Combined Modality Therapy of Pediatric Wilms' Tumor in Upper Egypt: A Retrospective Study


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Abstract
Background: We conducted a retrospective analysis to investigate the clinical outcome of combined modality therapy using multiagent chemotherapy, nephrectomy, and radiotherapy in treatment of children with Wilms' tumor.

Methods: This study was conducted on 91 cases of newly diagnosed Wilms' tumor from January 2001 until February 2012. Patients were categorized into two groups according to treatment approach: i) preoperative chemotherapy with delayed surgery (group A; n=66) and ii) immediate surgery (group B; n=25).

Results: Preoperative chemotherapy showed a 54.5% partial response rate in group A patients. A final stage distribution indicated that the majority of patients (64%) from both groups were considered to be in the early disease stages (I and II). The median follow up was 49 months (range 3-124). The five-year overall survival rate was 66.5%, whereas the event-free survival rate was 62.5%. In univariate analysis, factors associated with statistically significant reduction in overall ($P<0.0001$) and event-free survival ($P=0.0001$) rates included advanced disease stages ($P<0.0001$ for both) and blastimal subtype ($P=0.0067$ for overall survival; $P=0.012$ for event-free survival). Age of >24 months was associated with a significant reduction in the overall survival rate ($P=0.038$, HR: 0.438, 95% CI: 0.192-0.953), but was not significant in terms of event-free survival ($P=0.104$, HR: 0.539, 95% CI: 0.256-1.136). Age >24 months ($P=0.0095$), disease stage ($P=0.0014$), and blastimal subtype ($P=0.006$) were associated with significant increases in relapse rate.

Conclusion: Preoperative chemotherapy resulted in a final stage redistribution that placed the majority of patients in the early stages of the disease. Age at diagnosis, disease stage, and histological subtype significantly affected survival and relapse rates.

Keywords: Nephroblastoma, Chemotherapy and radiotherapy, Survival

Introduction
Most children affected with Wilms’ tumor (WT) can be cured. Treatment for WT has improved in the past two decades with the aid of multimodal therapy protocols.¹
Currently, the goal is to improve outcomes by identifying children at risk and assist them with more appropriate treatment. However, this may not be the case in developing countries where social as well as regional factors contribute to the outcome of the disease.²

Several multicenter trials and studies have been conducted by the International Society of Pediatric Oncology (SIOP) in Europe³,⁴ and the National Wilms’ Tumor Study (NWTS) in the United States.⁵,⁶ Both have contributed to the definition for current treatment of this tumor, which is a multidisciplinary approach of surgery and multidrug therapy associated, only when necessary, with radiotherapy (RT). Treatments are given according to well-defined risk groups with the intent to decrease the frequency and intensity of complications as well as the cost of therapy.⁷

The aim of this study is to assess the effect of combined treatment modalities on patient survival and relapse rates, and to define prognostic factors that may affect overall survival (OAS) and event-free survival (EFS) rates.

**Patients and Methods**

This retrospective study analyzed the medical records of patients with WT (n=91) who were seen at the Pediatric Oncology and Radiation Therapy Departments, South Egypt Cancer Institute (SECI), Assiut University during the period from January 2001 to January 2012. Informed consent was obtained from all patients and the Institutional Review Board at our center approved the study protocol.

Chart reviews included details of clinical presentation, clinical stage at presentation versus postoperative stage, operative and pathologic findings, treatment and outcome. We excluded patients with bilateral tumors (stage V) and anaplastic histology.

Patients were categorized into two groups according to their treatment. The majority of patients (n=66) were treated with preoperative chemotherapy and a delayed surgery approach according to the SIOP 9 protocol⁷,⁸ (group A). Others (n=25) were treated with immediate surgery according to National Wilms Tumor Study NWTS protocol (group B).

In group A, patients were initially staged radiologically according to NWTS V as follows: i) intrarenal disease (stage I); ii) local extrarenal extension amenable to complete local excision (stage II); iii) advanced local disease (stage III); and iv) distant metastasis (stage IV).⁹ Patients with stages I and II disease received a preoperative chemotherapy regimen of dactinomycin and vincristine for 4 weeks; those with stages III and IV, were treated for 6 weeks with additional adriamycin. One week after completion of chemotherapy we evaluated patients for clinical tumor response to preoperative chemotherapy and the possibility for resection. Operable patients underwent radical nephrectomies. Postoperative chemotherapy began one week after surgery according to SIOP 9 recommendations, taking into consideration stage and histology at the time of surgery.⁷

Treatment for stage IV patients depended on their clinical response to preoperative therapy.

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**Figure 1.** Overall survival (OAS) according to age.

**Figure 2.** Event free survival (EFS) according to age.
Patients with stage I disease had a regimen of two drugs (dactinomycin, vincristine) for 18 weeks. Patients with stage II and standard histology had a regimen of additional adriamycin. In cases with stage II disease and spillage during surgery (n=2) and/or in stage III (n=23), this therapy was supplemented with abdominal radiation. Patients with disease confined to the operative site were given only flank irradiation, with treatment portals that encompassed the tumor bed of the excised kidney and 2 cm margin. Patients with gross diffuse residual disease, diffuse peritoneal implants, and diffuse abdominal operative spillage received whole abdominal irradiation. The radiation dose was 10.8 Gy/6 fractions to the flank (or whole abdomen) plus a 10 Gy/5 fractions boost to gross residual disease (>3 cm) following surgery. Stage IV patients whose metastases had not adequately responded to treatment received a more intensified regimen that included ifosfamide. In cases of pulmonary residual disease, the whole lung was irradiated with 12 Gy/8 fractions at a dose of 150 cGy per fraction.

After determining surgical stage and histology, group B patients received postoperative chemotherapy according to NWTS V, which was administered one week after the initial nephrectomy. Patients in both groups had monthly followed up visits for the first year, every three months for the next two years, every six months for another two years, and annually thereafter. At each visit, patients underwent physical examinations and laboratory screening that included urine analysis and renal function tests.

CT scans of the abdomen and chest (if indicated) were performed every three months during the first year, then annually.

**Statistical analysis**

The study cutoff point was February, 2012. Event-free survival was defined as the interval from patient enrollment to the date of the first event (relapse, progression, or death from any cause).
cause) or to the date of the last follow-up. Overall survival was defined as the interval from enrollment to the date of death from any cause or to last follow-up. Event-free and OAS rates were estimated using the GraphPad prism program. The log-rank test was used to examine differences in EFS and OAS rates.

Results

Patients’ characteristics

The median age at the time of study enrollment was 24 months (range: 5-120). There were 52 (57%) male patients and 39 (43%) females, with a male to female ratio of 1.3:1. Disease stage distribution was as follows: stage I (48%, n=44), stage II (15%, n=14), stage III (25%, n=23), and stage IV (11%, n=10). The most common histology was mixed subtype (42 patients; 46%), followed by blastimal subtype (22 patients; 24%). The majority of patients were treated by preoperative chemotherapy (group A) according to the SIOP 9 protocol (66 patients; 72.5%) whereas 25 patients were treated with immediate surgery (group B). There were 25 (27.7%) patients who received postoperative RT (Table 1). The median follow-up from the date of enrollment was 49 months and ranged from 3 to 124 months.

Response to treatment and outcome

In group A (n=66), 4 stage IV disease patients died during chemotherapy administration due to septicemia (n=1) and disease progression (n=3). After preoperative chemotherapy, partial response (PR) was achieved in 36 (54.5%) patients, as

<table>
<thead>
<tr>
<th>Patients’ characteristics</th>
<th>No. (%)</th>
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<tr>
<td>Initial stage distribution (before preoperative chemotherapy; n=66)</td>
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<tr>
<td>I</td>
<td>10 (15.2%)</td>
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<td>II</td>
<td>14 (21.2%)</td>
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<td>III</td>
<td>35 (53%)</td>
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<td>IV</td>
<td>7 (10.6%)</td>
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<td>Final stage distribution (after preoperative chemotherapy; n=66)</td>
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<tr>
<td>I</td>
<td>36 (54.5%)</td>
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<tr>
<td>II</td>
<td>11 (16.7%)</td>
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<tr>
<td>III</td>
<td>12 (18.2%)</td>
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<tr>
<td>IV</td>
<td>7 (10.6%)</td>
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<td>Stage distribution in immediate surgery group (n=25)</td>
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<tr>
<td>I</td>
<td>8 (32%)</td>
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<tr>
<td>II</td>
<td>3 (12%)</td>
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<tr>
<td>III</td>
<td>11 (44%)</td>
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<tr>
<td>IV</td>
<td>3 (12%)</td>
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Figure 5. Overall survival (OAS) according to history.
Figure 6. Event free survival (EFS) according to history.
follows: stage I (n=10), stage II (3 out of 14), and stage III (23 out of 35). There were 26 (39.4%) patients with stable disease, as follows: stage II (n=11), stage III (n=12), and stage IV (n=3). In group B 25 patients underwent radical nephrectomies with stage I was found in 8 patients (n=8), stage II (n=3), stage III (n=11), and stage IV (n=3). The final stage distributions in patients treated with preoperative chemotherapy and those treated with immediate surgery are shown in Table 2. Radical nephrectomy was performed in 84 (92.3%) cases, of which 59 cases were performed after preoperative chemotherapy (with the exclusion of stage IV patients) and 25 from the immediate surgery group. Postoperative RT (n=25) was given to 2 patients with stage II disease who showed spillage during surgery and 23 patients with stage III disease (12 patients after preoperative chemotherapy, and 11 in the immediate surgery group).

**Relapse data**

There were 27 out of 87 (31%) patients who relapsed. Local recurrence was reported in 16 cases after a median follow up of 12 months and distant metastases in 11 after a median follow up of 5.5 months. Sites of distant metastases included the lungs (n=7), liver (n=3), and brain (n=1). These patients were treated with second line (salvage) chemotherapy, surgery and RT. Factors associated with a significantly higher relapse rate were: patients with age of >24 months (42%) compared to those ≤24 months (<24 months, P=0.0095); blastimal subtype (62%) compared to stromal (25%), epithelial (21%), and mixed (20%) subtypes (P=0.006); and advanced disease stage, stage IV (100%), stage III (35%), stage II (21%), and stage I (23%; P=0.0014). Other factors (gender, treatment protocol, and RT administration) did not affect relapse rate (Table 3).

**Survival analysis**

With a median follow up of 49 months (range: 3-124), the five-year rate for EFS was 65.3% and for OAS it was 69.2%. Patients ≤24 months of age had five-year EFS of 73.4% and OAS of 79.5%
compared to 56.5% ($P=0.104$, HR: 0.539, 95% CI: 0.256-1.136) for EFS and 58.2% ($P=0.038$, HR: 0.428, 95% CI: 0.192-0.953) for OAS in patients >24 months. Males had a five-year EFS of 58% and OAS of 68% compared to 68% ($P=0.42$, HR: 1.35, 95% CI: 0.65-2.77) EFS and 68% ($P=0.97$, HR: 1.01, 95% CI: 0.47-2.19) OAS for female patients. Those in group A had a five-year EFS rate of 67% and OAS rate of 69% compared to 61% EFS ($P=0.86$, HR: 1.06, 95% CI: 0.444-2.544) and 68% OAS ($P=0.89$, HR: 1.01, 95% CI: 0.47-2.19) for group B patients. The five-year EFS rates according to disease stage were stage I (77%), stage II (69%), stage III (62%), and stage IV (20%; $P=0.0001$). Five-year OAS rates were stage I (78%), stage II (75%), stage III (76%), and stage IV (20%; $P<0.0001$).

Histologically, five-year EFS according to subtypes was stromal (83%), epithelial (71%), mixed (76%), and blastimal (36%; $P=0.0039$), whereas OAS rates were 83% (stromal), 71% (epithelial), 83% (mixed), and 38% (blastimal; $P=0.0018$).

Those who underwent postoperative RT had five-year EFS rate of 66% and an OAS rate of 78% compared to a five-year EFS of 65% ($P=0.82$, HR: 0.91, 95% CI: 0.416-2.002) and OAS of 67% ($P=0.57$, HR: 0.78, 95% CI: 0.327-1.857; Table 4, Figures 1-6).

**Acute toxicity and late effects**

Significant preoperative chemotherapy-related hematological toxicities were reported in 9 out of 66 (13.6%) patients. Observed toxicities were grade II anemia (n=3) and grade III neutropenia (n=6). Postoperative complications were reported in 6 (6.6%) cases as delayed wound healing that resulted in postponement of postoperative treatment for two weeks. After exclusion of 4 patients who died due to septicemia during preoperative chemotherapy, chemotherapy-related toxicities were reported in 7 out of 87 (8%) patients.

**Discussion**

The present retrospective study analyzed patients with unilateral WT treated with a preoperative chemotherapy with delayed surgery and a group who underwent immediate surgery. The difference between groups was in stage distribution, where the incidences of lower stages (stages I and II) were 71% and 44%, respectively...
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The median age at diagnosis was 2 years (range: 5 months-10 years), which was comparable with the median age of 2.51-2.9 years in two European trials.12,13 The male to female ratio of 1.3:1 matched reports from studies conducted in developing countries, where the male to female ratio ranged from 1.1:1 to 1.6:1.14,15

In this study stage I comprised 48.3% of cases, stage II (15.4%), stage III (25.3%), and stage IV (11%). Similarly, Hung et al.,16 conducted a similar study where stage I constituted 43.2% of the cases, stage II (19.3%), stage III (23.9%), stage IV (6.8%), and stage V (6.8%) of cases.

In most studies from developed countries stage I disease was the most common stage12,13, however our study revealed that most of our cases in group A (42; 63.6%) presented with stages III and IV disease at initial presentation and 56% (14 out of 25 patients) in group B presented with stages III and IV disease. This difference might be a reflection of problems in developing countries, including Egypt with fundamental issues such as late presentation, poverty, ignorance, and poor compliance to treatment.14

In group A patients, preoperative chemotherapy resulted in a PR in 36 (54.5%) patients. Ritchey et al.,17 have shown PRs in 110 (85%) patients. The higher PR rate in the reported study compared with the current study might be due to the use of concurrent preoperative RT and chemotherapy for some patients or because of the lack of response in others. Therefore, down-staging by preoperative chemotherapy in the present study (group A patients) resulted in a final stage distribution with the majority of patients in both groups placed in early stages I and II (58; 64%). This was comparable to reported studies where the incidence of early stages following preoperative chemotherapy ranged from 63% to 79%.15,16

In the present study, the majority of patients presented with mixed histological subtype (46%), followed by blastimal subtype (24%). This agreed with Weirich et al.12 where the most common histology was mixed subtype (108 out of 329 patients, 33%), followed by blastimal subtype (52 out of 329 patients, 16%).

Radiation therapy could be omitted in patients with stage I and II disease and favorable histology (FH) disease, with excellent results.5,18 On the other hand, it should be given to stage III patients with a dose of 10 Gy to the flank6,19,20 and has been reported to reduce recurrence in 0%-4% of children with FH.21 Radiation therapy was indicated in only 21% of patients in SIOP 9.7 In our study, adjuvant RT was given to 25 (27.5%) patients, of which 23 had stage III disease and 2 had stage II disease with spillage during surgery.

In the present study, the relapse rate was 31% (27 out of 87 patients), which was significantly higher in patients >24 months of age when compared with younger patients (P=0.0095), in blastimal subtype compared with other subtypes (P=0.006), and in stage IV patients compared to patients with stages I–III diseases (P=0.0014).

In an Iranian study, relapse occurred in 25.4% of patients.20 Relapse was reported to be significantly affected by histological subtype and disease stage.22 It was reported that patients with the blastimal subtype were most likely to relapse, irrespective of stage.12 Cooperative group studies have shown that increasing patient age is associated with increased risk of recurrence in nonmetastatic WT.23,24

In the present study, with a median follow up of 49 months, five-year OAS rates were 69% for the entire group and 78% for those given postoperative radiation. This was comparable with a four-year OAS of 70% in an Egyptian study.15 In an Iranian study, there was a five-year OAS rate of 76% for the whole group and 82% for those who had adjuvant RT.20

Histologic features and disease stage have been traditionally regarded as the most important prognostic criteria.25 Age at diagnosis26 has been included to define different risk groups that have been used to stratify patients for modern therapeutic protocols. The present study showed that disease stage and histological subtype significantly affected both OAS and EFS rates. Patient age at diagnosis was found to affect OAS...
rate.

In an analysis of more than 2000 favorable WT, it has shown that the stromal predominant and the epithelial predominant were less aggressive with an excellent follow-up, as most cases with these patterns were stage I disease. This feature accounts for the high cure rate associated with this pattern prior to the advent of effective adjuvant therapy. The present study showed that the five-year EFS rates ranged from 71% to 83% in patients with epithelial, mixed, and stromal subtypes compared to 36% in those with the blastimal subtype \((P=0.0039)\). Five-year OAS rates were significantly lower \((P=0.0018)\) in patients with the blastimal subtype (38%) compared to the other subtypes (71%-83%). The favorable outcome for patients with epithelial and stromal subtypes WT in our series confirmed previous reports that have shown favorable prognosis, particularly among the lower stages.12,27

In the present study, stage significantly affected EFS \((P=0.0001)\) and OAS \((P<0.0001)\) rates. The impact of disease stage on OAS rate was confirmed by Abd el-Aal et al.,15 Faranoush et al.,20 Piannezza et al.,28 and Venugopal et al.29 In contrast, the NWTS group denied any significant impact of tumor stage on OAS.30 The impact of disease stage on EFS rate was confirmed by Abd el-Aal et al.15 where the four-year DFS was 73.4% for stages I and II, whereas it was 19.3% for stages III, IV, and V, respectively which was statistically significant. In addition, Zaghloul et al.30 and Hung et al.31 stated that histopathology and stage significantly affected DFS.

The present study showed that patient age at diagnosis significantly affected the OAS rate \((P=0.038)\). This was confirmed by Pritchard-Jones et al.24 and Green et al.32 who observed a high correlation with better outcome in patients who were less than 2 years of age when diagnosed.

The present trial studied both SIOP (group A) and NWTS (group B) protocols. Both protocols resulted in comparable results with regard to OAS (HR: 1.06, 95% CI: 0.444 - 2.544, \(P=0.89\)) or EFS (HR: 0.932, 95% CI: 0.415-2.09, \(P=0.86\)) rates. In the literature, large numbers of patients have been studied in several trials for both NWTS and SIOP. It has been reported that, although both treatment approaches have different philosophies on preoperative chemotherapy, they yield almost equivalent clinical outcomes. However a valid debate continues about the relative merits of each approach.33,34

**Conclusion**

Preoperative chemotherapy resulted in stage redistribution with final early stage predominance. Age at diagnosis, disease stage, and histological subtype significantly affected survival and relapse rates. Both treatment approaches had comparable clinical outcomes.

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**Authors’ contributions**

HAS participated in patient diagnosis, management, patient follow up, and manuscript writing.

MMS participated in radiation therapy given to patients, patient follow up, and manuscript writing.

MIE participated in radiation therapy given to patients, patient follow up, statistical analysis, manuscript drafting and writing the final manuscript.

All authors read and approved the final manuscript.

**References**


28. Pianezza ML, Rubin S, Bass J, Chou S, Pike JG,


