Urology Research, 2023, Volume 1, Issue 1
https://ojs.bbwpublisher.com/index.php/UR

Factors Associated with Survival in Wilms Tumor Patients

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Abstract: *Introduction:* Wilms tumor is the second most common abdominal tumor in the pediatric age group and accounts for more than 90% of renal tumors in pediatrics. Even though the described survival rate is greater than 90%, we found that it only reaches 70% among our patients. Therefore, we aim to evaluate which are the factors associated with these unfavorable results, in order to implement measures to improve the survival of our patients. *Methods:* An observational, cross-sectional study was conducted in two high-level care centers, which included a sample of 84 patients under 15 years of age, diagnosed with Wilms tumor. *Results:* Factors significantly associated with an increased likelihood of death were failure to complete the chemotherapy protocol (odds ratio [OR] = 34; 95% confidence interval [CI] = 3.7–312; *P* = 0.000) and tumor recurrence (OR = 35.7; 95% CI = 6.9–184; *P* = 0.000). Other minor factors with certain impact were bilateral presentation (OR = 4.1; 95% CI = 0.6–5.5; *P* = 0.147), surgical complications (OR = 3.2; 95% CI = 0.7–14.6; *P* = 0.136), lymph node involvement on CT scan (OR 2.4; 95% CI 0.7–8.4; *P* = 0.139), and distant metastases (OR = 2.5; 95%CI = 0.7–9; *P* = 0.143). *Discussion:* The survival of our patients with Wilms tumor is lower than that reported in literature is associated with factors like failure to complete chemotherapy, recurrence, and the need for bilateral surgery.

Keywords: Wilms tumor; Nephroblastoma; Surgery; Urology; Surgical oncology; Cancer survivors

Online publication: June 14, 2023

1. Introduction

Wilms tumor is the second most common abdominal tumors in the pediatric age group and accounts for more than 90% of renal tumors in pediatrics [1]. In the United States, Wilms tumor has an incidence rate of 8.1 cases per million per year [2,3] and in Colombia, the National Cancer Institute reports a frequency of 9.3% for nephroblastoma, with 3.2 cases per million inhabitants per year [4].

Survival in patients with Wilms tumor has improved in recent decades in developed countries, thanks to the studies done on multimodal chemotherapy, the development of surgical techniques, and the recognition of the role of radiotherapy, which increased from 73% in 1975 to 93% in 2012, and currently reaching 95% [5]. In one study, it was found that 108 months after diagnosis, survival is 71% and that the average relapse-free survival time is 97 months [5].

The aim of this study was to evaluate which factors are associated with unfavorable survival outcomes,

in order to implement measures to improve survival in our patients with Wilms tumor.

2. Methods

We conducted an observational, cross-sectional study that included a sample of 84 patients under 15 years of age that were diagnosed with Wilms tumor and were treated in the pediatric hemato-oncology department of two high-level care hospitals in Medellín, Colombia, between January 1, 2005, and May 31, 2018.

To define the factors associated with two-year survival, we evaluated sociodemographic variables (place of residence and sex), clinical variables (clinical presentation, laterality, history of malformation), pathological variables (tumor pathology, previous biopsy, presence of necrosis, and histology), surgical variables (resectability, procedure performed, bilaterality, tumor containment, and complications), chemotherapy (protocol used, complete termination of the protocol), radiotherapy, recurrence, and tomographic findings. As for data collection, medical records from the pediatric surgery, oncology, and pediatric nephrology department were reviewed.

As for statistical analysis, a database was constructed in Excel, with the relevant validation rules to ensure data quality, and calculations were made using SPSS 22.0. Qualitative variables were presented with absolute and relative frequencies and quantitative variables with measures of central tendency. Percentages were calculated based on the number of patients who had data on each variable.

Bivariate analysis was performed using contingency tables with a 5% independence test, to measure the relationship of the variables with two-year survival. Adjusted odds ratios (OR) were obtained using logistic regression analysis. Several models were constructed with the epidemiologically important variables, also noting the contribution of independent variables that were statistically significant with a $P < 0.25$. Independent variables whose correlations suggested collinearity were excluded from the analysis and tests were done to assess the fit through the likelihood ratio.

Informed consent: In accordance with Resolution 008430 of 1993 of the Colombian Ministry of Health, the research is classified as low risk because it is based on the review of data from medical records, so informed consent was not required. Prior authorization was requested from the research and ethics committees of both institutions, which approved the research.

3. Results

A total of 84 children with Wilms tumor were evaluated at the Pablo Tobón Uribe and San Vicente Fundación hospitals between 1 January 2005 and 31 May 2018. Only 61 of them could be followed up to establish survival at two years after diagnosis, which was 70.5 % ($n = 43$).

Forty-eight patients (57.8%) were found to be from Medellín and 43 (51.2%) were male. In 61 cases, (73.5 %) the reason for consultation was the symptom of abdominal mass, accompanied by other symptoms; the involvement was unilateral and there was no history of congenital malformations in 78 patients (92.9 %). In addition, pathology was predominantly blastemal in 23 cases (53.5 %), necrosis in eleven (17.7 %), and unfavorable histology in seven (8.8 %), as shown in **Figure 1**.

Variable	Categoría	n	%
Lugar de residencia	Medellín y área metropolitana	48	57,8
	Antioquia	25	30,1
	Otros departamentos	10	12,0
	Sin dato	1	
Sexo	Masculino	43	51,2
	Femenino	41	48,8
Presentación Clínica	Masa abdominal y otra sintomatología	61	73,5
	Dolor abdominal u otra sintomatología	22	26,5
Lateralidad	Bilateral	6	7,1
	Unilateral	78	92,9
Antecedente de malformación	Presencia de malformación	6	7,1
	Sin malformación	78	92,9
Patología tumoral	Tumor de Wilms o nefroblastoma con predominio blastemal	23	53,5
	Tumor de Wilms o nefroblastoma sin predominio blastemal	20	46,5
Biopsia previa	Si	16	25,8
	No	46	74,2
	Sin dato	22	
Patología con presencia de necrosis	Con necrosis	11	17,7
	Sin necrosis	51	82,3
	Sin dato	22	
Histología	Histología desfavorable	7	8,8
	Histología favorable	73	91,2
	Sin dato	4	

Figure 1. Characteristics of the patients with Wilms tumor in the study population

Regarding the surgical aspects (**Figure 2**), the tumor was found to be respectable in 51 (60.7 %) patients. Unilateral nephrectomy was performed in 78 cases (96.3 %), and in 51 (65.4 %) of these, the approach was unilateral prechemotherapy nephrectomy. Only three (3.7 %) patients required bilateral approach and ten (12.3 %) had complications during surgery.

Variable	Categoría	n	%
Resecabilidad quirúrgica	Tumor irresecable	33	39,3
	Tumor resecable	51	60,7
Lateralidad de la cirugía	Unilateral	78	96,3
	Bilateral	3	3,7
	Sin dato	3	
Momento de la nefrectomía unilateral	Previa a quimioterapia	51	65,4
	Posterior a quimioterapia	27	34,6
Contención tumoral	Tumor no contenido	35	43,2
	Tumor contenido	46	56,8
	Sin dato	3	
Complicaciones quirúrgicas	Cirugía con complicaciones	10	12,3
	Cirugía sin complicaciones	71	87,7
	Sin dato	3	
Protocolo de quimioterapia*	NWTS	58	70,7
	SIOP	24	29,3
	Sin dato	2	
Protocolo completo de quimioterapia	No	11	16,2
	Si	57	83,8
	Sin dato	16	
Recibió radioterapia	Si	38	46,9
	No	43	53,1
	Sin dato	3	
Presento recidiva	Si	20	27,4
	No	53	72,6
	Sin dato	11	
Presencia de trombo mural en la tomografía	Con trombo tumoral en tomografía	8	10,4
	Sin trombo tumoral en tomografía	69	89,6
	Sin dato	7	
Compromiso de ganglios linfáticos en tomografía	Compromiso ganglios linfáticos	23	31,1
	Sin Compromiso ganglios linfáticos	51	68,9
	Sin dato	10	
Presencia de metástasis a distancia	Presencia de metástasis a distancia	17	22,1
	Ausencia de metástasis a distancia	60	77,9
	Sin dato	7	
Sobrevida a dos años	Muerto	18	29,5
	Vivo	43	70,5

* NWTS: *National Wilms' Tumor Study*; SIOP: *Societe Internationale D'oncologie Pediatrique*

Figure 2. Treatment of patients with Wilms tumor in the study population

Variables		Muerto		Vivo		OR	$IC_{95\%}$	p
		n	%	n	%			
Lugar de residencia	Medellín y área metropolitana	10	32,3	21	67,7	1		
	Antioquia	5	26,3	14	73,7	1,3	0,4-4,7	0,657
	Otros departamentos	2	20,0	8	80,0	1,9	0,3-10,7	0,464
Sexo	Masculino	8	27,6	21	72,4	0,8	0,3-2,5	0,754
	Femenino	10	31,3	22	68,8	1		
Presentación clínica	Masa abdominal y otra sintomatología	15	30,6	34	69,4	1,2	0,3-5,1	0,827
	Dolor abdominal u otra sintomatología	3	27,3	8	72,7	1		
Lateralidad	Bilateral	3	60,0	2	40,0	4,1	0,6-27	0,147
	Unilateral	15	26,8	41	73,2	1		
Antecedente de malformación	Presencia de malformación	1	20,0	4	80,0	0,6	0,06-5,5	0,535
	Sin malformación	17	30,4	39	69,6	1		
Patología tumoral	Tumor de Wilms o nefroblastoma con predominio blastemal	5	33,3	10	66,7	3,2	0,5-20,4	0,195
	Tumor de Wilms o nefroblastoma sin predominio blastemal	2	13,3	13	86,7	1		
Biopsia previa	Si	4	30,8	9	69,2	1,2	0,3-5	0,518
	No	9	26,5	25	73,5	1		
Patología con presencia de necrosis	Con necrosis	1	14,3	6	85,7	0,4	0,05-4,1	0,414
	Sin necrosis	10	27,8	26	72,2			
Histología	Histología desfavorable	1	20,0	4	80,0	0,7	0,07-6,8	0,614
	Histología favorable	14	26,4	39	73,6			
Resecabilidad quirúrgica	Tumor irresecable	7	26,9	19	73,1	0,8	0,3-2,5	0,703
	Tumor resecable	11	31,4	24	68,6	1		
Momento de la nefrectomía unilateral	Previa a quimioterapia	11	31,4	24	68,6	2,6	0,6-10,7	0,178
	Posterior a quimioterapia	3	15,0	17	85,0			
Cirugía bilateral	Bilateral	2	66,7	1	33,3	5,9	0,5-69,7	0,181
	Unilateral	14	25,5	41	74,5			
Contención tumoral	Tumor no contenido	7	31,8	15	68,2	1,4	0,4-4,5	0,573
	Tumor contenido	9	25,0	27	75,0			
Complicaciones quirúrgicas	Cirugía con complicaciones	4	50,0	4	50,0	3,2	0,7-14,6	0,136
	Cirugía sin complicaciones	12	24,0	38	76,0			
Protocolo de quimioterapia	Protocolo SIOP	4	21,1	15	78,9	0,5	0,1-2	0,364
	Protocolo NWTS	13	32,5	27	67,5			
Protocolo completo de quimioterapia	No	8	88,9	1	11,1	34	3,7-312,1	0,000
	Si	8	19,0	34	81,0			
Recibió radioterapia	Si	7	25,9	20	74,1	0,8	0,3-2,5	0,708
	No	10	30,3	23	69,7			
Presento recidiva	Si	11	78,6	3	21,4	35,7	6,9-184,2	0,000
	No	4	9,3	39	90,7			
Presencia de trombo mural en la tomografía	Con trombo tumoral en tomografía	3	42,9	4	57,1	2,1	0,4-10,5	0,314
	Sin trombo tumoral en tomografía	13	26,5	36	73,5			
Compromiso de ganglios linfáticos en la tomografía	Con compromiso	7	43,8	9	56,3	2,4	0,7-8,4	0,139
	Sin compromiso	9	24,3	28	75,7			
Presencia de metástasis a distancia	Presencia de metástasis	6	46,2	7	53,8	2,5	0,7-9,1	0,143
	Ausencia de metástasis	11	25,6	32	74,4			

Figure 3. Factors associated with two-year survival in patients diagnosed with Wilms tumor

Through CT scans, 23 patients (31.1 %) were found to have lymph node involvement, 17 (22.1 %)

had distant metastases, and 8 (10.4 %) had mural thrombus. In relation to chemotherapy, the most commonly used protocol was the National Wilms Tumor Study (NWTS) in 58 patients (70.7 %). Fifty-seven patients (83.8%) completed the protocol and 20 (27.4%) had tumor recurrence.

Figure 3 shows the factors that were significantly associated with an increased fatality: failure to complete the chemotherapy protocol (OR = 34; 95% CI = 3.7–312; *P* = 0.000), and tumor recurrence (OR = 35.7; 95% CI = 6.9–184; *P* = 0.000). Other factors that increased this probability without being statistically significant but had certain impact were bilateral tumor (OR = 4.1; 95% CI = 0.6–5.5; *P* = 0.147), surgical complications (OR = 3.2; 95% CI = 0.7–14.6; *P* = 0.136), lymph node involvement on CT scan (OR = 2.4; 95% CI = 0.7–8.4; *P* = 0.139), and distant metastasis (OR = 2.5; 95% CI 0.7–9; *P* = 0.143). The other characteristics assessed were not significantly associated with fatality.

The final logistic regression model was composed of the following variables: failure to complete chemotherapy protocol (OR = 11.2; 95% CI = 0.4-329.9; *P* = 0.161), tumor recurrence (OR = 71.5; 95%CI 6.05–845; *P* = 0.011) and need for bilateral surgery (OR = 28; 95%CI = 1.2–1244; *P* = 0.041). It was calculated that 71% of the variability in survival was explained by these three factors.

4. Discussion

Prognostic factors for Wilms tumor according to the Children's Oncology Collaborative Group (COG) are tumor stage, histology, age, tumor weight, lung nodal response, and loss of heterozygosity (LOH) of 1p and 16q, while those of the International Society of Pediatric Oncology (SIOP) include age, histology, tumor volume, and response to therapy. Response to chemotherapy has been defined as decrease in tumor size, change in histology, and in stage IV cases, disappearance of metastases.

With respect to age, children younger than 2 years have better results compared to those aged 2–4 years (95 % event-free survival at 5 years vs. 88%). Other studies reported 96% survival in children under 1 year and 80% in children between 1 and 2 years [6]. However, in a paper by Aronson and Hadley from Africa, it was described that it is only during stage I with favorable histology that children under 4 years can have better results than older children [7].

Tumor volume can be considered a prognostic factor in intermediate risk tumors, excluding those with epithelial or stromal predominance [8]. In terms of tumor size, with the cut-off point of 500 mL in patients with intermediate risk tumors (excluding epithelial and stromal subtypes), the event-free survival was 88–95% in tumors smaller than 500 mL compared to 76–90% in larger tumors.

Histology is one of the most powerful prognostic factors in Wilms tumor. Anaplasia is present in 5–10% of cases, and studies have shown that blastemal predominance, as a histological subtype, and anaplasia, especially if diffuse, are poorer prognostic factors [8,9].

In our review, the factors shown to be statistically significantly associated with survival were bilateral tumor surgery, recurrence, and incomplete chemotherapy. Tumor size, stage, and histology were not found to be associated with shorter survival. It should be noted that molecular studies are not routinely performed in our setting and therefore cannot be analyzed in the results.

The factors associated with mortality have different results, which are linked to the level of development of the country studied. African studies reported a Wilms tumor incidence rate of 9% in the pediatric population aged 0-9 years, with a survival rate of 52.7%. Factors such as malnutrition, lack of access to optimal therapy and lack of health insurance have been described as factors associated with poor outcomes [10-12]. In another African study, Atanda *et al.* found that better outcomes were associated with early tumor stage at diagnosis, non-blastemal histology and receiving complete chemotherapy, the latter factor being similar to that found in our study [13]. Besides, we also found that Wilms tumor is often presented in advanced stages in Africa (up to 72%) [10,13-15].

Sangkhathat studied patients in Thailand, where the incidence rate is 2.2%, and found that the most

frequent stages of presentation were stages I and III (38%), with an overall survival of 65%. Factors associated with poor outcomes were failure of primary treatment in stage I patients, tumor size greater than 10 cm, and presentation with macroscopic hematuria. In our study, tumor size and form of presentation did not result in statistically significant differences, nor did gender, age, or histology [16].

Node status revealed a statistically significant association with overall survival. However, positive nodes may be thought to change the stage of disease, and this may represent the most important associated factor [16]. Other studies have found lymph node density to be a predictor of survival, reinforcing the importance of adequate sampling during surgery to improve staging and to achieve a possible reduction in the intensity of therapy in low-risk cases [17]. Failure of lymph node sampling during surgery has been shown to not only increase the likelihood of local relapse, but it is also an independent prognostic indicator of poorer survival [13].

In developing countries, delayed diagnosis, lack of resources such as chemotherapy and irradiation and poor therapeutic adherence to treatment (which may be associated with toxicity or poor follow-up) are crucial factors that lead to the poor outcome of children with Wilms tumor [10,19], which are similar results to those found in our review regarding incomplete chemotherapy.

In patients with stage III Wilms tumor with favorable histology, who usually have a good disease-free survival after management with chemotherapy and radiotherapy, the lymph node and LOH status have been found to be highly predictive of event-free survival, and intrarenal vessel invasion is not an independent prognostic factor [20,21].

A study in Japan found that patients with blastemal histology had a worse prognosis compared to the other histological subtypes, suggesting that in these cases treatment strategies should be different. They described that the overall 5-year survival in the epithelial type was 100%, 93% in the stromal type, and 90% in the mixed type, compared to the blastemal type which was 65%. On the other hand, the 5-year event-free survival was 100% in the epithelial type, 80% in the stromal type, 87% in the mixed type, and 52% in the blastemal type [22]. Another Japanese study found that initial stage and histological subtype were the only factors with statistically significant difference associated with tumor relapse in children with unilateral Wilms tumors and favorable histology who underwent nephrectomy followed by chemotherapy [23].

The UMBRELLA protocol validated new prognostic factors, such as tumor subtype, tumor volume, and molecular markers, in order to determine subgroups of patients with worse prognosis and increased relapse rates [24]. Surgical factors other than lymph node sampling and intraoperative rupture have also been analyzed as factors worsening prognosis, and it has been reported that leaving Gerota's fascia does not increase the risk of recurrence [25].

The need for bilateral intervention in our study was a factor that increased the likelihood of death, and if favorable histology is added, the negative impact on survival is greater. Other factors in addition to bilaterality, such as age, sex, tumor stage, and the presence of a target or synchronous tumor have not shown statistical significance [26].

The limitations of this study lie in the fact that, being a cross-sectional design, it is not possible to establish causal associations, although it is possible to establish the relationship of the variables with survival; and in the fact that it was not possible to randomize the patients.

5. Conclusion

The survival of our children with Wilms tumor is lower than that reported in literature (70 % versus more than 90 %), and the factors associated with this outcome were failure to complete the chemotherapy regimen, tumor recurrence, and bilateral surgery.

Disclosure statement

The authors declare no conflict of interest.

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