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Surgical outcomes with the determining prognostic factors of Wilms Tumors in Oman - A population-based cohort study

Abstract

Introduction: Wilms tumor (WT) forms 95% of pediatric renal malignancy. Five-year survival rates have dramatically improved and now approach 90 percent. We conducted this research with the specific research question of the recurrence rate, survival rate post treatment and post-surgical complications in WT.

Methods: This is a retrospective 10-year study done between January 2010 and August 2022. The study included all patients with WT who underwent treatment in The Royal Hospital, Oman; and had a minimum of one year of follow up. Patients with incomplete hospital records were excluded. Data was retrieved from the hospitals electronic system with ICD code. The retrieved master data sheet was analyzed for patients' demographics and outcome parameters.

Results: Out of the 47 cases, 40 were confirmed cases of Wilms tumor with predominance of males (62.5%). The mean age at presentation was 2.85±1.79 years. Abdominal lump was the most common presentation; Out of the total patients, nine had distant metastasis (most commonly the lungs). There were five recurrences in WT patients and two deaths. There was one case of secondary malignancy (synovial sarcoma). The post-operative complication rate is 17.5%.

Conclusion: 5-year Overall Survival was 92.3% (95% CI: 82.1% -102.5%) and 5-year Event (recurrence) Free Survival was 82.1% (95% CI: 68.0% - 96.3%). Post-surgical complications were seen in 17.5% of the patients. There was recurrence in 12.5% of patients. The study provides data for WT in Oman and can be used for reference comparison done in future analysis and in policy making resource distribution and planning of oncology services.

Keywords: wilms tumor, epidemiology, survival, recurrence, complications, outcome

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Introduction

Wilms tumor (WT) accounts for 5% of all childhood malignancies. It is the most common renal malignancy in children accounting for approximately 95 percent of all cases.[1–3] Two-thirds of cases of Wilms tumor are diagnosed before five years of age. Ten percent of cases, Wilms tumor occurs as a part of a multiple malformation syndromes, including WAGR syndrome (syndrome of Wilms tumor, aniridia, genitourinary anomalies, intellectual disability and renal impairment), Denys-Drash syndrome, and Beckwith-Wiedemann syndrome.[4] The treatment of Wilms tumor involves multimodality therapy with chemotherapy, radiation, and surgery.[5] Five-year overall survival rates have dramatically improved with multimodal therapy and now approach 90 percent.[6,7] Several prognostic factors at the time of initial diagnosis are associated with an increased risk of tumor recurrence or death and include: Tumor histology, Tumor stage, Molecular and genetic markers, and age.[8] Surgical excision is a crucial part of treatment plan and is curative for early stages. For late-stage disease surgery is complementing for disease free survival. In Oman, Wilms tumor is the most common renal malignancy and we conducted this study with the following objectives: to study the clinical characteristics, to study the prognostic factors affecting disease outcomes, to determine the 5-year overall survival and event free survival for treated patients with WT in Oman.

Patients and methods

This is a single center retrospective cohort study done between January 2010 and August 2022. Ethical approval for retrospective retrieval of patients' data was taken from the hospital review board. The inclusion criteria were all patients with confirmed diagnosis of Wilms tumor referred to The Royal Hospital, Oman; and underwent treatment with entry in hospital records. All included patients had minimum of one year of follow up. Some patients who received treatment elsewhere but later had chemo-radiation in our hospital were also included. Patients with incomplete hospital records and lost to follow up were excluded. The patient data was retrieved from the electronic health records of the hospital. ICD codes of Wilms tumor C64 and C64.1 were used to filter eligible patients. The retrieved master data sheet was analyzed. SPSS version 26 was used for data analysis. Survival was assessed using Kaplan Meier survival functions, as well as proportions with 95% confidence intervals and the associations were assessed by Chi-square and log-rank test along with KM curves. P value less than 0.05 was considered significant. Last follow up of all the patients was recorded to know the surviving patient's status. The general management protocol for Wilms tumor in our institute is as follows, on clinical suspicion the patients are evaluated with initial ultrasound followed by CECT. Staging of the tumor is done from imaging and resectability is assessed. If the tumor

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is small in size, with no features of metastasis, no vascular extension and patient fit for surgery then the patient is handed over to the surgical team for primary excision. However, if the tumor is stage III or above with large mass and metastasis then a guided needle biopsy is performed by the radiologist to characterize the histology and the patient is then subjected to neoadjuvant chemotherapy. The patient will then come back to surgeon once chemotherapy is completed and repeat imaging shows features of resectability. Once the resected tumor staging is done based on intraoperative findings the decision is taken in tumor board for adjuvant treatment with chemo-radiation. After completion of treatment, the patient is subjected to routine surveillance with duration of follow up depending on the initial tumor grade and risk assessment.

Results

A total of 47 records were retrieved from the hospital archives. Out of these seven were excluded because the final diagnosis was non-Wilms renal tumor. The remaining 40 patients were analyzed. Of these, 25 (62.5%) were males and 15 (37.5%) were females. The age at presentation ranged from 0.4 to 7 years (Mean age at diagnosis was 2.85±1.79). The mean age at diagnosis among females was higher (3.37±1.92) compared to males (2.53±1.67). The site of the Wilms tumor was in the right kidney in 19 patients (47%), left kidney in 18 patients (45%), bilateral in two patients (5%), and extrarenal (originating from the left ovary) in one patient (3%). Regional distribution of these patients was as follows: 30% were from the North Batinah, 22.5% were from Muscat, 12.5% were from the Dakhiliyah, 12.5 % were from Dhofar, 7.5% were from the South Batinah, 7.5% were from the Dhahirah, and 2.5% were from the South Sharqiyah region.

Abdominal lump was the most common presenting feature (31 patient 77.5%). There was incidental detection on imaging in seven patients (17.5%) which was a clinical surprise (Table 1). One patient had left side tumor in a horseshoe kidney. Associated syndromes and diseases included one case of Beckwith-Wiedemann syndrome and two cases of acquired VWD..

Table 1 Characteristics of Omani children with Wilms tumor treated in the Royal Hospital between 2010 and 2022

Characteristic	n (%)
Gender	
a) Male	25 (62.5%)
b) Female	15 (37.5%)
Age in years	
a) Mean	2.85±1.79
b) Range	0.4 to 7
Wilms Tumor site	
a) Right kidney	19 (47%)
b) Left kidney	18 (45%)
c) Bilateral kidneys	2 (5%)
d) Extra renal (ovarian)	1 (3%)
Clinical presentation	
a) Abdominal lump	31 (77.5%)
b) Incidental detection on imaging	7 (17.5%)
c) Hematuria	5 (12.5%)
d) Hypertension	1 (3%)
e) Low urine output	1 (3%)
Associated syndromes	
a) Beckwith-Wiedemann syndrome	1 (3%)
b) Acquired VWD	2 (5%)

CT evaluation was done as per protocol and 17 patients (42.5%) had stage 1 disease, five patients (12.5%) had stage 2 disease, eight patients (20%) had stage 3 disease, eight patients (20%) had stage 4 disease and two patients (5%) had stage 5 disease. Vascular involvement was seen in five out of the 40 patients (12.5%), two of them involved renal vein only and three of them involved renal vein extending to infra-hepatic IVC. Nine out of the 40 patients with Wilms tumor (22.5%) had distant metastasis (all of them had pulmonary metastasis, one had mediastinal and pericardial metastasis, and one had liver metastasis). (Table 2)

Table 2 Disease management (investigations, hitolopathology and treatment)

Management	n (%)
Staging (CT scan)	
a) Stage 1	17 (42.5%)
b) Stage 2	5 (12.5%)
c) Stage 3	8 (20%)
d) Stage 4	8 (20%)
e) Stage 5	2 (5%)
Vascular involvement (CT scan)	5 (12.5%)
Distant metastasis (CT scan)	9 (22.5%)
a) Pulmonary metastasis	9 (22.5%)
b) Mediastinal and pericardial metastasis	1 (3%)
c) Liver metastasis	1 (3%)
Type of surgery	
a) Nephrouretrectomy	36 (90%)
b) Debulking	2 (5%)
c) One side nephrouretrectomy and the other side nephron sparing surgery	2 (5%)
Post-operative histology	
a) Favorable	33 (82.5%)
b) Unfavorable	7 (17.5%)

Preoperative biopsy was done in 18 patients (45%), all were consistent with WT and correlated with the final histology. Preoperative chemotherapy was given to 18 patients with an average of five cycles per patient. Of these, 14 had reduction in the tumor size and went for surgery.

Surgical excision was done for all 40 patients. Mean age at surgery was 3.1±0.324 years. Of all the operated patients, 31 patients (77.5%) underwent surgery at the Royal Hospital (RH), seven patients (17.5%) underwent surgery abroad and two underwent first surgery in RH and the second surgery (NSS) abroad. Regarding type of surgery, 36/40 patients had nephrouretrectomy (two of them along with IVC thrombectomy), 2/40 patients had debulking, 2/40 had one side nephrouretrectomy and the other side nephron sparing surgery (NSS).

The post-operative course was uneventful for 33 patients. Perinephric urinoma was seen in two patients whom underwent NSS. Five patients had intestinal obstruction and all of them were managed conservatively. The overall post-operative complication rate was 17.5%.

Secondary malignancy was seen in one patient in the form of metastatic synovial sarcoma eight years after the initial diagnosis. He was treated initially with surgery and chemoradiation for stage 4 disease.

The final histology after surgery was favorable in 82.5% of the patients and unfavorable in 17.5% of the patients. Unfavorable histology is defined by the presence of diffuse anaplasia or blastemal predominant histology after the administration of neoadjuvant chemotherapy. The tissues were also examined for any genetic

linkage. Isolated WT1 gene was reported in 26 patients. One of the patients expressed the P53 gene. Other genes like AE1/AE3 were of lower frequencies.

The median duration of follow up (IQR) of all the patients is 6 (8-3) years. There is recurrence in follow up in five patients (12.5%), four of them were stage 3 disease and higher. One of them had P53+WT1 expression. Two of them had diffuse anaplasia on histology. Four out of the 5 patients had complete excision at first surgery. One patient had metastasis in mediastinum with thoracotomy done for clearance, this patient is alive at last follow up. One had pulmonary and liver recurrence. Three patients had local relapse. One patient who underwent nephron sparing surgery developed metachronous tumor on the contralateral kidney three months after the initial surgery. (Table 3)

Table 3 Post-operative complications and disease outcomes during the follow up period of Omani children treated in the royal hospital

Outcome	n (%)
Post-operative complications	7 (17.5%)
a) Perinephric urinoma	2 (5%)
b) Intestinal obstruction	5 (12.5%)
Secondary malignancy (metastatic synovial sarcoma)	1 (3%)
Disease recurrence	5 (12.5%)
a) Local relapse	4 (10%)
b) Pulmonary and liver recurrence	1 (3%)
c) Mediastinal relapse	1 (3%)
Mortality	2 (5%)
5-year Overall Survival	92.3%
5-year Event (recurrence) Free Survival	82.1%

There were two patients (5%) who died in this series. Both of them were stage 3 disease and both had diffuse anaplasia on histology. One died due to chemotherapy related complications seven months after surgery (febrile neutropenia, hemorrhagic cystitis requiring cystostomy and clot evacuation twice, and septic shock leading to multiorgan failure) while the other patient died due to tumor related complications 17 months after surgery and he developed recurrence as well during this period.

The 5-year Overall Survival was 92.3% (24/26) (95% CI: 82.1% - 102.5%) and the 5-year Event Free Survival was 82.1% (23/28) (95% CI: 68.0% - 96.3%) (This is represented in the Kaplan Meier curve in Figure 1).

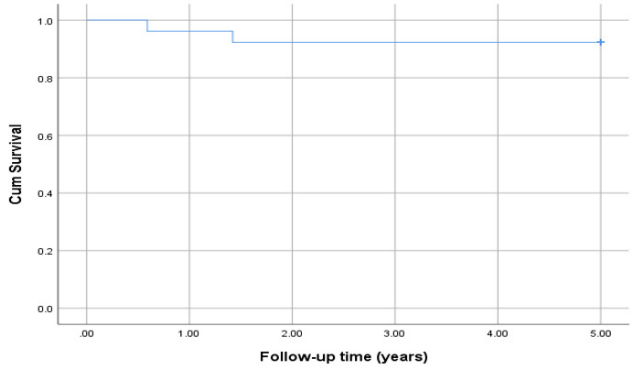

Figure 1 Kaplan-Meier curve for overall five-year survival.

The study duration of 2010 to 2022 included the pandemic phase due to COVID19. The treatment of these cases was unaffected because oncology patients were not held back and were treated on priority during this time.

Discussion

Wilms tumor is primarily a sporadic disease; Familial Wilms tumor is rare and is associated with mutations in the BRCA2 or TP53 genes (Li-Fraumeni syndrome). In 10 percent of cases, Wilms tumor occurs as a part of a multiple malformation syndrome, including WAGR syndrome (syndrome of Wilms tumor, aniridia, genitourinary anomalies, intellectual disability and renal impairment), Denys-Drash syndrome, and Beckwith-Wiedemann syndrome (BWS).[4] In our study, Associated syndromes with Wilms tumor was one case of Beckwith-Wiedemann syndrome. That's why, screening is recommended for high-risk patients (eg, children with BWS, WAGR syndrome or history of familial WT) by using serial abdominal ultrasonography.[9]

The definitive diagnosis of Wilms tumor is made by histologic confirmation at the time of either surgical excision or biopsy. Abdominal ultrasonography is typically the initial study performed for evaluation of abdominal mass. In patients with a suspected renal tumor, Doppler ultrasonography can be performed to detect tumor infiltration of the renal vein and inferior vena cava and to assess patency of blood flow. Contrast-enhanced CT or magnetic resonance imaging is recommended to further evaluate the nature and extent of the mass, including evidence of preoperative rupture or ascites. Preoperative imaging helps the surgeon determine whether the tumor is operable at diagnosis. Patients with any of the following findings generally undergo biopsy and preoperative chemotherapy rather than initial primary nephrectomy[10]: (Tumor thrombus above the level of the hepatic veins, pulmonary compromise from massive tumor or extensive pulmonary metastases, resection requiring removal of contiguous structures other than adrenal gland, surgeon judges that attempting nephrectomy would result in significant morbidity, tumor spill, or residual tumor).

The presented series is a review of patients who have undergone surgical treatment at an apex institute of Oman and represents the national data over 12-year period. This is the first ever report from this region regarding Wilms tumor survival and outcomes. The presented data provides several insights into the clinical characteristics of the Wilms tumor patients. The interesting figures are the regional preponderance with 30% of patients coming from North Batinah region and can be attributed to its higher population. The presence of abdominal lump is the most common presentation which is same as reported in literature. Sixteen patients out of 40 had either Stage III or Stage IV disease which can be taken as delayed diagnosis. The mean age at diagnosis was 2.85±1.79 which is consistent with what is reported in literature (22415585).

Early complications after surgery are generally related to therapy and include adverse effects of chemotherapeutic drugs and surgical complications such as bowel obstruction, hemorrhage, and wound infection.[11] Patients who received more intense chemotherapy and radiation therapy are more likely to have late complications. These include kidney impairment; cardiotoxicity; hepatotoxicity; orthopedic, growth, and pulmonary problems; infertility; and secondary malignancies.[12]

In our study, the early complications were five cases of intestinal obstruction and two with urinary leak. All cases of intestinal obstruction were treated conservatively and the cases of perinephric urinoma required intra-abdominal drain, nephrostomy and/or JJ stenting. The late complications included one case of secondary malignancy in the form of metastatic synovial sarcoma eight years after the initial diagnosis.

In one study conducted between 1969 and 1995, the overall survival rate was 84 % through 2002.[13] Ninety-one percent of deaths occurred early within the first five years of diagnosis and were primarily due to the original tumor (94 percent). In contrast, the causes of late deaths were evenly distributed between the late effects of therapy (39 percent) and tumor-related mortality (40 percent).

In our study the recurrence rate is 12.5% and mortality rate is 5%. The 5-year Overall Survival was 92.3% (24/26) (95% CI: 82.1% - 102.5%) and the 5-year Event Free Survival was 82.1% (23/28) (95% CI: 68.0% - 96.3%). 1-year overall survival was significantly affected by tumor histology (p= 0.03) but not tumor stage. 1-year event free survival was not significantly affected by tumor stage or tumor histology (p > 0.05). Patients with unfavorable histology were 4.7 times more likely to develop poor outcome (Relative risk 95% CI: 1.19 to 18.68).

There were some limitations in this study due to the retrospective nature, Patients treated abroad cause data irregularities, and the small sample size (n=40) compared to the other series in literature. But considering the relatively smaller national population of 4.6 million this is an adequate sample for assessment of disease which can be used for policy making and planning of healthcare. In addition, lack of proper protocol (COG or SIOP).

Conclusions

This study was done with the aim of defining the clinical characteristics of Wilms tumor patients and to know the 5-year OS and EFS rates, post-surgical complications, recurrence, and mortality in the treated patients with WT in Oman. With the presented data it is clear that the 5-year Overall Survival was 92.3% and the 5-year Event Free Survival was 82.1% with 17.5% of early post-surgical complication rate. There was recurrence in 12.5% of patients. The mortality rate is 5%. The study provides data for overall healthcare burden from Wilms tumor and can be used for reference comparison done in future analysis. We suggest that a national registry for the Wilms tumor should be established for accurate nationwide data and future analysis. This will greatly help in policy making, resource distribution and planning of oncology services.

Acknowledgments

None.

Authors' contribution

SAK and MSB were responsible for data collection. SAK analyzed the data. SAK and RPK drafted the manuscript. All the authors reviewed and approved the manuscript before submission.

Ethical approval

Ethical approval for the retrospective retrieval of patients' data was taken from the Royal Hospital review board (Ref no: MoH/CSR/23/27512).

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Conflicts of interest

The authors declare no conflicts of interest.

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