The management of bilateral Wilms tumor

Derya Özyörük[1], Suna Emir[2]

[1]Pediatric Oncologist, Department of Pediatric Hematology Oncology, [2]Associate Professor of Pediatrics, Department of Pediatric Hematology Oncology, Ankara Children's Hematology Oncology Training and Research Hospital, Altındağ, Ankara, Turkey

Correspondence to: Suna Emir, MD. Ankara Children's Hematology Oncology Training and Research Hospital, İrfan Başтuğ Cadde Kurtdereli sokak No: 10 Dışkapı Altındağ Ankara Turkey. Email: sunaemir@yahoo.com.

Abstract: Wilms tumor (WT) is the most common malignant renal tumor in childhood. Approximately 5-7% of WT patients present with bilateral disease, either synchronously or metachronously. Bilateral WT usually occurs in younger children and more often in girls. Management of a child with bilateral WT is very challenging. In contrast to unilateral WT, there has not been uniform agreement about the therapeutic strategy in the management of bilateral WT. As surgery is a critical component in the treatment of WT, the aim is to achieve a high cure rate while maintaining adequate long-term renal function in patients with bilateral WT. In the past, radical surgical procedures which lead to the patients on dialysis have been traditionally recommended in these patients. After several multicentre trials, bilateral biopsies followed by pre-operative chemotherapy and then renal salvage surgery have been recommended. The management of bilateral WT has evolved from primary surgical extirpation to kidney-preserving resection after preoperative chemotherapy. Preoperative chemotherapy often results in significant reduction in tumor size, thereby facilitating subsequent renal salvage. The analysis of children with bilateral WT shows that preservation of renal parenchyma is possible following initial preoperative chemotherapy. Only centers with experience in bilateral WT should treat the cases with bilateral WT to provide optimal treatment.

Keywords: Wilms tumor (WT); bilateral; stage V

Submitted Jan 03, 2014. Accepted for publication Jan 09, 2014.
doi: 10.3978/j.issn.2224-4336.2014.01.04
View this article at: http://www.thetp.org/article/view/3229/4103

Wilms tumor (WT), is the most common malignant renal tumor in childhood. In the United States there are approximately eight cases of WT per million children less than 15 years of age per year, with the total number of new cases being estimated at about 500 cases per year. Current therapy of WT consists of unilateral nephrectomy, systemic chemotherapy and ionizing radiation. The prognosis of this previously lethal malignant tumor improved with developments in surgical techniques in the 20th century. Owing to the treatment guidelines from the National Wilms Tumor Study Group (NWTSG) and the International Society of Pediatric Oncology (SIOP), survival has dramatically improved. The overall survival (OS) rate of localized disease is currently greater than 90% and it is one of the real successes of modern medicine. Today, the primary objective of new treatment protocols is to increase cure rate with minimal treatment related toxicities (1,2).

Approximately 5-7% of WT patients present with bilateral disease, either synchronously or metachronously (3). According to NWTS-4, it was reported 5.6% (4), however, other studies recorded a higher incidence of 10-14% that may be attributed to the relatively small sample size in these studies (5,6). Bilateral WT usually occurs in younger children and more often in girls (3).

Bilateral WT, Stage V is defined bilateral renal involvement at initial diagnosis (*Table 1*). Management of a child with bilateral Wilms tumor (BWT) is very challenging. Preservation of the maximum amount of renal parenchyma is needed to prevent renal failure, but complete resection is required to optimize the chances for cure of the malignancy. In contrast to unilateral WT, there has not been uniform agreement about the therapeutic strategy in

Table 1 Staging of Wilms' tumor (1)

Stage	NWTSG (before chemotherapy)	SIOP (after chemotherapy)
I	(I) Tumor is limited to the kidney and completely excised; (II) Tumor was not ruptured before or during removal; (III) The vessels of the renal sinus are not involved beyond 2 mm; (IV) There is no residuel tumor apparent beyond the margins of excision	(I) Tumor is limited to kidney or surrounded with fibrous pseudocapsule if outside of the normal contours of the kidney, the renal capsule or pseudocapsule may be infiltrated with the tumor, but it does not reach the outer surface and is completely resected (resection margins "clear"); (II) The tumor may be protruding into the pelvic system and dipping into the ureter (but it is not infiltrating their walls); (III) The vessels of the renal sinus are not involved; (IV) Intrarenal vessel involvement may be present
II	(I) Tumor extends beyond the kidney, but is completely excised; (II) No residuel tumor is apparent at or beyond the margins of excision; (III) Tumor trombus in vessels outside the kidney is stage II, if the trombus is removed en bloc with the tumor (*Although tumor biopsy or local spillage confined to the flank were considered stage II by NWTSG in the past, such events will be considered stage III in the upcoming COG studies*)	(I) Tumor extends beyond the kidney or penetretes through renal capsule and/or fibrous pseudocapsuleinto perirenal fat but is completely resected (resection margins "clear"); (II) Tumor infiltrates the renal sinus and/or invades blood and lymphatic vessels outside the renal parenchima, but is completely resected; (III) Tumor infiltrates adjacent organs or vena cava, but is completely resected
III	Residuel tumor confined to the abdomen: (I) Lymph nodes in the renal hilum, the periaortic chains, or beyond are found to contain tumor; (II) Diffuse peritoneal contamination by the tumor; (III) Implants are found on the peritoneal surface; (IV) Tumor extends beyond the surgical margin either microscopically or grossly; (V) Tumor is not completely resectable because of local infiltration into vital structures	(I) Incomplete exscision of the tumor, which extends beyond resection margins (gross or microscopical tumor remains postoperatively); (II) Any abdominal lymph nodes are involved; (III) Tumor rupture before or intraoperatively (irrespective of other criteria for staging); (IV) Tumor has penetrated through the peritoneal surface; (V) Tumor thrombi present at the resection margins of vessels or ureter, trans-sected or removed piecemeal by surgeon; (VI) Tumor has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery. *Regional lymph node involvement was considered stage II in the previous SIOP staging system*
IV	Presence of hematogenous metastases or metastases to distant lymph nodes	Hematogenous metastases (lung, liver, bone, brain, etc.) or lymph node metastases outside of abdominopelvic region
V	Bilateral renal involvement at the time of initial diagnosis	Bilateral renal tumors at diagnosis

the management of bilateral WT (3-8).

Until the establishment of the NWTS in 1969, organized clinical investigation was limited. Five sequential trials have been completed, with the basic goal of each successive NWTS trial having been to maintain a high cure rate for patients with WT, while reducing the intensity and duration of therapy, based on surgical stage and histologic evaluation. NWTS-1 showed that postoperative abdominal radiotherapy was not necessary for children who were less than two years of age and whose tumors were limited to the kidney and completely resected. Also, the combination of vincristine and dactinomycin was shown to be more effective for the treatment of children with tumors that extended beyond the kidney than either drug alone. NWTS-2 demonstrated that six months of combination chemotherapy with vincristine and dactinomycin was

effective treatment for children with tumors limited to the kidney and completely resected, none of whom received abdominal radiation. The combination of adriamycin to vincristine and actinomycin D was found to improve the relapse-free survival of other patients. The separation of WT into distinct histopathologic categories based on prognosis was used to stratify patients in NWTS-3. NWTS-4 examined the utility of dose intensive scheduling to cut down on the duration of therapy. NWTS-5, a single-arm therapeutic trial designed to evaluate the prognostic value of certain biologic markers in WT, demonstrated that loss of heterozygosity (LOH) for genetic material on chromosomes 1p and 16q in stage I and II favorable histology WT was associated with a poorer prognosis. Recently, loss of heterozygosity of 1p and 16q, is now being used to further stratify patients in the current Children's Oncology Group (COG) trial for WT (2).

A succession of SIOP studies began in 1971 and determined the optimal preoperative therapy regimen for patients with renal tumors to reduce the risk of tumor rupture during surgery, and likelihood of local and distant recurrence. The maximizing cure while minimizing toxicity is being evaluated in the ongoing SIOP-2001 protocols, in which postoperative chemotherapy is tailored according to histologic features (1).

The management of bilateral WT has evolved from primary surgical extirpation to kidney-preserving resection after preoperative chemotherapy. Preoperative chemotherapy often results in significant reduction in tumor size, thereby facilitating subsequent renal salvage. Extended follow-up of patients with bilateral WT who were enrolled on NWTS-2 and -3 showed no difference in survival rates between those treated initially with surgical resection and those treated with biopsy and preoperative chemotherapy (7). On NWTS-4, the risk of local recurrence for patients who underwent kidney-sparing resection was 8.2% (8). The analysis of children with BWT treated on NWTS-4 shows that preservation of renal parenchyma is possible following initial preoperative chemotherapy (9). The NWTS-5 recommendation for the management of bilateral WT includes initial biopsy and local staging followed by chemotherapy (according to abdominal stage and histologic features) and second-look surgery at week 5. If needed, additional chemotherapy or radiation therapy is given, but definitive surgery is recommended within 12 weeks of diagnosis to limit the risk of chemoresistant clonal expansion (10).

According to the SIOP-93 guidelines, preoperative chemotherapy with vincristine (1.5 mg/m^2, day 1) and dactinomycin (15 microgram/kd/day, days 1, 2, and 3) every two weeks, with extra dose of vincristine on day 8 are recommended in bilateral WT. Treatment is continued as long as there is imaging evidence of tumor regression. When regression is not sufficient to perform nephron sparing surgery, other drugs can be used. Bilateral or at least unilateral nephron sparing surgery is performed when technically possible. Surgery is performed in one step (bilateral surgery at the same time) or two steps to improve patient tolerance, or by a few weeks (>1 month) to allow for the administration of chemotherapy matched to the type and stage of the resected tumor. Post-surgical management is chemotherapy, adjusted to fit the highest histological grade and local stage of the tumor. In patients with stage III disease, complementary radiotherapy is delivered to a maximum dose of 12 Gy (11).

A common recommendation has previously been to perform initial nephrectomy on the more affected side, to proceed with chemotherapy aiming at a possible later resection on the remaining kidney. Initial biopsy only, followed by pre-operative chemotherapy, reduces the tumor burden and has been more recently recommended to facilitate parenchymal-sparing surgery, instead of primary nephrectomy (12). The duration and intensity of chemotherapy depends very much on the other therapeutic modalities used. Three drug conventional chemotherapy regimens are today commonly used in patients with bilateral WT (12).

Bilaterality of a WT poses unique challenges to the surgeon who is attempting to eradicate the tumor while preserving sufficiently functioning renal parenchyma (if possible at least an equivalent to 2/3 of one kidney) (13). While in earlier days surgical exploration of the contralateral kidney was the only method to detect a contralateral tumor, the necessity of this way of assessment has been questioned with the introduction of modern imaging techniques, particularly, computed tomography (CT) and magnetic resonance imaging (MRI). But even these modalities miss up to 50% of lesions below 1 cm in its greatest dimension. Paya *et al.* reported in their study, bilaterality could not be determined despite the use of all available imaging methods prior to surgery in three out of the seven cases, so they recommended the routine contralateral exploration (13).

Radiotherapy has traditionally been one of the treatment modalities in WT. In the NWTS-2 and NWTS-3, 57% of the patients received radiotherapy versus 21.4% of the patients in NWTS-4 (8). Although radiotherapy usage

following partial nephrectomy for bilateral disease had been advocated, this policy may impair kidney growth (14). Local irradiation has been omitted, however, in low-stage (I-II) tumors. In bilateral WT, radiotherapy should be administered according to local stage, although definite indications are somewhat less clear regarding bilateral tumors. In the NWTS protocols this has meant staging evaluated at initial surgery. It is harder to apply staging rules after a period of preoperative chemotherapy, particularly after partial kidney resections along sharp resection lines where microscopic or even macroscopic residual tumour may or may not be left behind. This creates difficulty in assessing the true need for local irradiation. More importantly, irradiation is harmful for renal tissue, both in potentially impairing renal function, and, particularly in patients with bilateral WT, in possibly increasing the risk of second malignancies. Total avoidance of radiotherapy would therefore be desirable, not only in low local stages and small tumors, but also in higher local stages and/or massive tumors. In recent study, radiotherapy was replaced by consolidation with high-dose melphalan and autologous bone marrow rescue. They reported that on patients with bilateral WTs with pre-operative chemotherapy, late kidney- sparing surgery, and consolidation with high-dose melphalan plus ABMT resulted in good preservation of kidney parenchyma and renal function (12).

Prior to the initiation of the NWTS, ablative surgery was considered essential for cure, since these patients were thought to have a poor survival. For some patients with synchronous bilateral tumors, this resulted in significant renal insufficiency or an anephric patient requiring renal transplantation (7,12,15). Approximately 12% of patients with synchronous, bilateral WTs who were treated on Children's Oncology Group protocols developed renal failure, usually because of the need for bilateral nephrectomy for persistent or recurrent tumor in the remaining kidney. Partial nephrectomy is more complex technically than complete nephrectomy and has greater potential for postoperative complications, including bleeding and urinary leak (16).

According to the NWTSG, metachronous bilateral WT has lower survival rates than synchronous bilateral tumors. Long-term survival rates for patients with synchronous bilateral WTs are approximately 70-80% (7). Metachronous bilateral WT accounts for approximately 2% of all WTs. Paulino *et al*. showed that the OS rate for patients with metachronous bilateral WT was 49.1% at five years and 47.2% at ten years, and a second tumor developed at a median interval of 23.1 months. Children in whom a contralateral tumor developed more than 18 months after the initial diagnosis had a better OS rate than did those in whom it developed less than 18 months after diagnosis (10-year OS rate, 55.2% versus 39.6%). Children younger than 12 months who have perilobar nephrogenic rests are at markedly increased risk of contralateral disease and require frequent and regular surveillance for several years (17).

The focus of treatment is survival, and especially in this group of patients the preservation of good longterm renal function is of utmost importance. Nevertheless, the surviving individual may develop renal failure or late effects due to anticancer treatment. The first four NWTSG publications reported 55 cases of renal failure, 39 of them had bilateral involvement. Increasing efforts to preserve renal parenchyma in bilateral cases have been noticed in the successive NWTSG reports resulting in a decline in the incidence of renal failure from 16.4% in NWTSG-1 and -2 to 9.9% in NWTSG-3 and 3.8% in NWTSG-4 (6). The incidence of end-stage renal failure (ESRF) was 0.6% for unilateral tumors, 11.5% for bilateral tumors, and >50% for Denys-Drash syndrome (DDS)/WAGR syndrome (11). Metachronous tumors have a higher incidence of ESRF as compared to synchronous tumors (18% *vs.* 9%). Causes were bilateral nephrectomy for persistent or recurrent tumor (74%), DDS, radiation nephritis, chemotherapy toxicity, and surgical complications. Of these, DDS and radiation nephritis were the most significant causes (18).

In conclusion, the management of bilateral WT is still being challenging despite current modern multimodal treatments and warrant further investigations.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist 2005;10:815-26.
2. Davidoff AM. Wilms' tumor. Curr Opin Pediatr 2009;21:357-64.
3. Sulkowski J, Kolon T, Mattei P. Nephron-sparing partial

nephrectomy for bilateral Wilms' tumor. J Pediatr Surg 2012;47:1234-8.
4. Hamilton TE, Green DM, Perlman EJ, et al. Bilateral Wilms' tumor with anaplasia: lessons from the National Wilms' Tumor Study. J Pediatr Surg 2006;41:1641-4.
5. Kullendorff CM, Wiebe T. Bilateral Wilms' tumor. Pediatr Surg Int 1999;15:46-9.
6. Millar AJ, Davidson A, Rode H, et al. Bilateral Wilms' tumors: a single-center experience with 19 cases. J Pediatr Surg 2005;40:1289-94.
7. Montgomery BT, Kelalis PP, Blute ML, et al. Extended followup of bilateral Wilms tumor: results of the National Wilms Tumor Study. J Urol 1991;146:514-8.
8. Horwitz JR, Ritchey ML, Moksness J, et al. Renal salvage procedures in patients with synchronous bilateral Wilms' tumors: a report from the National Wilms' Tumor Study Group. J Pediatr Surg 1996;31:1020-5.
9. Hamilton TE, Ritchey ML, Haase GM, et al. The management of synchronous bilateral Wilms tumor: a report from the National Wilms Tumor Study Group. Ann Surg 2011;253:1004-10.
10. Kalapurakal JA, Dome JS, Perlman EJ, et al. Management of Wilms' tumour: current practice and future goals. Lancet Oncol 2004;5:37-46.
11. Sudour H, Audry G, Schleimacher G, et al. Bilateral Wilms tumors (WT) treated with the SIOP 93 protocol in France: epidemiological survey and patient outcome. Pediatr Blood Cancer 2012;59:57-61.
12. Saarinen-Pihkala UM, Wikström S, Vettenranta K. Maximal preservation of renal function in patients with bilateral Wilms' tumor: therapeutic strategy of late kidney-sparing surgery and replacement of radiotherapy by high-dose melphalan and stem cell rescue. Bone Marrow Transplant 1998;22:53-9.
13. Paya K, Horcher E, Lawrenz K, et al. Bilateral Wilms' tumor--surgical aspects. Eur J Pediatr Surg 2001;11:99-104.
14. Paulino AC, Wilimas J, Marina N, et al. Local control in synchronous bilateral Wilms tumor. Int J Radiat Oncol Biol Phys 1996;36:541-8.
15. DeLorimier AA, Belzer FO, Kountz SL, et al. Treatment of bilateral Wilms' tumor. Am J Surg 1971;122:275-81.
16. Davidoff AM, Giel DW, Jones DP, et al. The feasibility and outcome of nephron-sparing surgery for children with bilateral Wilms tumor. The St Jude Children's Research Hospital experience: 1999-2006. Cancer 2008;112:2060-70.
17. Paulino AC, Thakkar B, Henderson WG. Metachronous bilateral Wilms' tumor: the importance of time interval to the development of a second tumor. Cancer 1998;82:415-20.
18. Aronson DC, Slaar A, Heinen RC, et al. Long-term outcome of bilateral Wilms tumors (BWT). Pediatr Blood Cancer 2011;56:1110-3.

Cite this article as: Özyörük D, Emir S. The management of bilateral Wilms tumor. Transl Pediatr 2014;3(1):34-38. doi: 10.3978/j.issn.2224-4336.2014.01.04