

## Wilms' Tumor: The Experience of the Pediatric Unit of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK)

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### ABSTRACT

**Aim of the Work:** The aim of the present work is to study the treatment results of Wilms' tumor patients who had attended the pediatric unit of Kasr El-Aini center of radiation oncology and nuclear medicine (NEMROCK) from January 1994 to January 2001.

**Patients and Methods:** Sixty-two new Wilms' tumor patients attended the clinic (NEMROCK) from January 1994 until January 2001. The diagnosis was confirmed pathologically. Stage I included 22 cases, stage II 17 cases, stage III 16 cases, and stage IV included 4 cases, whereas stage V included only 3 cases.

Stage I cases received 6 months of vincristine and dactinomycin. Stage II with favorable histology (FH) received 1 year of vincristine and dactinomycin. Stage III and IV received 1 year of vincristine, dactinomycin and doxorubicin. Abdominal radiation therapy, 1080cGY, was given in case of tumor spillage during surgery either to the involved flank or the whole abdomen depending on whether contamination was limited to the flank only or the whole abdomen. In addition, radiation was given to metastatic sites in stage IV. Stages II, III, IV with unfavorable histology (UH) received 1 year of dactinomycin, vincristine, doxorubicin and cyclophosphamide in addition to radiation therapy. Stage V cases were diagnosed by surgical biopsy and were managed according to stage and pathology.

**Results:** Forty patients (64.5%) had favorable histology while twenty-two patients (35.5%) had unfavorable histology. The 4-year overall survival rate was 70.1%. Stage I, II, and stages III+IV+V with favorable histology had a 4-year overall survival of 82.3%, 56% and 41%, respectively. Stages I to IV with unfavorable histology had a 4-year survival of 65.7%.

**Conclusion:** Multivariate analysis revealed that stage and residual disease after surgery significantly affected overall survival; while histopathology and stage affected significantly disease-free survival. Moreover, our study revealed that residual disease after surgery affected sig-

nificantly the incidence of local recurrence and distant metastases.

**Key Words:** Wilms' tumor - Favorable histology - Unfavorable histology.

### INTRODUCTION

Wilms' tumor is the most common malignant renal tumor in children. Its incidence is 8.1 cases per million in Caucasian children less than 15 years of age each year in North America [1]. In 1996, the total incidence was estimated at 470 cases per year in the States [1,2]. The incidence rate is approximately three times higher for blacks in the United States and Africa than for East Asians, with rates for Caucasian populations in Europe and North America intermediate between these extremes [3].

The multidisciplinary management of Wilms' tumor has resulted in a striking improvement in survival from 30% in the 1930s to more than 85% nowadays and has become a paradigm for successful cancer therapy. Currently, the primary objective of clinical trials on Wilms' tumor cases has shifted towards refinement of therapy for children with low-risk tumors so that they can be spared modalities resulting in unwanted long-term side-effects, without compromising the excellent cure rates. At the same time, investigators continue to look for novel strategies, including treatment intensification, for patients with high risk tumors for whom outcome might be further improved.

### PATIENTS AND METHODS

The present study is a retrospective analysis of the results of treatment of sixty-two new

cases of pediatric Wilms' tumor who had attended the pediatric unit of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1994 to January 2001. All patients were subjected to clinical, pathological and laboratory examination.

History taking included history of consanguinity, family history, and onset of the disease, presence of congenital anomalies and the method of surgical interference. Clinical examination included examination of any congenital anomalies as aniridia, genitourinary malformations, hemi-hypertrophy or signs of overgrowth and hypertension. Radiological examination included chest X-ray (CXR), abdomeno-pelvic CT scan for any residual or metastatic disease. Laboratory examination included complete blood picture (CBC), renal and liver profiles. According to National Wilms' Tumor Study Group (NWTSG), patients were divided into 5 stages [4].

Stage I cases received 6 months of chemotherapy; vincristine 1.5mg/m<sup>2</sup> IV weekly and dactinomycin-D 0.04mg/kg I.V every three weeks. Stage II with favorable histology (FH) received the same regimen for 1 year [5,6], stage III and IV (FH) received vincristine, dactinomycin-D and doxorubicin 30mg/m<sup>2</sup> I.V every three weeks for 1 year [5,6] in addition to radiation therapy (within a maximum of 10 days post-operatively) 1080cGY to the tumor bed (180cGY per fraction) or 1050cGy to the whole abdomen (150cGY/fraction), depending on the extent of spillage with supplementation of 1080cGy boost to any gross residual disease [7-9]. Lung metastases were treated by 1200cGY to the whole thorax (150cGY/fraction). Liver metastases received 1800cGy, 180cGY/fraction [7,8,9]. Stages II, III and IV with unfavorable histology (UH) received 1 year of chemotherapy which included vincristine, adriamycin, dactinomycin-D and cyclophosphamide 10mg/Kg d1 to d3 in addition to radiation therapy. Stage V was managed according to the stage of each kidney and pathology of the disease with surgical sparing of as much renal tissue as possible (at least 30-50% of one kidney) [9].

Relapsing cases received salvage chemotherapy in the form of carboplatin 16.4mg/kg I.V infusion, vp-16 100mg/m<sup>2</sup> D1 to D3 I.V infusion alternating every 3 weeks with endoxan

13.4mg/kg D1 to D3 with mesna 3.3mg/kg/dose D1 to D3 and vp-16 100mg/m<sup>2</sup> D1 to D5 for 6 months [10,11]. WHO grading criteria were used for recording toxicity whether for chemotherapy or for radiotherapy and the findings were analyzed.

All patients were followed up for 4 years with assessment of overall survival (from the date of diagnosis to the date of death or the date of last follow-up), disease-free survival (duration of time from complete remission to clinical and radiological progression of disease), and assessment of response rate was as complete response (complete disappearance of any clinically documented disease), partial response (>50% reduction in the size of the residual disease), stable disease (SD), (<25% reduction in the size of the residual disease) and disease progression. Correlation of the various prognostic factors with overall survival, disease free survival (DFS), and multivariate analysis was done to assess the most important prognostic factors affecting overall survival and disease-free survival. Treatment related complications were also assessed. The patients who achieved complete remission were followed up every 3 months for 4 years by chest X-ray, abdominal imaging, liver and kidney profiles with assessment of treatment related complications.

#### *Statistical Methods:*

Comparison of proportions was done using Chi-square or Fisher exact test. Kaplan Meier estimated overall survival and Breslow compared survival curves were plotted. Cox regression analysis was done to show which of the prognostic factors had an independent effect on overall survival. *p* value was significant at a 0.05 level [12].

## **RESULTS**

Males constituted 61.3% of the cases (38/62 cases). History of consanguinity was present in 8% of the cases (5 cases). The median age of the patients was 5 years (age ranged from 30 days to 10 years). Favorable histology was found in 40 cases (64.5%), while unfavorable histology was found in 22 cases (35.5%). None of the cases were clear cell sarcoma or with anaplastic pathology. The most common complaint was abdominal swelling in 51 cases (82.3%), followed by abdominal pain in 8 cases

(13%), haematuria in 9 cases (14.5%) and 2 cases (3.2%) presented with intestinal obstruction.

Complete surgical excision of the tumor (total nephrectomy and lymph node sampling) evidenced both pathologically and radiologically was done in 53 cases (85.5%) and incomplete surgery (debulking surgery) with a gross ( $\geq 2.5$ cm) or microscopic residual evidenced either pathologically or radiologically was performed in 9 cases (14.5%). As regards favorable histology (FH), 14 cases were stage I (35%), 10 cases were stage II (25%), 11 cases were stage III (27.5%), 2 cases were stage IV (5%), and 3 cases were stage V (7.5%). As regards unfavorable histology (UH), 8 cases were stage I (36%), 7 cases were stage II (32%), 5 cases were stage III (23%), and 2 cases were stage IV (9%).

The 4-year overall survival rate was 70.1% (Fig. 1). The overall survival rate for stage I was 85.7%, for stage II 71%, and for stages III+IV+V it was 50.11% (Fig. 2), the difference was statistically significant ( $p < 0.001$ ). The 4-year survival for all stages with UH was 65.71% and for FH it was 92.86% (Fig. 3). However, this difference was statistically insignificant ( $p = 0.25$ ). Favorable histology patients, stages I, II, and III+IV+V, enjoyed a 4-year survival of 82.3%, 56% and 41%, respectively (Fig. 4). The difference was statistically significant ( $p = 0.008$ ). Patients who underwent complete surgical excision of the tumor had a 4-year survival of 66.8%. Patients who underwent incomplete surgical excision with gross tumor left behind had a 4-year survival of 36.2%. The difference between the two procedures was statistically significant ( $p < 0.001$ ) (Fig. 5). The 4-year survival for UH patients with ages  $< 2$  years and  $\geq 2$  years was 66.4% and 47.6%, respectively. However, this difference was not significant statistically ( $p = 0.344$ ). For FH patients, the 4-year survival with ages  $< 2$  years and  $\geq 2$  years was 87% and 56%, respectively, with a significant statistical difference ( $p = 0.0042$ ). On multivariate analysis, it was found that the stage and tumor residuum after surgery significantly affected survival. The overall 4-year disease-free survival (DFS) was 58% (Fig. 6). The 4-year DFS for (FH) and (UH) was 63% & 55%, respectively ( $p = 0.0334$ ) (Fig. 7). The 4-year DFS for stage I+II was

73.36% and for stage III+IV+V it was 19.3%; ( $p = 0.0202$ ) (Fig. 8). The 4-year DFS for ages  $< 2$  years and  $\geq 2$  years was 77.38% and 42.98%, respectively, with a statistically significant difference ( $p = 0.0442$ ). On multivariate analysis, it was found that histopathology and stage significantly affected disease free survival ( $p = 0.003$  and  $0.0042$ , respectively).

Fifteen patients out of 62 (24.2%) recurred. Five cases recurred locally 33.3%; 1 case with (FH) and 4 cases with (UH). One case with (UH) had local and distant recurrence (4.5%). Nine patients recurred distantly (60%) (2 cases with FH and 7 cases with UH). The lung was the most common site of metastases in 7 cases (70%), followed by bone in 2 cases (20%), and finally the liver in 1 case (10%). There was no statistically significant difference between (FH) and (UH) regarding incidence of distant metastases and local recurrence. In patients who underwent debulking surgery with tumor residual, 2/9 (22.2%), recurred. One case recurred locally and one case recurred distantly. For patients who underwent complete surgical resection, 4/53 cases recurred locally (7.5%), 1 case recurred with local and metastatic disease (1.8%) and 8 cases (15%) recurred distantly. The difference was statistically significant ( $p = 0.0001$ ).

After a median of 3 years follow up (range 2-5.5 years); 33 cases (53.2%) were alive free of disease, 14 cases (22.6%) were alive with disease and 15 cases (24.2%) had died. Among the 15 patients who relapsed, a salvage complete remission was achieved in 1 case (6.6%), partial remission in 3 cases (20%), SD (stationary disease) in 1 case (6.6%) and DP (disease progression) in 10 cases (66%) with a 2-year survival rate less than 20% in case of relapsing patients. Grade I leucopenia occurred in 60% of the cases, and grade II leucopenia in 40% of the cases. Dehydration occurred in 1 patient (1.6%). Diarrhea occurred in another patient (1.6%). Septicemia developed in 2 cases (3.2%), grade II renal failure in 2 cases (3.2%), pneumonia and respiratory distress in 1 case (1.6%), and internal hemorrhage in 1 case (1.6%).

As regards the late effects of treatment; cardiomyopathy developed in 2 cases (3.2%), dorsolumbar scoliosis in 1 case (1.6%) and stunted growth developed in 8 cases (12.9%).

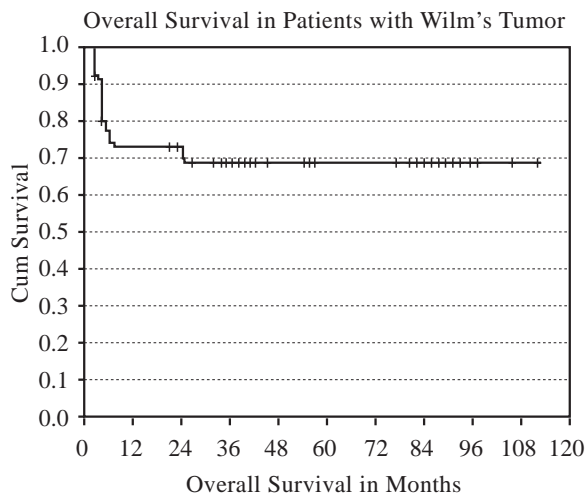


Fig. (1): Overall survival in 62 patients of pediatric Wilm's tumor.

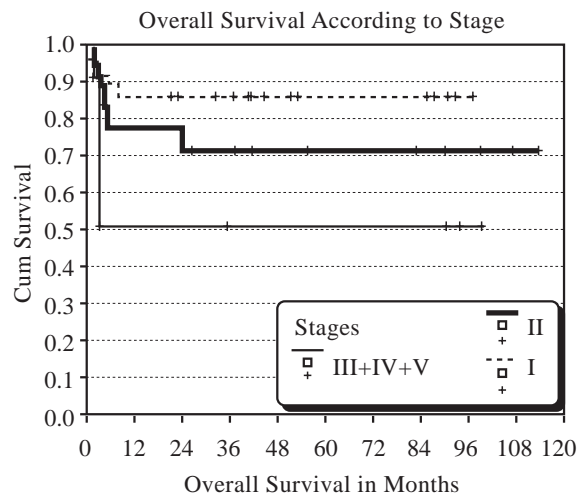


Fig. (2): Overall survival of 62 patients of pediatric Wilm's tumor according to stage.

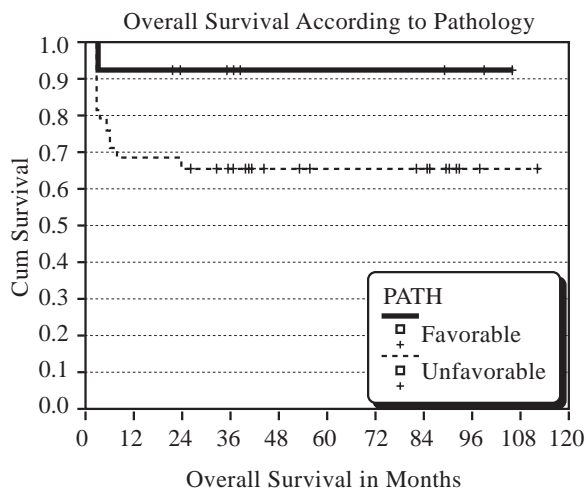


Fig. (3): Overall survival of 62 patients of pediatric Wilm's tumor according to pathology.

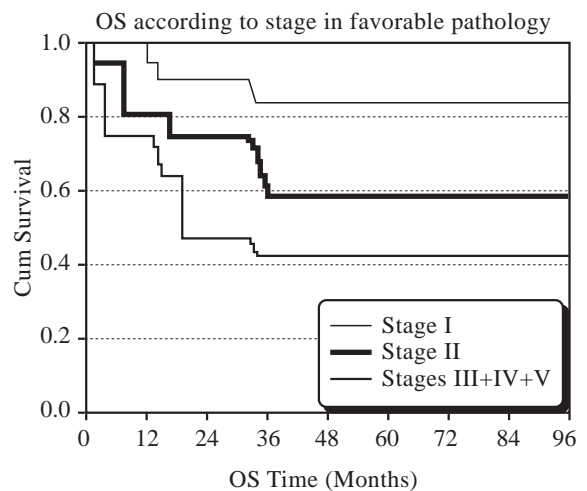


Fig. (4): Overall survival of 62 patients of pediatric Wilm's tumor according to stage and pathology.

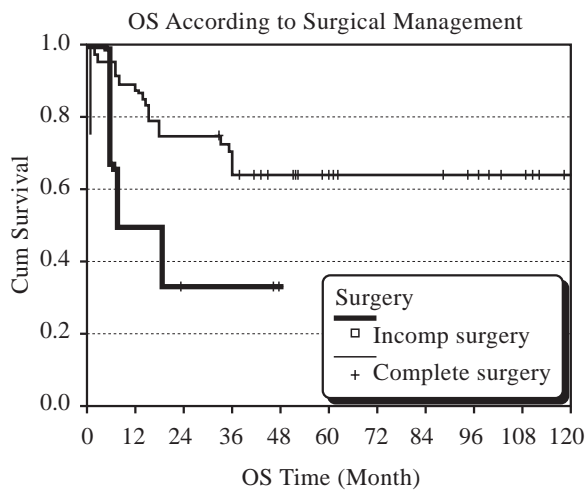


Fig. (5): Overall survival of 62 patients of pediatric Wilm's tumor according to surgical maneuver.

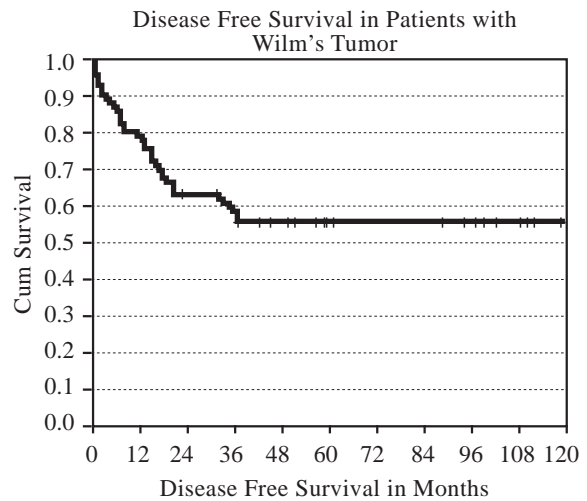


Fig. (6): Overall disease free survival of 62 patients of pediatric Wilm's tumor.

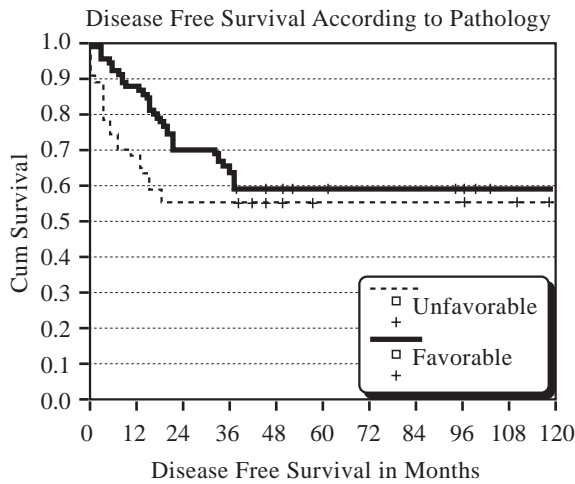


Fig. (7): Overall disease free survival of 62 patients of pediatric Wilm's tumor according to pathology.

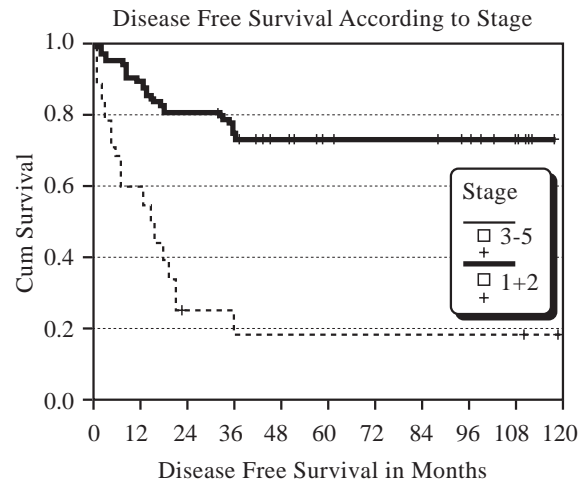


Fig. (8): Overall disease free survival in 62 patients of pediatric Wilm's tumor according to stage.

## DISCUSSION

The present study is a retrospective analysis of the treatment results of patients with Wilms' tumor treated at (NEMROCK) from the period of January 1994 till January 2001.

In the present study, males constituted 61.3% of the cases; this is similar to the work of Plesko and Kramarova where males formed 60% of cases [13]. In the present study, history of consanguinity was present in 8% of cases (5 cases), this coincides with the work of Plesko and Kramarova where consanguinity was present in 8% of the cases too [13]. In the present study, favorable histology was present in 64.5% of cases and unfavorable histology was present in 35.5% of the cases. Paul et al., obtained similar results, where favorable histology was present in 62.3% of cases and unfavorable histology was present in 37.7% of cases [14].

In the present study, the most common complaint was abdominal swelling (82.3%), followed by haematuria (14.5%), then abdominal pain (13%), and finally intestinal obstruction (3.2%). This coincides with the work of Pianezza et al., where an abdominal mass was the most common presenting feature (85%), followed by abdominal pain (17%), and then haematuria (10%) [15].

In the present study, 22 patients (35.5%) had stage I disease, 17 cases (27.4%) had stage II, 16 cases (25.8%) had Stage III, 4 cases (6.5%) had stage IV and 3 cases (4.8%) had

stage V disease. Similarly, Hung et al., who conducted a similar study noticed the following: Stage I constituted 43.2% of the cases, stage II 19.3%, stage III 23.9% and stage IV 6.8% and stage V 6.8% of the cases also [16].

In the present study, the 4-year overall survival was 70.08%. The 4-year survival for stage I-IV unfavorable histology was 65.71%. The 4-year survival for cases with a tumor residual after surgery was 36.2% and with complete surgery it was 66.8%. Stages I, II, and stages III+IV+V favorable histology cases had a 4-year survival of 82.3%, 56% and 41%, respectively. Age and histopathology had no significant impact on survival. On multivariate analysis, it was found that stage and tumor residual after surgery significantly affected overall survival. Moreover, Zaghoul et al., who conducted a similar study but with a 10-year survival rate reporting, concluded that tumor residuum significantly affected survival. Contradictory to that, the NWTS group denied any significant impact of tumor stage on overall survival [17]. Pianezza et al., obtained results comparable to ours, where the 4-year survival for stage I FH was 100%, for stage II FH 77%, for stage III FH 50% and for stage IV FH 45% and the overall survival was 86% [15]. Moreover, Venugopal et al., had a 4-year survival rate of 100% for stage I and II FH and 55% for stage III FH [18]. This work does contradict the work of Corez et al., who used dose intensification with growth factor rescue if needed where their 4-year survival for UH was 87.3% [19].

In the present study, the 4-year disease-free survival (DFS) was 58%, the 4-year disease free survival for FH and UH was 63% and 55%, respectively (with a statistically significant difference). The 4-year disease-free survival (DFS) was 73.4% for stages I+II, and it was 19.3% for stages III+IV+V, respectively (showing a statistically significant difference). In addition, Zaghoul et al., stated that histopathology and stage significantly affected the disease-free survival [17]. Hung et al. [20], who performed a similar study, had a relapse-free survival of 69.4% at 5 years. He also reported that tumor histology and clinical stage significantly affected the disease-free survival. Moreover, Tilcling et al. [21], who performed a similar study, achieved a 4-year disease-free survival of 76.6%, which is superior to our results.

The overall recurrence rate was 24.2% (15 cases) in the present study. Five cases recurred locally (33.3%), 1 case recurred locally and distantly (6.7%) and 9 cases recurred distantly (60%). Postoperative tumor residue is of utmost significance regarding the incidence of local recurrence and distant metastases, whereas, histopathology is of no significant impact. These results coincide with the work of Zaghoul et al. [17], where postoperative tumor residue significantly affected the incidence of local recurrence and distant metastases. On the contrary, Zaghoul et al., found that histopathology affected significantly the incidence of distant metastases [17]. Our current study results coincide with the work of Spurrier et al., where recurrence rate was 20%. Ten cases recurred locally (40%) and 15 cases recurred distantly (60%) and the lung was the most common site of metastases [22].

Only one relapsed patient achieved CR (6.6%) in the present study; and another patient had SD. Three cases attained PR (20%) and DP occurred in 10 cases (66.7%) with a 2-year survival rate less than 20%. Miser and Tournade, who also performed a study on relapsing cases, achieved a survival rate that did not exceed 30% [10].

Regarding late effects of treatment in this study, cardiomyopathy occurred in 2 cases (3.2%), dorso-lumbar scoliosis in 1 case (1.6%) and stunted growth in 8 cases (12.9%); this coincides with the work of Hung et al., where cardiomyopathy, scoliosis and stunted growth

were the major long-term sequelae of treatment [20].

#### *Conclusion:*

Based on multivariate analysis, we conclude that stage and residual disease after surgery significantly affect overall survival; whereas, histopathology and stage affect significantly disease free survival. Moreover, our study revealed that residual disease after surgery affects significantly the incidence of local recurrence and distant metastases.

We noticed that our survival indices are somewhat lesser than a number of similar studies survival figures. This may be because of the poor performance and nutritional status of many of the patients and the limited supportive care resources.

In general, treatment of children with Wilms' tumor is very successful. Current treatment research is directed towards defining the minimal necessary therapy for successful treatment of Wilms' tumor by reducing the group of patients exposed to anthracyclines. This is achieved by using biological prognostic factors, to identify patients with stage III-IV FH who have a low risk of relapse. In addition, it is of utmost importance to identify the patients who strictly need radiation therapy. Moreover, it is very important to define and discover the minimally recommended overall dose and the smallest dose per fraction to be given to reduce the irreversible side-effects without risking the treatment outcome; as the late effects of radiation therapy can affect the quality of life of those long-term survivors. We believe that further research is needed to improve the treatment results of patients with high stage unfavorable histology as drug intensification, or trials involving new investigational therapy.

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