Journal of Oncology Medicine & Practice
ISSN: 2576-3857
Omar et al., J Oncol Med & Pract 2019, 4:2
Research Article Open Access

The Clinical Outcome of Wilms Tumour: A 6-Years-Experience of King Fahad Specialist Hospital, Dammam

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Abstract

Introduction: Wilms' tumor is the most prevalent renal tumor of childhood that accounts for about 5% of all their cancers. It is also one of the successes of pediatric oncology with long term survival above 90% for localized disease. The aim is to evaluate the disease characteristics and the clinical outcome of children with Wilms' tumor at King Fahad Specialist Hospital Dammam over six years from 2011 to 2016.

Methods: Our study is a retrospective review of the medical files of children (under 16 years) with Wilms' tumor who were managed at King Fahad Specialist Hospital Dammam in the interval between January 2011 until December 2016. We analyzed all the Patients' and disease features, histopathological results, staging, treatment modalities, and outcome, according to the system of the National Wilms Tumor Study Group (NWTSG). Descriptive analysis using frequencies was applied to describe the study variables.

Results: A total of 22 patients, 9 (40.5%) were males and 13 (59.5%) were females (male ratio=M/F=0.69). were identified, with median age of 37.2 months. The majority of the cases were stage III (31.8%), followed by stage 1 (27.3%) Around 70% had favorable histology, 10% had anaplasia, and 20% had mixed pathology. The relapse rate is 18.2%, and the mortality is about 9%, EFS In This Study Was Estimated As 80%, and the OS As 90%.

Conclusion: In a comparison of our results to that of NWTS-5, we noticed that the majority of our patients presented with stage 3, but despite that, the rate of relapse/progressive disease is comparable to international figures, and the overall survival of our patients of 90% is still comparable to the Western experience.

Keywords: Wilms' tumor; Metastatic disease; Hemihypertrophy

Introduction

Wilms' tumor is the most frequent renal tumor of childhood; it accounts for 5% of all childhood cancers. Moreover, approximately 90% of all pediatric tumors of the kidney [1]. Wilms tumor occurs in 7.1 cases per 1 million children younger than 15 years [2].

The male to female ratio is 0.92 to 1.00 in unilateral cases of Wilms tumor, but in bilateral cases, it is 0.60 to 1.00. At diagnosis, the mean age is 44 months in unilateral cases and 31 months in bilateral cases of Wilms tumor [2]. It considered as one of the successes of pediatric oncology with long term survival above 90% for localized disease and 75% for metastatic disease. That improvement in the management of Wilms tumor comes as the result of the efforts and collaboration between the multidisciplinary team, which involves pediatric oncologists, surgeons, pathologists, and radiation oncologists. More than 80% of children diagnosed with Wilms' tumor below the age of five years and the median age at diagnosis is 3.5 years [1].

Clinically identified malformations and predisposition syndromes observed in (17.6%) of patients. Genetically known tumor predisposition syndromes frequently observed were syndromes associated with alterations of the chromosome WT1 gene, which encodes the transcription factor WT1, that is essential for renal and gonadal embryogenesis such as WAGR and Denys–Drash syndromes. Hemihypertrophy and genito-urinary malformations were the most frequently identified malformations. Other different syndromes or malformations were less frequent [3]. Moreover, over 50 such syndromes have been described [1].

The typical treatment strategy in most patients is a combination of surgery and chemotherapy, with the addition of radiotherapy in patients with high-risk features. However the current treatment protocols are built on risk assignment to minimize toxicity for low-risk patients and improve outcomes for those with high-risk disease; the future remains in identifying novel molecular, tumor biomarkers and more refined clinical risk factors for stratification of treatment plan and intensity

Methods

Our study is a retrospective study conducted at King Fahad Specialist Hospital, Dammam from January 2011 to December 2016. This tertiary care hospital located in the eastern province in Saudia Arabia and provides services in the following specialties: Oncology, Neurosciences, Organ Transplant, Cardiac Services Programs, and Genetic Sciences. Revision of the medical records for all the cases with Wilms tumor under age of 16 years old was done after obtaining approval from the Institutional Review Board.

In each case, demographic data (age, Gender, Nationality), date of symptoms & diagnosis, site, presentation symptoms and signs, associated syndromes, imaging's, diagnostic workup surgical data, staging, treatment options, and outcome were all collected, the definitive diagnosis of WT based on the histological evaluation of the operative specimen. Tumor stage and histological subtype followed the guidelines set by the NWTSG.

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Received September 09, 2019; **Accepted** September 17, 2019; **Published** September 30, 2019

Citation: Omar H, Salah Abdelbaki H, Alharbi Q (2019) The Clinical Outcome of Wilms Tumour: A 6-Years-Experience of King Fahad Specialist Hospital, Dammam. J Oncol Med & Pract 4: 126.

Results

A total of 22 patients enrolled between January 2011 until December 2016. Out of the 22 patients, 9 (40.5%) were males and 13 (59.5%) were females (male ratio=M/F=0.69).

The overall median age at time of diagnosis was 3.78 years (37.02 months), with a median age for males of 35.27 months and females of 38.77 months. As per Nationality; 20 (90.9%) were Saudi, 2 (9.1%) were Non-Saudi, Only six patients (27.3%) had parent consanguinity and nine patients (41%), had positive Family history of malignancies, though none of them reported renal cancers. CA colon is the most reported malignancy in family (33%-44%).

The Wilms tumor was located on the left side on ten patients (45.5%), while it was on the right side on 12 patients (54.5%). No cases with bilateral Wilms tumor within the period of study. The majority in 15 patients (68.2%) were presented with abnormal mass as main complain, 5 cases (22.7%) presented with abnormal distension and only two patients (9.1%) had hematuria at presentation. In none of the patients, the presenting complains of fever, anorexia, nor non-specific abdominal pain were documented as the main complains.

Only three patients (13.6%) were hypertensive at the time of diagnosis time. Four patients (18%) had identified syndromes among them, as two patients were diagnosed to have wager syndrome, one patient had denys drash syndrome, and one patient has Beckwith Widman syndrome mentioning diagnostic imaging, we found that the Ultrasound abdomen was done initially in all the patients (100%), CT abdomen done initially in 19 out of 22 (86.3%). Three cases were unknown. Mild Hyper Calcaemia >2.64 Mmol/L Were reported In 4 Out Of 22 Cases (18%), and similarly Elevated Alanine transaminase than baseline was reported in 4 Cases (18%). None Of our Cases Had Abnormal Creatinine Level nor Abnormal Coagulation Profile Initially. Initial echocardiogram done for all the patients, IN 4 out of the 22 patients (18%) associated valvular abnormalities identified with Tricuspid Valve was noticed to be the most frequent associated valve with insufficiency, 1 case diagnosed to have Rt atrial thrombus, All patients have normal cardiac function initially.

The tumor staging workups revealed that in our cases stage III was found to be the most predominant, 7 out of the 22 (31.8%), followed by stage 1, 6 cases out of 22 (27.3%), then stage IV in (22.7%) in 5 case, and the least one was stage II in only 4 patients (18.2%). Among those 5 cases who diagnosed with stage IV, 3 out of them had metastases to lungs, and in the other 2 cases, they had distant metastases to both lungs and liver.

Around 68.2% had favorable histology 9.1% had anaplasia, and on 20% they reported to have mixed pathology. With regard to the time to diagnosis, that in this study was defined as the time from onset of symptoms till confirmation by pathology, we found that 5 cases (22.73%) diagnosed within 7 days, 9 cases (40.9%) diagnosed between 16-24 days, and the rest of 8 cases (36.3%) diagnosed between 25-90 days. The operational data showed that complete resection without rupture was done on 17 cases (77.3%), while tumor rupture at resection time was documented in 4 cases (18.2%) and one case had unknown status.

Concerning the chemotherapy management, more than half of our patient that is about 54.5% treated with three chemotherapeutic agents as per NWT DD4A protocol and 40.9% was given only two chemotherapeutic agents as per NWT EE4A, and only one patient (4.5%) treated per SIOP protocol. Radiation therapy used in management of 14 cases 63.6%. 4 out of 22 cases had disease recurrence with make our study relapse rate about 18.2% that all occurred within a maximum period of 20 months from end of therapy. 2 out of 22 (9%) patients died both after disease relapse, 20 (91%) were alive, Event-free survival (EFS) time calculated in this study as the time from date of diagnosis to Relapse or/and death. Moreover, it estimated as 81%, and the OS in this study was 91%.

Discussion

Wilms Tumor is the most common renal tumor of infancy and childhood. Its incidence is one per 10,000 children under the age of 15 years worldwide. The present study showed that Wilms' tumor was slightly more predominant in females (59.5%) with (male ratio=M/F=0.69). This result was very near to study from Lebanon by Wisam et al. [3] in which they reported their male to female ratio is 1:1.7=0.58 and it is nearly comparable to the data from the Jordan published by Khader with 54.1% female and approaching also similar old data from same eastern province of Saudi Arabia on 1997 by Mulhim [4] where the male: female (M/F) ratio was 0.8:1.

The median age for presentation in this study was 37.02 months however, it was similar to that in 1997 study from same eastern region in Saudi Arabia where the median age at diagnosis was between 3 to 4 years, and not far different from NCI data with median age for unilateral Wilms tumors of 44 months [2]. Although it is well known that approximately 5% to 10% of individuals with Wilms tumor have bilateral involvement, none of our cases within the defined study period was diagnosed with bilateral Wilms tumor, possibly for the relatively short study duration and small sample number.

Our study described the stages of Wilms' tumor in pediatric age as per the NWTS Group group staging system, and as seen in Figure 1 that showed that we found the higher advanced stages(stage III and IV) were unfortunately commoner than those percentages in NCI data [2] as they are accounting for 31.8% and 22.7% respectively in our study, while it represents 21% for stage III and 11% for stage IV in NCI data, though our results were similar to those obtained from the same region reported more than 20 years ago by Mulhim [4] when he reported more than 50% of his study patients were on stage III and IV (44%, 6%) respectively. The reported joint presentation with advanced stages may indicate that the families are still not much aware of the need for early medical advice to reach specialized centers for early diagnosis and treatment. Searching on the data from some middle east area we found that advanced stages III and IV were also reported by one study from children cancer institute in Lebanon by Wisam et al. [3] that done on the period from 2002 to 2013 while in another study from Egypt done in unit of Kasr El-Aini center [5] of radiation oncology and nuclear medicine (NEMROCK). They found that earlier stages were typical (Table 1).

Histopathologically, 68.2% (15 cases) of our patients had favorable, and 9% (2 cases) had anaplastic histology, while the rest of the cases had reported as mixed histology, These findings are very close to study from

Stages	Frequency	Percent (%)
Stage I	6	27.30%
stage II	4	18.20%
Stage III	7	31.80%
Stage IV	5	22.70%
Total	22	100.00%

Table 1: Earlier stages.

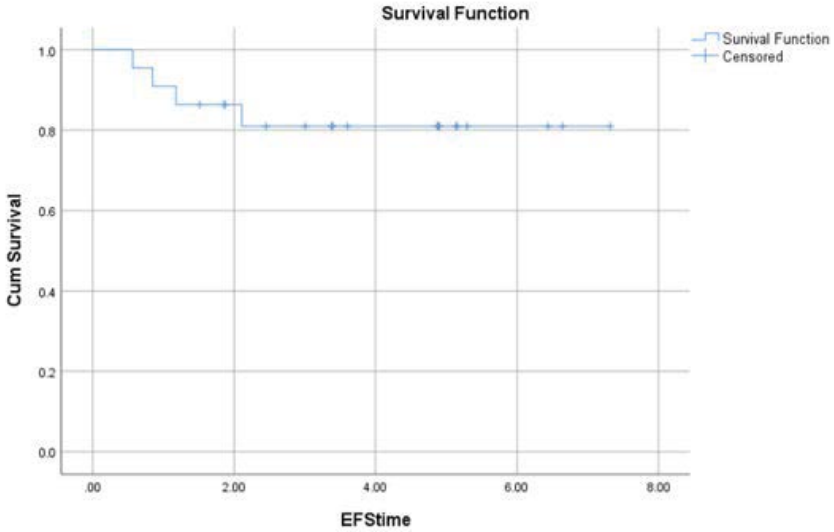

Figure 1: Higher advanced stages (stage III and IV).

China on 2012 by Yao et al. [6] on which they found (68.7%) of their cases of had favorable histology and quite high unfavorable (anaplastic) histology of (31.3%) that 3 times of higher than our study and then that known in NCI data. However, in another study from Jordan, they reported the Favourable histology accounted for 86.9% in their A Single Institution 10-Year Experience by Mustafa [7]; this indicates the unpredictable wide variability in the histopathologic findings between the different countries.

In Saudi Arabia, reports from Saudi cities such as Riyadh and Dammam indicated prevalence rates of 51.3% and 52.0% [8-10], respectively, in our study showed parent consanguinity noticed in 27.3% with family history of other types of malignancies reported in (41%) of the total patients. CA colon was the most reported malignancy in families (33%-44%), but none of them had renal cancer.

Approximately 10% of children with Wilms tumor have been reported to have a congenital anomaly as per NCI data, in the present study we found that 18% of the cases had identifiable syndromes with WAGAR syndrome been the most common with 9.1%, in one national study from military hospital -Riyadh -Saudia Arabia done from 1983 to 1995 by El Mouzan et al. [11]. They found that the prevalence of associated congenital abnormalities was as high as 20%. Those results are quite comparable to a study done by Dumoucel et al. [2] published in Pediatr Blood Cancer 2014, in which they found that the clinically identified malformations and predisposition syndromes were observed in (17.6%) of patients of Wilms tumor [3]. Another study by Naguib addressed the consanguinity and significant genetic disorders in Saudi children; their data suggest a significant role of parental consanguinity in congenital heart diseases [12]. However, a relationship between consanguinity and other genetic diseases could not be established in that study, though that study was relatively of a short duration for two years, however a significant number with a total of 11,554 mothers participate in it. The relation between the high consanguinity rate and the increased associated with congenital abnormalities maybe need to be studied and confirmed by further national studies.

Abdominal ultrasound (US) examination is the initial imaging study that done almost in all our cases (100%), US abdomen was reported to be a very simple important tool in diagnosing wilms tumor as it confirms the presence of a renal mass without the risk of ionizing radiation in addition to the value of preliminary assessment of the contralateral kidney as well as the presence of metastatic disease and the presence of a tumor thrombus. However, magnetic resonance imaging (MRI) or computerized tomography (CT) are key tests to obtain in order to gain all necessary information for diagnosis and staging. Chest CT is the standard modality for thoracic metastatic assessment [13].

The therapy consisted of surgery, radiation, and chemotherapy according to the NWTS protocols. In the present study, tumor relapse was seen in 18.2% of the entire group, highest in stage III (28.5%); However 75% of the relapsed cases had favorable histology, and all the relapses occurred as early as 20 months from completion of therapy. A 2nd CR could be achieved in 50% of them, and as shown in Table 2, we found that Patients who relapsed >12 months after 1st CR had achieved 2nd CR and maintain remission status till the time of study reporting compared to 0% survival in those who relapsed <12 months after 1st CR. So in this study, the early relapse with distant spread out of the tumor bed carries a worse prognosis with a high mortality rate.

Comparable study from Egypt Naguib et al. [12] reported at the National Cancer Institute (NCI) in Cairo University between January 2002 and December 2004 that relapse after remission occurred in 14%. A 2nd CR could be achieved by 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

Case number	Stage	Histology	Chemotherapy protocol	Relapsed time from end of therapy	Relapse site	Outcome	Remarks
1	I	FH	EE4A	20 months	Tumor bed	Remission	-
2	III	Focal anaplasia	DD4A	13 months	Tumor bed	Remission	-
3	III	FH	DD4A	During therapy	Tumor bed liver	Died	-
4	IV	FH	DD4A	1 month	Tumor bed liver lung	Died	2ry AML

Table 2: Chemotherapy stage after the 1st CR.

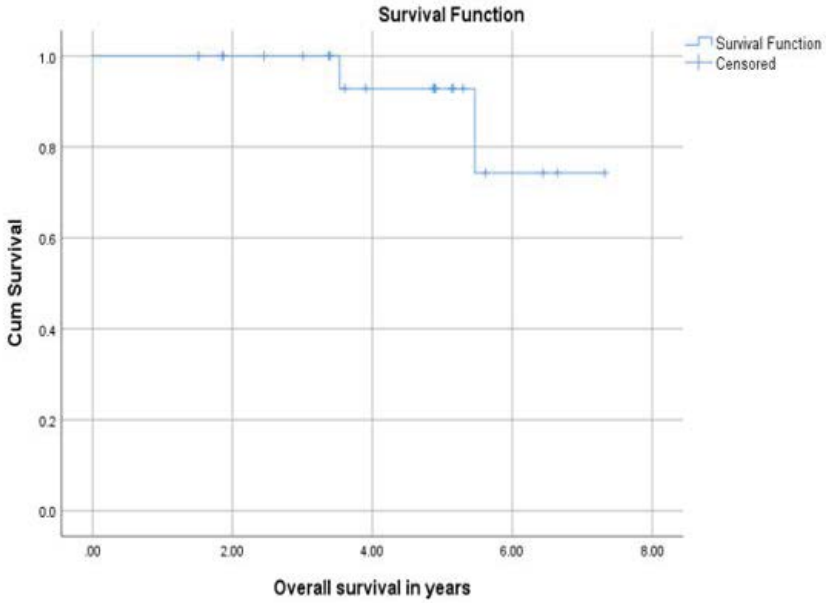

Figure 2: Overall survival in years.

to 0% in those who relapsed <12 months after 1st CR. Internationally the NWT5 data stated Wilms tumor recurs in 15-20% of cases [14].

The event-free survival in this study was calculated as the time from date of diagnosis to relapse or/and death and estimated as 81% (Figure 1), and the overall survival (OS) time was calculated as the time from diagnosis to death and estimated as 91% (Figure 2). Comparing our results with those of the same region data that been done by Mulhim [4]. About 20 years earlier it showed mild inferior outcome with overall survival rate of 88.8%. This may indicate a better improvement in diagnosing and managing Wilms tumors that include a multidisciplinary team approach with combined therapeutic approaches (surgery, radiotherapy, and chemotherapy) as well as the provision of supportive care. This study has limitations such as Lacking of cytogenetics data in most of the cases is thought to be a significant limitation for completing the biological data of the Wilms tumor disease.

The period defined for the study is not long enough for the estimation of the five years OS for all the subjects. The retrospective nature of the study with a small sample size and representing the experience of a single institution.

Conclusion

Although our national data for overall survival is going well along with the international figures, yet still significant number of the cases presented in advanced staged with relatively higher relapses rate than international rates indicating the need for more national efforts and plans involving the importance of collaboration and coordination between different levels of health service provision starting from primary care services all the way to the tertiary care centers.

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