

Prognostic Impact of HER/2 Expression on Survival of Preoperatively Treated Children with Wilms Tumor at South Egypt

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How to cite this paper: Sayed, H.A., Refaiy, A. and Salem, M.A. (2017) Prognostic Impact of HER/2 Expression on Survival of Preoperatively Treated Children with Wilms Tumor at South Egypt. *Journal of Cancer Therapy*, 8, 801-813.
<https://doi.org/10.4236/jct.2017.89070>

Received: April 13, 2017

Accepted: September 8, 2017

Published: September 11, 2017

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Abstract

Aim: Wilms tumor (WT) is the most frequent type of pediatric renal tumors. Her/2 is an oncoprotein, its over-expression revealed to play a very vital role in the progress and improvement of certain tumors. This study evaluates the possible role of Her/2 as a prognostic indicator in formerly treated WT. **Method:** Immunohistochemical expression of Her/2 was studied in paraffin material of 40 WT patients followed SIOP 9 protocol. Patients' medical records reviewed for clinical, pathological and outcome data and correlated with HER2 expression. Additional 15 samples of normal surrounding kidney tissue specimens were included. **Results:** Her/2 was often expressed in normal kidney tissue (renal tubules but not glomeruli) and at variable levels in the three elements of WT. At a median of 84 months, 70% of patients are living and under follow-up, surgical stage and pathologic subtypes were the only two factors significantly affect the outcome of our patients ($p = 0.000$, $p = 0.007$ & $p = 0.004$, $p = 0.005$ for OS (Overall survival) and DFS (Disease Free survival) respectively). Her/2 expression was associated with epithelial differentiation ($p < 0.001$). There was non-significant effect of Her/2 expression on OS or DFS of studied group. **Conclusion:** while the major progress in studying biology of WT, stage and pathological subtype continues the only predictive factors of significant value affecting the outcome of patients with WT. There was important association between Her/2 expression and histological differentiation in formerly treated Wilms tumor. Non-conclusive results regarding influence of Her/2 expression on the result of WT patients were found.

Keywords

Wilms Tumor, Her/2, Preoperative Chemotherapy

1. Introduction

The most common of the tumors in childhood are Wilms tumor (WT). Also, WT is the second most common malignant retroperitoneal tumor [1]. The total survival rate for WT is about 90% [2]. A multidisciplinary approach in keeping with rules of National Wilms' Tumor Study Group (NWTSG) and International Society of Pediatric Oncology (SIOP) for the treatment of WT has considerably contributed to those results. However, WT is known for its unpredictable tendency of recurrence or metastasizing, sometimes years after primary treatment [3]. The most important predictors of treatment insufficiency for children with WT are tumor histology and stage of disease, each of that are used to stratify patients for appropriate modern therapeutic protocols [4] [5].

The preoperative chemotherapy for WT treatment is increasingly being popular. The SIOP in Europe exhibited that preoperative chemotherapy facilitated surgery and reduced the occurrence of tumor spillage at the time of surgery and this will result in a good survival outcome [6]. Meanwhile, it doesn't significantly obscure important histopathologic parameters [7] [8].

A vast amount of prognostic markers in WT has been reviewed [9] [10] but no biological marker providing consistent predictive information regarding the clinical outcome was found. Tumor-specific loss of heterozygosity (LOH) for chromosome 1p or 16q has shown to be related to with a poorer prognosis in favorable-histology WT entered in NWTSG-5 [11].

More recently, amplification or over-expression of some markers such as Her/2 (human epidermal growth factor receptor 2), which is an oncoprotein [12], that normally mediated cellular growth, proliferation, survival and differentiation through binding of growth factor ligands; [13] has been illustrated to play a major role in the development and progression of invasive types of breast cancer. Her/2 protein has become a vital biomarker and target among the most significant advances in breast cancer therapeutics (about 30% of breast cancer patients) [14]. Also, over-expression of Her/2 oncoprotein had been implicated in the development of other types of tumors like ovary, GIT, prostate, lung, Kidney, liver and bladder cancer to increase the metastatic potential and to promote chemoresistance [15]. Her/2 expression in normal kidney tissue specimens showed positive immunoreactivity within the cell membranes of renal tubules, suggesting that this protein could be a normal membrane constituent of epithelial renal tissue but not of glomeruli [12].

Few reports proposed that Her/2 expression in WT could be a marker for epithelial differentiation and its expression could be a perfect predictor of overall survival and longer recurrence-free survival [16] [17]. Meanwhile, there have been few papers published to give insight into possible different expression patterns of Her/2 in patients previously treated with chemotherapy.

The goal of the this study is to evaluate the expression patterns and the prognostic significance of Her/2 in a set of patients with WT preoperatively treated with chemotherapy to investigate its relation to other prognostic factor and its

impact on treatment reaction and survival outcome.

2. Patients and Methods

2.1. Patients and Sample Selection

The clinical and pathological data were reviewed from medical records of forty patients with WT preoperatively treated by chemotherapy, followed by nephrectomy and postoperative chemotherapy, according to the SIOP 9 protocol at Department of Pediatric and Surgical Oncology, South Egypt Cancer Institute, Assiut University. The median follow up for patients was 84 months.

1) Inclusion Criteria

- a) All patients between 1 year and 18 years;
- b) Received neoadjuvant chemotherapy.

2) Exclusion Criteria

- a) Patients previously operated outside our institute;
- b) Patients younger than 1 year old.

2.2. Histopathology

All specimens were formalin fixed paraffin embedded. The H & E stained slides were reviewed to determine predominant cell type, histological differentiation and stage. Adjacent control (normal) kidney tissue was available for 15 cases.

2.3. Immunohistochemistry

Immunohistochemistry for Her/2 was done according to manufacturer's protocol. Briefly, 4 microns sections were cut from paraffin blocks and placed on coated slides. Then sections were deparaffinized and rehydrated in descending grades of ethanol, and were subjected to blocking of endogenous peroxidase activity using H₂O₂ (hydrogen peroxide) for 5 min. Antigen retrieval was done by heating the slides in citrate buffer 10% for 12 min. After cooling in room temperature, the slides were incubated overnight at 4C with primary antibody (mouse monoclonal antibody) against Her/2 antigen at a concentration 1\50 (her/2-neu Ab-17 (clone e2-4001 + 3b5 Thermoscientific, USA). The slides were then incubated for 10 min with biotinylated goat antipolyvalent followed by streptavidin peroxidase for another 10 min. The slides were washed three times with PBS between each step and the other. Diaminobenzidine were applied for 5 min. The slides were rinsed in distilled water, counterstained with Mayer's haematoxylin, dehydrated and mounted. Negative control slides were done by deleting primary antibody. Sections from breast carcinoma were stained as positive control.

2.4. Evaluation of Immunohistochemistry

Staining for Her/2 was membranous with some cytoplasmic staining. Only membranous staining was considered as positive. Evaluation was done according to ASCO/CAP 2013 scoring criteria [18].

IHC 0 = no staining or incomplete membrane staining and faint/barely perceptible membrane staining in $\leq 10\%$ of tumor cells.

IHC 1+ = faint/barely perceptible incomplete membrane staining in $>10\%$ of tumor cells.

IHC 2+ = circumferential, incomplete and/or weak/moderate membrane staining in $>10\%$ of tumor cells or complete and circumferential intense membrane staining in $\leq 10\%$ of tumor cells IHC 3+ = complete and intense staining of $>10\%$ of tumor cells.

Scores 0 and 1 are considered as negative and scores 2 and 3 are considered positive.

2.5. Statistical Analysis

Data was analyzed using SPSS version 21 (IBM Corporation). Data was described as number and percentage for categorical data. For quantitative data (age), it was described using mean and standard deviation. To evaluate difference between groups, we used: Chi square for categorical data and Student t-test for quantitative data.

Survival analysis [overall survival (OS) and disease free survival (DFS)] was done using Kaplan Meier. Log Rank test was done to detect the significance of difference between groups. *P* value was considered significant if it is ≤ 0.05 .

3. Results

The current study included 40 patients; 16 males and 24 females. The patients were 6 to 96 months of age; the median age at time of diagnosis was 24 months. One patient had horseshoe kidney, two patients had genitourinary malformation. Thirty eight tumors were removed from patients with a localized disease at diagnosis. One case showed bilateral nephroblastoma and another case presented with metastasis at the time of diagnosis. All patients were treated by neoadjuvant chemotherapy before nephrectomy according to SIOP 9 protocol. Most of our cases had stage I (29/40) (72.5%) followed by stage III&II (5/40 & 4/40 respectively).

All studied tumor specimens (according to SIOP 9 protocol) were intermediate risk WT (12 cases were epithelial predominant, 13 blastemal predominant, 4 stromal predominant and 11 cases were mixed). None of our cases had displayed any anaplastic features. According to histological differentiation: epithelial element was identified in 37 (92.5%) of cases, Blastemal in 35 (87.5%) of cases and mesenchymal or stromal element in 32 (80%) of cases.

Patterns of Her/2 Expression and Prognosis

Normal kidney tissue showed that Her/2 was expressed in collecting tubules and to lesser extent in proximal and distal convoluted tubules. The glomeruli were completely negative (**Figure 1(a)** and **Figure 1(b)**).

In Wilms tumor Her/2 expression varied according to cell type. In epithelial element, 22 out of 37 cases (59.4%) showed positive expression of Her/2 (score 2

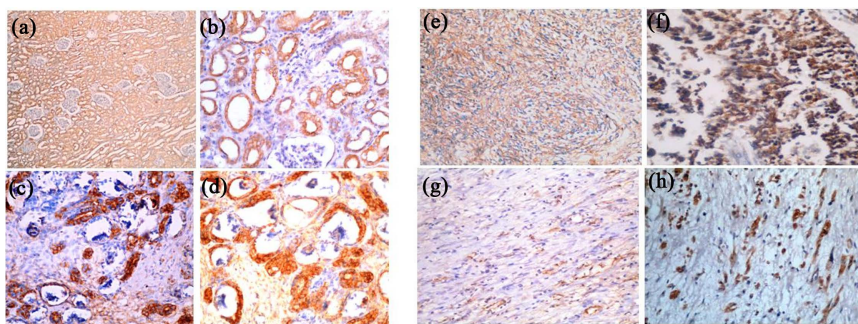


Figure 1. Immunohistochemical expression of Her/2 in normal Kidney ((a) & (b)), epithelial ((c) & (d)), stromal ((e) & (f)) and blastemal elements ((g) & (h)). (IHC (A) & (e) $\times 100$, (b), (c), (d), (f), (g), (h) $\times 400$).

and 3) and 15 cases showed negative expression (scores 0 and 1). In blastemal element Her/2 was expressed in 8 out of 35 cases (22.9%) as no cases showed score 3 and was negative in 27 cases (77.9%). In stromal element only weak expression (score 1) was detected in 25% of cases (**Table 1**) and (**Figures 1(c)-(h)**). Although cytoplasmic expression was shown in some cases, only membranous staining was considered as positive.

Seventy percent of cases were surviving and under follow up at a median of 84 months, the mean OS of the studied cases was 117.425 ± 10.335 months (95% CI 65.4 - 89.3) and the mean DFS was 115.225 ± 10.853 months (95% CI 65.4 - 89.3). Surgical stage and histopathologic subtypes were the merely two factors among other clinic-pathological factors that considerably affect the result of our patients ($p = 0.001$, $p = 0.007$ and $p = 0.004$, $p = 0.005$ for OS and DFS respectively), and by doing multiple cox regression analysis stage was the only significant factor that related to OS ($p = 0.005$) and DFS ($p = 0.004$) (**Figure 2** and **Figure 3**).

When we studied the relation among the expression of Her/2 and clinicopathological variables, significant association was detected between histological differentiation and Her/2 expression as nearly 60% of epithelial elements had expressed Her/2 versus 22.9% & 0% for blastemal and stromal elements respectively ($p < 0.001$).

However no significant relation was detected between Her/2 expression and other studied factors (age, gender, predominant type and stage).

Also, we found that Her/2 expression had non-significant effect on OS of our patients as we reported that among the 25 patients who expressed Her 2 on their tumor cells 72% survive versus 66.7% in those with negative expression the mean survival was (120.280 ± 12.799 and 105.867 ± 15.454 for both group respectively; $p = 0.8$). Similar case was reported considering the DFS; the mean was 117.6 ± 13.60 vs. 102.867 ± 16.308 for those with +v expression vs. -ve expression; $p = 0.729$).

4. Discussion

Wilms tumor is classified as a primitive, multi-lineage malignancy of embryonic

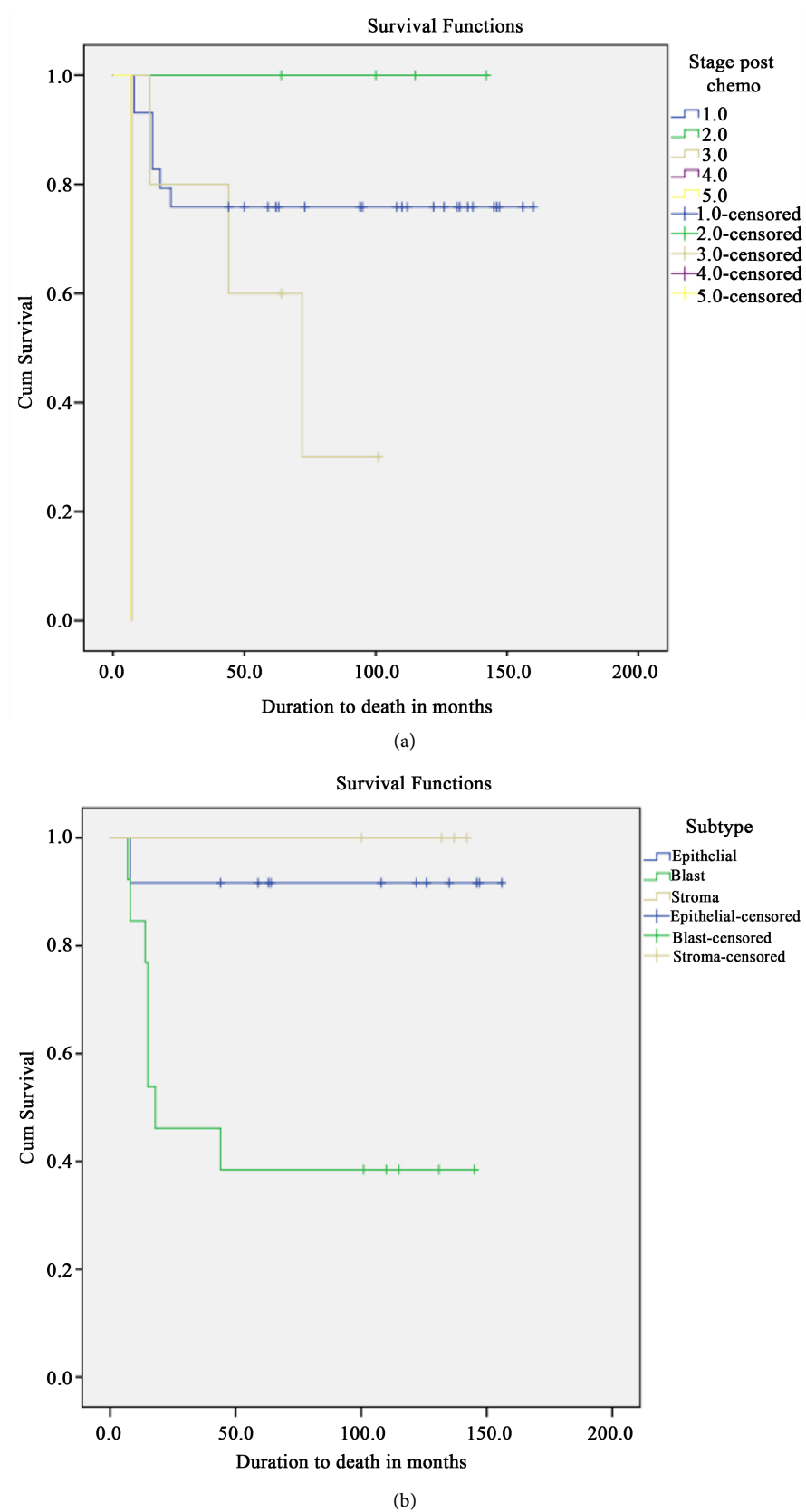
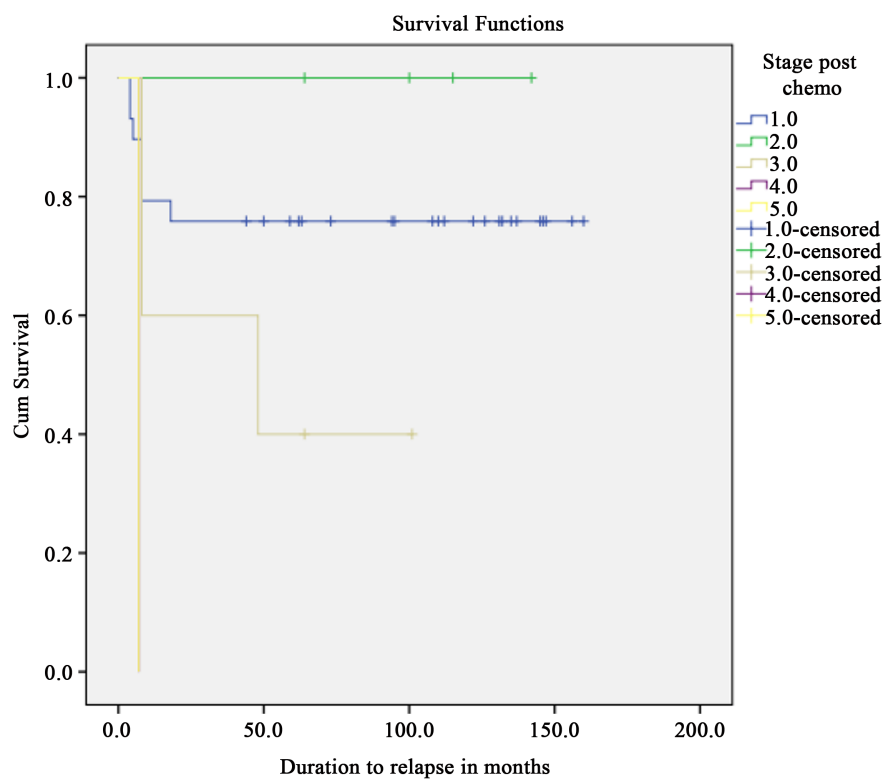
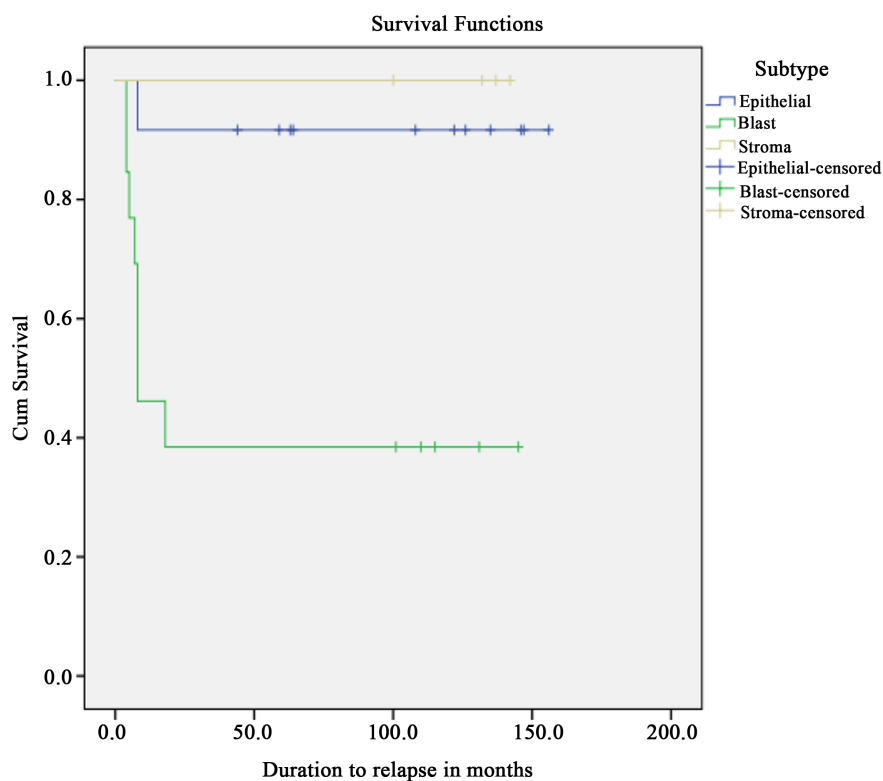


Figure 2. Overall survival of the study group WT patients: (a) for the different stages post chemotherapy; (b) for the different pathologic subtypes.



(a)



(b)

Figure 3. Disease free survival of the study group WT patients: (a) for the different stages post chemotherapy; (b) for the different pathologic subtypes.

Table 1. Expression of Her/2 in different cell types.

Pvalue	Total	Immunohistochemistry score of Her/2				Type of cells
		+3 N (%)	+2 N (%)	+1 N (%)	0 N (%)	
<0.001	37	6 (16.2)	16 (43.2)	3 (8.1)	12 (32.4)	Epithelial
	35	0 (0)	8 (22.9)	4 (11.4)	23 (65.7)	Blastemal
	32	0 (0)	0 (0)	8 (25)	24 (75)	Stromal

renal precursors. Furthermore, it has histological features similar to the developing normal kidney, and is usually cited as a case of impaired differentiation in tumorigenesis [19]. The three histologic components of WT (blastemal, epithelial and stromal) have completely different proliferating potential and every component might have different proliferating activity in each different histological types of WT [19].

Her/2, is an oncoprotein [11], that mediated cellular growth, proliferation, survival and differentiation through the binding of growth factor ligands [12]. In the last years there has been great attention in the Her/2 proto-oncogene concerning tumor biology [20]. The presence of epidermal growth factor receptor (EGFR) has been found in normal kidney during development [21] and is essential for tubulogenesis [22]. Amplification or over-expression of this oncogene has been reported to play a major role in the development or progression of certain aggressive types of breast cancer [13].

Although reports suggested that Her/2 expression in WT is also a marker for epithelial and homologous differentiation and its expression may be a predictor for better overall survival and longer recurrence free survival [16] [17]. However, limited published data are available about the possible variations within the expression patterns of Her/2 in tumors of patients receiving chemotherapy.

In this study, we evaluated the expression patterns of Her/2; using immunohistochemistry in different components of post-chemotherapy WT specimens, and investigated its relationship to other prognostic factor as well as its impact on survival outcomes and treatment response to compare it with the available reports regarding these issues.

Salem *et al.*, [16] Rivera & Haber [20] and Ragab *et al.* [17] had proposed that Her/2 might be one of the chemical directors of ureteric bud variation during nephrogenesis. After they had detected expression of Her/2 in control (normal) kidney tissue specimens with positive immunoreactivity in the cell membranes of renal tubules, and suggested that Her/2 protein is a normal constituent of membrane of epithelial renal tissue but not of glomeruli. This result is compatible with our results as Her/2 was expressed in the renal tubular structures but not the glomeruli.

In previously treated WT samples of our studied group, the staining patterns appear to differ regarding each component. Her/2 protein expression in immunoreactive epithelial cells was (59.4%) followed by blastemal element (22.9%),

whereas the stromal constituent showed only weak expression (+1). There was statistically significant association between Her/2 expression and epithelial differentiation ($p < 0.001$). Similar finding have been reported in previously treated WT samples and in non-treated patients as well [15] [16] [17]. Salem *et al.* [16] suggested that as high levels of HER/2 detected in control (normal) kidney tissue and in tumors with epithelial differentiation, so HER/2 is a growth factor required for generation of epithelial component and other growth factors may be needed for blastemal and stromal differentiation. However their study included non-treated cases only.

Some of our cases have shown cytoplasmic expression of Her/2. Although cytoplasmic expression of Her/2 has been stated in many other tumors as colon adenocarcinoma [23] and Ewing's sarcoma [24], possible correlation of this expression with patient endurance and response to therapy has not been evaluated.

Wilms' tumor is a curable disease and more than 90% of patients live 4 years after diagnosis [25] [26]. In this study, 70% of the studied cases were survived and under follow up at median follow up of 7 years, the mean OS of the studied cases was 117.425 ± 10.335 months (95% CI 65.4 - 89.3) and the mean DFS was 115.225 ± 10.853 months (95% CI 65.4 - 89.3).

Several factors were considered in the prognosis of WT; with early stage and favorable pathology being the most important predictors for survival [27] [28] [29] [30]. We reported that surgical stage and pathologic subtypes were the only two factor among other demo-clinic-pathological factors that significantly affect the outcome of our patients ($p = 0.000$, $p = 0.007$ & $p = 0.004$, $p = 0.005$ for OS and DFS respectively).

The biologic behavior of WT is difficult to prognosticate on the basis of histopathology findings only [3]. Although the last two decades had carried progress in the Her/2 proto-oncogene regarding tumor biology to an extent that Yokoi *et al.* [31] suggested that *cerbB-2* in an *in vivo* model may serve as a therapeutic target. However, the possible prognostic effect of this marker in WTs and its relationship to other clinic-pathological features or its influence either on response to chemotherapy or clinical outcome is still not obvious. In this study, we investigated the relation between Her/2 expression and other prognostic factors as well as its impact on survival outcomes and treatment response of previously treated WT samples. According to our results, we reported that Her/2 expression was not significantly affect the outcome of our patients ($p = 0.72$ & $p = 0.8$ for OS and DFS respectively. This is in agree with the results reported by Ghanem *et al.* [3] who suggested that *c-erb B2* of no prognostic impact on the clinical outcome of patients and may not play a vital role in the aggressive behavior of WT in a similar study set of patients (previously treated with chemotherapy). In contrast, Salem *et al.* [16] suggested that an over-expression of Her/2 might be associated with a perfect prognosis in WT; (however, it was difficult to conclude that due to few number of cases under study) and Ragab *et al.* [17] who reported a good impact of Her/2 on overall and recurrence free survival of their patients. And before jumping to explain this controversy in the results by the

exposure of the samples in this study and Ghanem *et al.*'s [3] to chemotherapy, we found that the expression pattern of Her/2 among both groups (previously treated vs. previously non treated samples) was similar as mentioned earlier in this report. Also, in an additional study of a set of patients getting no chemotherapy before surgery by Ghanem *et al.* [3] Similar results were gained which made him suggests that chemotherapeutic treatment didn't significantly affect the predictive value of the studied markers.

5. Conclusion

Although the major progress in studying of biology of wilms' tumor, stage and pathologic subtype remains the only predictive factors of significant value when talking about the result of patients with wilms' tumor. Although there is a significant association between Her/2 expression and cell differentiation, as we see inconclusive results regarding the influence of Her/2 expression on the result of patients with WT either previously treated with chemotherapy or untreated have been established, and more conclusive results may be obtained with multinational or international studies to include improved numbers of patients that can give accurate results.

Conflict of Interest Statement

No conflict of interest regarding this issue.

Acknowledgments

The authors thank dr Mikahil N for his help in statistical analysis.

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