotherapy techniques.

The rate of 2nd complete remission (CR) in our study was 28.6% which is higher than in the NEMROCK study[38] which reported a 2nd CR in only 6.6% of the cases. This reflects more efficient follow-up and salvage chemotherapy in our patients. Nevertheless, the survival rate of these patients was lower than that of the St. Jude Children’s Research hospital[50] (21.4% versus 50%-60%). In our study, the 1-year post-relapse survival for those who relapsed >12 months post 1st CR was 37.5% with a cure rate of 50%. This compares favorably with the figures reported by the 2nd and 3rd NWTS where the 3-year post relapse survival for patients who relapsed >12 months post-diagnosis was 41% with a cure rate of 60%[51].

Surgical complications were confined to adhesive intestinal obstruction which occurred in 5.9% of cases. This is comparable to the figure reported by Ritchey et al., in the NWTS[28] which was 5.1% and close to that reported in the large German study by Seseke et al.[52] which was 8.8%. When compared to the 19.8% rate of overall operative complications of the NWTS-3[28], our results are slightly better probably due to aversion of heroic resections involving adjacent organs.

Tumor stage was found to affect survival, confirming findings of previous Egyptian and western studies. Nevertheless, we did not find it statistically significant (p=0.284 and 0.071 for DFS and OAS, respectively). According to stage distribution, our 2-year DFS rates were 90%, 100%, 72.2%, 71.4% and 66.7%; while our 2-year OAS rates were 100%, 100%, 61.2%, 77.8% and 100% for stages I to V, respectively. Similar findings were reported by other Egyptian studies, yet survival figures were higher in our study. Ahmed et al.[39] reported a 3-year DFS of 90%, 76%, 67%, 31% and 62% and their 3-year OAS were 93%, 88%, 72%, 40% and 62% for stages I to V, respectively. This improvement in survival, mainly in stages II, III and IV, is probably due to improvement in diagnosis of stage IV patients by using chest CT at initial evaluation thus giving chest irradiation accordingly, to the judicious application of combined treatment modalities (surgery, radiotherapy and chemotherapy) and to the proper supportive care delivered to the patients.

Nevertheless, our survival figures were barely comparable to some, or even lower than, other large western studies. The 2-year DFS of the 9th SIOP study for stages I to III with favorable histology were 88%, 85% and 71% respectively[49]. Similar results were described by the UKW-2 and UKW-3 where the 4-year DFS were 86.5%, 82%, 82%, 70% and 70% for stages I to V respectively[43]. Yet, our 2-year DFS rates are still lower than those of the 4th NWTS mainly for stages III and IV and which were reported to be 90.6% at 2 years and 88.9% at 8 years[53] indicating better local and metastatic control in their patients.

Similarly, our OAS was comparable to other western studies except for stage III which showed lower rates among our patients (61.2%) compared to other studies reporting OAS for stage III to be 85% at 2 years[49], 84% at 4 years[43] and 93% at 8 years[53] reflecting better salvage strategy and outcome in their patients.

Histological differentiation was also found to affect survival, confirming findings of previous Egyptian and western studies. Nevertheless, we did not find it statistically significant (p=0.586 and 0.726 for DFS and OAS, respectively). To illustrate this finding, our 2-year DFS and OAS for favorable histology (FH) were 83.4% and 80.6% respectively compared to 66.7% and 66.7% for unfavorable histology (UH). A previous Egyptian study by Ahmed et al.[39] similarly reported 3-year DFS and OAS for favorable histology (FH) to be 78% and 87% respectively compared to 54% and 58% for unfavorable histology (UH). Except for the OAS of cases with FH, our survival figures are higher than those of this previous Egyptian study as we tailored our chemotherapy regimens in accordance with different tumor pathologies.
Our 2-year DFS for FH (83.4%) is similar to some western studies as the UKW-2 [43] and the SIOP-9 [49] which reported 83% and 85%, respectively.

On the other hand, our 2-year OAS for FH was 80.6% which is lower than the figures reported by many other Egyptian and western studies and which were 87% at 3 years [39], 91% at 2 years [43], and 90% at 5 years [49] reflecting their better salvage outcome.

Within the FH group, our 2-year DFS for patients with blastemal predominance was 66.7% and for those without blastemal predominance, it was 89.1%. The same difference was reported by Ahmed et al. [39]. The SIOP 93-01, reported 5-year DFS for blastemal predominance (after preoperative chemotherapy) to be 79% and for those without blastemal predominance, it was 90% [49]. Our figures in patients without blastemal predominance are comparable to those reported by the SIOP 93-01 while those obtained with blastemal predominance are lower. This is mostly due to the fact that they up-graded the latter group considering it as high risk group that was given different chemotherapeutic agents.

**Conclusion:**

Histologic differentiation, age of patient and tumor stage were found to be the most important determinants of prognosis of Wilm’s tumor in our study and they deserve priority in designing future therapeutic requirements. Therefore, good communication between the surgical, medical and radiation oncologists, together with the pathologist, is indispensable for better management of the patients. Moreover, biopsy from regional lymph nodes and accurate marking of residual disease, if present, in addition to a detailed surgical report with particular attention to correct tumor stage and pathology are essential for adequate patient treatment.

The value of the SIOP strategy advocating neoadjuvant therapy before tumor resection remains a fertile source of debate. The lower rate of surgical complications and intraoperative spillage so obtained remains to be weighed against the risk of administering chemotherapy to benign cases, that of modifying tumor histology and missing accurate pre-treatment determination of stage or histology.

In spite of achieving comparable survival rates in our study when compared to others adopting the NWTS strategy, the SIOP policy could possibly be more appropriate to our patients, aiming to reduce the use of post-operative radiotherapy and its potential complications. In the near future, a prospective randomized study is needed to evaluate whether avoiding postoperative radiotherapy, by down-staging the tumor with pre-operative chemotherapy, will influence our local control rates or not.

The timing of postoperative radiotherapy could influence outcome since better disease-free (DFS) and overall survival (OAS) were achieved in our patients when they received radiotherapy >19.5 days postoperatively compared to <19 days. This issue requires more detailed study.

Also, further studies are needed to augment therapy for the blastemal predominance subtype aiming at improved survival, especially for those with persistent viable blastemal element after neoadjuvant chemotherapy.

Molecular markers are also needed to confirm findings concerning higher risk of relapse and death among patients with favorable histology associated with loss of heterozygosity (LOA) at chromosomes 1p and 16q. The aim is to augment therapy for these patients in the future.

**REFERENCES**


Multidisciplinary Approach to Wilms' Tumor


