Late effects of Wilms' tumor treatment

S. Silvente Bernal, O. Girón Vallejo, A. Sánchez Sánchez, C. Menacho Hernández, J. Rodón Berrío, B.A. Parra Gelder

Pediatric Surgery Department. Hospital Clínico Universitario Virgen de la Arrixaca. Murcia (Spain).

ABSTRACT

Introduction. Wilms' tumor (WT) is the most frequent renal tumor in childhood. Therapeutic management progression has increased survival rates, and as a result, long-term adverse effects.

Materials and methods. A descriptive retrospective study of a case series from 1977 to 2023 was carried out. The characteristics of the treatments received and the adverse effects listed on medical records were analyzed via phone surveys.

Results. 50 patients (25 boys-25 girls) with a mean age of 3.6 years (3 months-11 years) at diagnosis were included. Most of them (94%) were treated according to the protocol established by the European standards of pediatric oncology, which are characterized by the use of neoadjuvant chemotherapy. In one patient, the American treatment scheme was followed. The most common drugs used were vincristine and actinomycin D (78%). Only 12 patients (28%) received anthracyclines. Unilateral nephrectomy was the most frequent surgical technique (84%). Renal disorders were the most common (46%). However, the occurrence of second neoplasias (9%) and reproductive disorders (8% between boys and girls) had a greater impact on patients' quality of life. Multiple – cardiac (23%), endocrine (26%), and pulmonary (15%) – disorders associated with the treatments received were reported.

Conclusions. WT treatment has an impact on health. Adequate and rigorous surgery, close follow-up, and limiting chemotherapy doses and radiation exposure can minimize long-term sequels.

KEY WORDS: Wilms' tumor; Long-term adverse effects; Survivors.

EFECTOS TARDÍOS DEL TRATAMIENTO DEL TUMOR DE WILMS

RESUMEN

Introducción. El tumor de Wilms (TW) es el tumor renal más frecuente en la infancia. La evolución del manejo terapéutico ha incrementado la tasa de supervivencia y como consecuencia, los efectos secundarios a largo plazo.

Material y métodos. Realizamos un estudio retrospectivo descriptivo a partir de una serie de casos entre 1977 y 2023. Estudiamos las características de los tratamientos recibidos y los efectos secundarios que constan en su historia clínica y a través de cuestionarios telefónicos.

Resultados. Localizamos 50 pacientes (25 hombres-25 mujeres) con edad media al diagnóstico de 3,6 años (3 meses-11 años). La mayoría fueron tratados según protocolo vigente de las guías europeas de oncología pediátrica (94%) caracterizadas por el uso de quimioterapia neoadyuvante. En un paciente Se siguió el esquema americano de tratamiento. Los fármacos más utilizados fueron vincristina y actinomicina D (78%); solo 12 pacientes (28%) recibieron antraciclinas. La nefrectomía unilateral fue la técnica quirúrgica más empleada (84%). Las alteraciones renales fueron las más frecuentes (46%). Sin embargo, la aparición de segundas neoplasias (9%) y aquellas alteraciones relacionadas con la reproducción (8% entre hombres y mujeres) suponen un mayor impacto en la calidad de vida de los pacientes. Se describen múltiples alteraciones: cardíacas (23%), endocrinas (26%) o pulmonares (15%) relacionadas con los tratamientos recibidos.

Conclusiones. El tratamiento del TW afecta a la salud general. Una cirugía adecuada y rigurosa, limitar las dosis de quimioterapia, minimizar la exposición a la radiación y un seguimiento estrecho puede minimizar las secuelas a largo plazo.

PALABRAS CLAVE: Tumor de Wilms; Efectos secndarios a largo plazo; Supervivientes.

INTRODUCTION

Wilms' tumor (WT), or nephroblastoma, is the most frequent renal tumor in childhood (85% of renal tumors)[1,2]. It was first described by Thomas Rance in 1814, but it was named after Carl Max Wilhem Wilms in 1899[3]. It occurs in the first years of life, especially in children under 5 years of age[4], with a mean age of 3.5 years at diagnosis and no differences in terms of sex[2,5,6]. Ethnical-geographical and genetic reasons, as well as prenatal and professional parental exposure[2,6,9], are some of the risk factors described. Clinically speaking, it typically

DOI: 10.54847/cp.2024.03.13
Corresponding author: Dr. Sara Silvente Bernal. Pediatric Surgery Department. Hospital Clínico Universitario Virgen de la Arrixaca. Ctra. Madrid-Cartagena, s/n. 30120 El Palmar, Murcia (Spain). E-mail address: ssbcpe@gmail.com

This work was presented as an oral communication at the National Congress of the Spanish Pediatric Surgery Society held in Tenerife (Spain) in May 2024.

Date of submission: May 2024 *Date of acceptance:* June 2024

occurs as an asymptomatic, incidentally found abdominal mass, but symptoms such as macroscopic hematuria, abdominal pain, and high blood pressure (HBP), among others, can also exist[2]. Physical exploration can reveal congenital abnormalities suggestive of syndromic WT[6]. Today, treatment depends on tumor stage and histology. It involves a cross-disciplinary approach with surgery, chemotherapy, and radiotherapy. There are two treatment strategies in the world – the European ISPO (International Society of Pediatric Oncology) scheme and the American NWTSG (National Wilms' Tumor Study Group) scheme, with similar survival rates of around 85-90% five years post-diagnosis[8-11]. The ISPO advocates the use of neoadjuvant chemotherapy followed by nephroureterectomy, whereas the NWTSG suggests treatment be administered in the opposite order –first surgery and then chemotherapy, if required[11]. Throughout the history of WT, treatment has progressed, with better survival results, which in turn has caused adverse effects to increase as a result of the treatments employed in WT survivors (WTS). In the occurrence of these long-term effects, radiotherapy and chemotherapy have played an important role, since they have been frequently used since the first protocols were implemented[15]. Today, cardiac, renal, endocrine, and fertility disorders have been described[1,4,10,13]. Another adverse effect reported is predisposition to second neoplasias (SN), which are the main cause of death in WTS despite being rare[7,9,10,13,16]. To understand and prevent these effects, follow-up protocols minimizing consequences and allowing patients to have a quality of life similar to that of the healthy population should be created.

MATERIALS AND METHODS

A descriptive retrospective study of a case series from our hospital between 1977 and 2023 was carried out. Patients who died as a result of WT progression or any other cause, patients referred to another hospital, and patients who changed residence were excluded. Data was collected from various sources –old operating room books from 1977 to 1996, and the Pediatric Oncology Unit database from then on.

Once patients had been selected, the following variables were collected: age at diagnosis, tumor presentation (unilateral or bilateral), tumor stage (I, II, III, or IV), treatment protocol (ISPO/NWTSG), neoadjuvant chemotherapy, surgical procedure (total or partial nephroureterectomy), adjuvant chemotherapy, radiotherapy, relapse (YES/NO and in which organ), relapse treatment, and other relevant considerations.

Treatment-related adverse effects were also searched for in each patient. A series of variables ordered by human body systems were included at data collection. Dental, cardiac, neurological, fertility, pregnancy –in case gestations had occurred–, renal, endocrine, dermatological, musculoskeletal, pulmonary, gastrointestinal, otorhinolaryngological, ophthalmological, and psychosocial disorders, as well as disorders in other organs, genetic factors, second neoplasias, and other relevant data, were gathered.

To complete adverse effect data from patients with little information available, phone surveys were conducted in 12 patients (24%). A self-made item-based questionnaire assessing current health condition was applied.

RESULTS

64 WT patients were identified in the study period, 50 of whom met inclusion criteria. The series consisted of 25 boys and 25 girls. 86% of the patients were diagnosed under 5 years old, with a mean age of 3.6 years (3 months-11 years) at diagnosis. Unilateral WT presentation was the most frequent (85%), while only 6 patients (12%) had bilateral WT. 1 patient with extrarenal WT at the left pararenal region was identified. 1 patient with Denys-Drash syndrome, bilateral WT, bilateral cryptorchidism, and heterozygous mutation of the WT1 gene was found.

A total of 28 patients (56%) had stage I WT at diagnosis, 7 patients had stage II WT (14%), and 7 patients had stage III WT (14%). 5 patients (10%) had metastatic disease at diagnosis. 94% of the patients received treatment according to the ISPO protocol in force at diagnosis. Only 1 patient received NWTSG treatment as he had been referred from Latin America.

In most cases, total nephrectomy was carried out (84%), and in the remaining patients, nephron-sparing surgery or tumor removal in bilateral cases was conducted.

Regarding chemotherapy treatment, 45 patients (90%) received neoadjuvant chemotherapy, with actinomycin D and vincristine being the most commonly used drugs (35 patients, 70%). 9 patients (20%) also received anthracyclines, with doxorubicin being the most frequent in our series (applied in 15 patients, 32%). Other drugs such as daunorubicin or epirubicin (3 patients, 6%) were also employed. In 1 patient, neoadjuvant treatment had to be intensified with other drugs as response to baseline therapy was insufficient. 88% of the patients received adjuvant chemotherapy, 29 of whom (58%) continued with actinomycin D and vincristine only. In 1 of them, treatment was intensified with vincristine alone. 12 patients (24%) followed a treatment scheme including actinomycin D, vincristine, and anthracyclines, whereas 3 patients (6%) received a more intense treatment with etoposide, carboplatin, cyclophosphamide, and doxorubicin.

34% of the total of patients received radiotherapy. In 1 patient –namely the first patient in our series, dating back from 1977–, preoperative tumor radiation had been carried out, whereas the remaining patients received radiotherapy postoperatively.

Table 1. Treatment of WT survivors.

Variable		*N (%)*
Sex	Male	25 (50%)
	Female	25 (50%)
Age at diagnosis (mean: 3.6 years)	≤ 12 months	9 (18%)
	1-5 years	34 (68%)
	> 5 years	11 (14%)
Tumor	Bilateral	6 (12%)
	Unilateral	42 (84%)
	Other	1
Stage	I	28 (56%)
	II	7 (14%)
	III	7 (14%)
	IV	5 (10%)
	Unknown	3
Treatment strategy	ISPO	47 (94%)
	NWTSG	1 (2%)
	Unknown	2
Neoadjuvant chemotherapy	Yes	45 (90%)
	A and/or V	32
	A, V + anthracyclines	9
	Other	1
	No	5 (10%)
Surgery	TN	42 (84%)
	PN	3 (6%)
	Combination of both	3 (6%)
	TN and/or PN + metastasis removal	2 (4%)
Adjuvant chemotherapy	Yes	44 (88%)
	A and/or V	29
	A, V + anthracyclines	12
	HR-2	3
	No	6 (12%)
Radiotherapy	Preoperative	1 (2%)
	Postoperative	15 (30%)
	No	34 (68%)
Relapse	Yes	5 (11%)
		Total N = 50

ISPO: International Society of Pediatric Oncology; NWTSG: National Wilms' Tumor Study Group; A: actinomycin D; V: vincristine; TN: total nephrectomy; PN: partial nephrectomy; HR-2: etoposide, carboplatin, cyclophosphamide, and doxorubicin.

5 patients (11%) had primary WT relapse. Most of them (4 patients) had pulmonary (extrarenal) relapse, whereas 1 patient had local relapse.

The various disorders listed by organs or systems are featured in Table 2. The most frequent were renal disorders (46%), followed by skin disorders (36%). On the other hand, SN was not common, since it only occurred in 4 patients (9%).

The most relevant disorders classified by systems were the following:

Cardiac disorders. 23% of the patients had cardiovascular disorders. HBP was the most common one (13%), with amlodipine being the drug most frequently used. Echocardiography confirmed the presence of myocardial disfunction in 2 patients, and septal hypertrophy and bicuspid aortic valve, respectively, were revealed in other 2, without any clinical repercussion.

Renal function disorders. 5 patients (11%) had a glomerular filtration rate under 90 ml/min and developed chronic renal disease (CRD) –4 grade II CRD and 1 grade III CRD. In no less than 25% of the cases, multiple urinary tract infections and/or inflammation were found, associated with renal lithiasis in 1 case.

Reproductive and offspring disorders. In the case of girls, fertility disorders were only present in 2 patients

Table 2. Adverse effects in WT survivors.

Variable		*N (%)*
Genetic factors		2 (4%)
Dental disorders		9 (19%)
Cardiac disorders	Total	11 (23%)
	HBP	6
	Myocardial disfunction	2
	Other	3
Neurological disorders		7 (15%)
Renal function disorders	Total	22 (46%)
	CRD	5
	Hematuria	0
	Proteinuria	1
	APN	0
	UT infection/inflammation	9
	Combination of the former	3
	Other	4
Reproductive and offspring disorders	**Females**	
	Total	6 (13%)
	Menstrual disorders	3
	Fertility disorders	2
	Other	1
	Males	
	Total	4 (9%)
	Fertility disorders	2
	Other	2
Endocrine disorders	Total	12 (26%)
	Subclinical hypothyroidism	6
	Obesity	3
	Other	3
Skin disorders	Total	17 (36%)
	Dermatological changes	8
	Tumors	5
	Benign	4
	Malignant	1
	Other	4
Musculoskeletal disorders	Total	13 (28%)
	Bone pain	5
	Spinal disorders	7
	Tumors	1
Pulmonary disorders		7 (15%)
Gastrointestinal disorders		8 (17%)
ORL disorders		13 (28%)
Ophthalmological disorders		7 (15%)
Second neoplasias		4 (9%)
Disorders in blood tests	Total	15 (32%)
	Blood count disorders	4
	Biochemical disorders	11
		N = 50

HBP: High blood pressure; CRD: Chronic renal disease; APN: Acute pyelonephritis; UT: Urinary tract; ORL: Otorhinolaryngological.

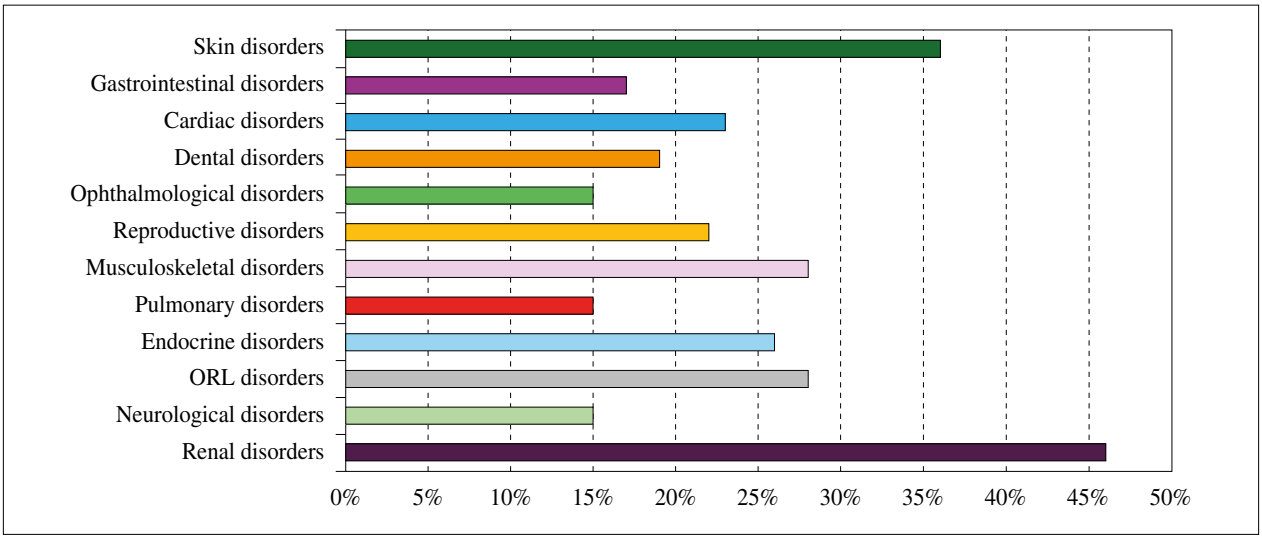

Figure 1. Frequency of the adverse effects noted in WT survivors.

(8%), both with a diminished ovarian reserve. 2 patients did have children, with gestations being uneventful. Among boys, 1 patient had azoospermia, and 1 patient required a fertility study.

Second neoplasias. 4 patients (9%) developed SN over time. 1 patient had multiple basal cell carcinoma, 1 patient had pituitary adenoma, 1 patient had osteochondroma, and 1 patient had breast carcinoma.

Other disorders (Fig. 1). Subclinical hypothyroidism was the most frequent endocrine manifestation (13%). As for pulmonary disorders (7 patients, 15%), 1 patient had recurrent episodes of left pneumothorax, 1 patient had mild restrictive lung disease and a history of previous thoracotomies, and 1 patient had multiple upper airway infections and gastroesophageal reflux as a result of congenital esophageal atresia. 12% of the patients had scoliosis, and 1 patient had lumbar hyperlordosis, with musculoskeletal manifestations being the most common disorders.

In terms of psychosocial disorders (Table 3), including the social, psychological, school, and family environment, psychological issues were the most frequent (21%). 14% of the patients had anxiety or depression anytime following WT diagnosis. 1 patient had eating disorder, and 2 patients had reduced quality of life in the emotional sphere and the school environment.

Table 3. Psychosocial disorders in WT survivors.

Variable		*N (%)*
Family environment		0
Social environment		2 (4%)
School environment		4 (9%)
Psychological environment	Total	10 (21%)
	Anxiety	5
	Depression	2
	Sleeplessness	0
	Other	3
		N = 50

DISCUSSION

WT treatment may cause significant long-term adverse effects in patients. Renal and cardiac are two of the most concerning treatment-related long-term effects. Regarding renal effects, partial or total nephroureterectomy can alter renal function and increase the risk of developing CRD[10]. Chemotherapy and radiotherapy can also have toxic effects on the kidney, thus entailing a higher risk of chronic renal issues[12]. In our study, up to 11% of WTS (5 patients) had deteriorated renal function with a glomerular filtration rate under 90 ml/min/1.73 m^2 [1,4,12,15].

The presence of cardiac abnormalities in WTS is more frequent than in the general population. Anthracycline treatment is the main risk factor, but not the only[9,17-19,26]. Doxorubicin, which was frequently found in our series (32%), is the drug most commonly associated with cardiotoxicity[19]. Chest radiotherapy has also been described as a factor[9,15], especially in the incidence of congestive heart failure[26]. In our series, 38% of the patients received anthracyclines, 4% of whom developed left ventricle systolic disfunction, with a dilated ventricular cavity. These 2 patients did not receive a combination of radiotherapy and chemotherapy, but the fact they had been treated with anthracyclines can explain why they developed ventricular disfunction[12].

In the phone surveys, fertility concerns were detected in WTS. Indeed, having received high doses of pelvic and abdominal radiation is associated with a higher risk of infertility and pregnancy complications[21,23]. Radiotherapy is the treatment modality that is most detrimental to female reproduction[12,15,21,22,26] as radiation causes ovarian follicles to decrease and alters follicular maturation[15,21]. Consistent with the literature, 2 cases (4%) with a diminished ovarian reserve and previous radiotherapy treatment were found in our series. 2 patients have had offspring, with gestation being uneventful. 1 of them had received radiotherapy –the other had not.

On the other hand, chemotherapy and radiation can affect the testicles, which are more sensitive to cytotoxic therapies than the ovaries, since these therapies prove more detrimental to male than to female fertility at identical treatment regimens[20,21]. 1 of our patients, who had primary tumor relapse and was treated with cyclophosphamide, ifosfamide, carboplatin, and radiotherapy, developed azoospermia.

Radiation can also damage growth and bring about spinal disorders, with scoliosis being a common manifestation in the various series published (up to 40%)[15]. In our series, of the seven patients with scoliosis (14%), four (4/7) had received radiation therapy.

WTS have a higher risk of developing SN[7,12,13,25]. Even though this is not the most frequent sequel, SN is regarded as the most severe, since it has a dramatic impact on survival, with mortality increasing 15-fold[14]. It is the most frequent cause of death in WTS[25]. Bone and soft tissue sarcoma, breast cancer, lymphoma, gastrointestinal tumor, melanoma, and acute leukemia have been reported[12].

In our series, up to 4 patients (9%) developed SN. 1 of them has pituitary adenoma, with no clinical repercussion today –this tumor is rare within the context of WT. Another patient has developed osteochondroma in the second lumbar vertebra, which can occur in 10% of WT cases, and is more common in patients receiving radiotherapy[15].

Radiotherapy can also increase the risk of developing skin neoplasms in the area involved, but this risk is relatively low and depends on various factors, such as radiation dose, patient age, and individual sensitivity to radiation[24]. In addition, certain studies confirm that female WTS have a greater risk of developing breast cancer after they turn 40, especially if they were treated with radiotherapy[27]. In our study, 2 of the patients who developed SN –basal cell carcinoma and breast cancer, respectively– received previous radiotherapy treatment. On the other hand, of the 32% (16 patients) who received radiotherapy, 68.75% were women; however, only two of them are over 40 years old and have not developed breast cancer today.

Regarding the quality of life of these patients, the fact the cancer does not end once treatment has been completed can be considered a challenge for survivors. Survivors of any pediatric cancer can experience reduced cognitive function, learning issues, school failure, and even trouble finding a job in the future[17]. This has been the case in some patients from our series (13%), who report to have suffered from social isolation and lack of self-esteem during childhood, with repercussion on academic performance.

In conclusion, long-term adverse effects in WTS are critical in the quality of life following treatment. Even though therapeutic advances have caused survival to improve, challenges persist in the form of cardiovascular and renal sequels, among other. It is key that healthcare systems implement long-term follow-up protocols adapted to the specific needs of this population, focusing not only on the early detection and treatment of physical complications, but also on emotional and psychological support.

Regarding study limitations, some patients remain under treatment, which prevents certain adverse effects that emerge in the long-term from being studied. Other patients did not respond to the phone survey, which means this clinical information is not available.

REFERENCES

1. Kostel Bal AS, Yalcin B, Susam-Sen H, Aydin B, Varan A, Kutluk T, et al. Renal late effects after the treatment of unilateral nonsyndromic Wilms tumor. J Pediatr Hematol Oncol. 2016; 38(4): 147-50.
2. Popov SD, Sebire NJ, Vujanic GM. Wilms' tumour - Histology and Differential diagnosis. En: Van den Heuvel-Eibrink MM, editor. Wilms Tumor. 1ª ed. Brisbane (AU): Codon Publications; 2016. p. 3-23.
3. Raffensperger J. Max Wilms and his tumor. J Pediatr Surg. 2015; 50: 356-9.
4. Neu MA, Russo A, Wingerter A, Alt F, Theruvath J, El Malki K, et al. Prospective analysis of long-term renal function in survivors of childhood Wilms tumor. Pediatr Nephrol. 2017; 32: 1915-25.
5. Lamb MG, Aldrink JH, O'Brien SH, Yin H, Arnold MA, Ranalli MA. Renal tumors in children younger than 12 months of age: A 65-year single institution review. Pediatr Hematol Oncol. 2016; 39(2): 103-7.
6. Vargas Solórzano Y. Tumor de Wilms. Rev Méd Costa Rica Centroam. 2013; 605: 55-7.
7. Taylor AJ, Winter DL, Pritchard-Jones K, Stiller CA, Frobisher C, Lancashire E, et al. Second primary neoplasms in survivors of Wilms' tumour--a population-based cohort study from the British Childhood Cancer Survivor Study. Int J Cancer. 2008; 122(9): 2085-93.
8. Sánchez Sánchez A, Girón Vallejo O, Ruiz Pruneda R, Fernández Ibieta M, Villamil V, Giménez Aleixandre MC, et al. Función renal a largo plazo en supervivientes de tumor de Wilms. Cir Pediatr. 2019; 32: 86-92.
9. Van Dijk IW, Oldenburger F, Cardous-Ubbink MC, Geenen MM, Heinen RC, de Kraker J, et al. Evaluation of late adverse events in long-term Wilms' tumor survivors. Int J Radiat Oncol Biol Phys. 2010; 78(2): 370-8.
10. Cost NG, Sawicz-Birkowska K, Kajbafzadeh AM, Tourchi A, Parigi GB, Guillén G, et al. A comparison of renal function

outcomes after nephron-sparing surgery and radical nephrectomy for nonsyndromic unilateral Wilms tumor. J Pediatr Urol. 2014; 83(6): 1388-93.

11. Van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, van Tinteren H, Furtwängler R, Verschuur AC, et al. Rationale for the treatment of Wilms tumor in the UMBRELLA SIOP-RTSG 2016 protocol. Nat Rev Urol. 2017; 14(12): 743-75.
12. Wright KD, Green DM, Daw NC. Late effects of treatment for Wilms tumor. Pediatr Hematol Oncol. 2009; 26(6): 407-13.
13. Termuhlen AM, Tersak JM, Liu Q, Yasui Y, Stovall M, Weathers R, et al. Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer. 2011; 57(7): 1210-6.
14. Breslow NE, Lange JM, Friedman DL, Green DM, Hawkins MM, Murphy MFG, et al. Secondary malignant neoplasms after Wilms tumor: an international collaborative study. Int J Cancer. 2010; 127(3): 657-66.
15. Paulino AC, Wen BC, Brown CK, Tannous R, Mayr NA, Zhen WK, et al. Late effects in children treated with radiation therapy for Wilms' tumor. Int J Radiat Oncol Biol Phys. 2000; 46(5): 1239-46.
16. Breslow NE, Takashima JR, Whitton JA, Moksness J, D'Angio GJ, Green DM, et al. Second malignant neoplasms following treatment for Wilms' tumor: A report from the National Wilms' Tumor Study Group. J Clin Oncol. 1995; 13(8): 1851-9.
17. Ryerson AB, Wasilewski-Masker K, Border WL, Goodman M, Meacham L, Austin H, et al. Pediatric quality of life in long-term survivors of childhood cancer treated with anthracyclines. Pediatr Hematol Oncol. 2016; 63(12): 2205-11.
18. Chalavon E, Lampin ME, Lervat C, Leroy X, Bonnevalle M, Recher M, et al. Dilated cardiomyopathy caused by Wilms tumor. Pediatr Emer Care. 2015; 33(1): 41-2.
19. Van Dalen EC, Raphaël MF, Caron HN, Kremer LCM. Treatment including anthracyclines versus treatment not including anthracyclines for childhood cancer. Cochrane Database Syst Rev. 2014; 4(9): CD006647.
20. Daw NC, Gregornik D, Rodman J, Marina N, Wu J, Kun LE et al. Renal function after ifosfamide, carboplatin and etoposide (ICE) chemotherapy, nephrectomy and radiotherapy in children with wilms tumour. Eur J Cancer. 2009: 45: 99-106.
21. Van Dorp W, Haupt R, Anderson RA, Mulder RL, van den Heuvel-Eibrink MM, van Dulmen-den Broeder E, et al. Reproductive function and outcomes in female survivors of childhood, adolescent, and young adult cancer: A review. J Clin Oncol. 2018; 36(21): 2169-80.
22. Schuck A, Hamelmann V, Brämswig JH, Könemann S, Rübe C, Hesselmann S, et al. Ovarian function following pelvic irradiation in prepubertal and pubertal girls and young adult women. Strahlenther Onkol. 2005; 181: 534-9.
23. Green DM, Lange JM, Peabody EM, Grigorieva NN, Peterson SM, Kalapurakal JA, et al. Pregnancy outcome after treatment for Wilms tumor: A report from the national Wilms tumor long-term follow-up study. J Clin Oncol. 2010; 28(17): 2824-30.
24. Prasad M, Bhatia S, Singh Arora R. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Children's Oncology Group. 2018.
25. Taylor AJ, Winter DL, Pritchard-Jones K, Stiller CA, Frobisher C, Lancashire ER, et al. Second primary neoplasms in survivors of Wilms' tumour—A population-based cohort study from the British Childhood Cancer Survivor Study. Int J Cancer. 2008; 122: 2085-93.
26. Sadak KT, Ritchey ML, Dome JS. Pediatric genitourinary cancers and late effects of treatment. Nat Rev Urol. 2013; 10(1): 15-25.
27. Lange JM, Takashima JR, Peterson SM, Kalapurakal JA, Green DM, Breslow NE. Breast cancer in female survivors of Wilms tumor: A report from the national Wilms tumor late effects study. Cancer. 2014; 120(23): 3722-30.