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A Role of brachytherapy in bilateral Wilms tumors: A long-term follow-up of three highly selected cases and literature review

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ABSTRACT

PURPOSE: To describe experience with partial nephrectomy combined with brachytherapy as part of the local management of bilateral Wilms tumor (WT) including a review of the available literature.

RESULTS (METHODS AND CASE DESCRIPTION): Between 2011 and 2014, three highly selected patients (age nine months, 16 months, and 4 years) with bilateral WT (two synchronous and one metachronous) underwent enucleation and perioperative brachytherapy to the tumor bed. With a minimum follow-up of 5 years, all three patients are in continuous complete remission with preserved kidney function.

CONCLUSIONS: Although nephron sparing surgery aiming at tumor free-margins remains the gold standard for bilateral WT, tumor enucleation followed by brachytherapy may be considered in carefully selected patients at high risk for end-stage kidney failure. Given the rarity and complexity of the procedure, concentration of care of such patients is mandatory.

Keywords: Wilms tumor; Brachytherapy; Enucleation

Introduction

Wilms tumor (WT) presents bilaterally in around 4%–8% of the cases and is classified as Stage V (1–3). For patients with Stage V WT, worldwide, the standard treatment includes chemotherapy followed by surgery. The standard surgical approach for unilateral WT remains nephrectomy. However, in case of synchronous or metachronous WT, surgical strategy includes, whenever feasible, partial nephrectomy intending to preserve renal parenchyma capacity as much as possible to maintain good long-term renal function aiming for complete surgical excision with free margins (4, 5). Usually, centrally located tumors are considered

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unsuitable for partial nephrectomy and most of these patients undergo total nephrectomy, resulting in end-stage renal disease and subsequent dialysis when previously total nephrectomy of the contralateral kidney had been performed. In case of microscopic irradical resection (R1, local Stage III) after partial nephrectomy, adjuvant external beam radiotherapy (EBRT) is recommended for patients with intermediate- and high-risk histology to reduce the risk of local relapses. Efforts have been made to limit the radiation dose to the remaining kidney parenchyma under 10-12 Gy aiming to preserve renal function. However, about 35% of these patients undergoing postoperative radiotherapy have some measurable renal impairment and about 12% will end up having end-stage renal failure (6). To minimize the delivered dose to the healthy-appearing renal tissue, a renal sparing brachytherapy technique has been previously described, in a limited series of patients (3, 7, 8). Between 2001 and 2014, this procedure was considered in three patients with bilateral WT at the Amsterdam University Medical Centers (location Academic Medical Center). In these exceptional cases limited partial nephrectomy, so called enucleation was performed, followed by brachytherapy with the purpose of sparing renal parenchyma, while maintaining oncological safety. A description of these three cases and long-term follow-up is presented, as well as an overview of the literature.

Results (methods and case description)

Case 1

A 4-year-old woman presented at the age of 4 months with a genetically confirmed aniridia, genitourinary malformation, mental retardation syndrome (WAGR) (chromosome 11p13 deletion), and bilateral nephroblastomatosis. The patient was subsequently treated with weekly vincristine (VCR) and actinomycin-D (ACD) for 8 weeks resulting in stable disease. After 1 year, one lesion in the left kidney increased in size and total left nephrectomy was performed. Histology revealed Stage I, intermediate-risk (IR) WT, and stromal type. Adjuvant chemotherapy (VCR-ACD) was administered during 1 year as per the SIOP-WT-2001 protocol. The lesion in the right kidney was centrally located and remained stable for 2 years after completion of postoperative chemotherapy, after which it started to increase in size. At the time of referral, the tumor size was 1.2 cm in all planes. On MRI, no suspicious lymph nodes were reported. Because of central location of the tumor, no radical surgery with preservation of the renal parenchyma was feasible. Extensive discussion in the multidisciplinary tumor board (MTB), eventually lead to enucleation of the tumor with intraoperative placing of a brachytherapy applicator, which consisted of a Porges Folisyl Foley 12Fr catheter with an intraluminal dummy afterloading tube and partially inflated balloon (3 mL of sterile physiological salt solution) filling the tumor bed for perioperative brachytherapy. The renal capsule was closed over the catheter ensuring stability of the brachytherapy implant. Intraoperative frozen sections identified intermediate-risk WT mixed-type in the surgical specimen with a close surgical margin. After 24 h, a planning CT scan for pulsed dose rate (PDR) brachytherapy was performed. The clinical target volume (CTV) was defined as 5 mm of tissue from the surface of the Foley balloon to encompass the potential microscopically residual tumor. Dose calculations were performed using the Oncentra Brachy treatment planning system (Elekta, Stockholm, Sweden). From day 1–2 postsurgery, a prescribed dose of 14 Gy in 28 pulses of 50 cGy each, with an interpulse period of 1 h, was delivered. The dose was specified at the reference dose-rate curve encompassing the CTV. The minimum dose received by 90% of the CTV (D_{90}) was 15.8 Gy, whereas the dose received by 50% of the remaining right kidney ($D_{50\%}$) was 3.3 Gy. The volume of the remaining right kidney receiving 10 Gy (V_{10Gy}) excluding the CTV was 6.4%. Details on patient characteristics and dosimetry parameters are depicted in Table 1. Treatment was delivered successfully without postoperative complications. Removal of the brachytherapy applicator did not require any new surgical intervention or sedation: deflating the Foley catheter balloon and pulling the catheter out of the patient was sufficient. Definite histology analysis reported the presence of IR nephroblastoma, mixed-type, reaching the specimen resection margin focally. At present, 8 years after completion of treatment, the patient is in continuous complete remission with no evidence of chronic kidney disease.

Case 2

The second patient was a woman referred with a synchronous nonsyndromic bilateral WT diagnosed at the age of 16 months. Ultrasound and MRI scan revealed the presence of bilateral heterogeneous centrally located kidney lesions without pathologically enlarged lymph nodes. The left-sided renal mass showed solid and cystic components and had a maximum diameter of ±7.5 cm and the right-sided mass ±6.5 cm. Chemotherapy as per the SIOP-WT-2001 protocol was administered consisting of 4 weeks of intravenous VCR and ACD. After 3 weeks, doxorubicin (DOX) was added because of poor radiological response at first assessment (i.e. the left- and right-sided tumors had shrunk to a maximum diameter of 5.4 cm and 5.1 cm, respectively) (Fig. 1). Partial nephrectomy with wide surgical margins was not feasible because of the localization of both tumors. As agreed in the MTB, both kidneys were operated on during the same session: a left-sided total nephrectomy was performed followed by a right-sided kidney sparing surgical procedure. The right-sided tumor was enucleated after which the brachytherapy catheter was placed for perioperative irradiation of the tumor bed. The same PDR brachytherapy prescription dose and reference

Table 1
Patients characteristics and brachytherapy dosimetric parameters of the at-present published patients with Wilms tumor treated with brachytherapy in first-line treatment

Patient	Author	Gender/ age	Side	Syndrome	CHT	Histology	BT dose/ pulse or fraction dose (Gy)	BT source	Volume of remaining R kidney at time of BT (cm3)	CTV D90 (Gy) [EQD2 α/β 10]	CTV D98 (Gy) [EQD2 α/β 10]	D50% remaining kidney treated by BT excluding CTV (Gy) [EQD2 α/β 3]	V14 Gy remaining kidney treated by BT excluding CTV (%)	V10 Gy remaining kidney treated by BT excluding CTV (%)	Renal function after treatment	Outcome
1	Dávila *et al.*	Female/4y	Right	WAGR	VCR, ACD	IR mixed-type	14/0.5	PDR (^{192}Ir)	60	15.8	12.3	3.3	1.6	6.4	Normal	NED
2	Dávila *et al.*	Female/ 16 mo	Right	None	VCR, ACD, DOX	IR mixed-type	14/0.5	PDR (^{192}Ir)	80	13.2	10.7	1.7	0.3	1.7	Normal	NED
3	Dávila *et al.*	Female/ 9 mo	Right	Frasier	VCR, ACD, DOX	CPDN	14/0.5	PDR (^{192}Ir)	53	14.6	11.9	3.1	0.3	4	Discrete declined serum creatinine with adequate eGFR	NED
4	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, DOX, CP, VP-16, Carbo	Favorable	10/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	NED
5	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, DOX	Favorable	30/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	NED
6	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, DOX	Favorable	20/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	NED
7	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, DOX, CP, VP-16, Carbo, IFO	Anaplasia	15/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	Alive with metastatic disease
8	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, CP, VP-16	Favorable	10/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	DOD
9	Cooper *et al.* (3)	NR	NR	NR	VCR, ACD, DOX, CP, VP-16, Carbo	Anaplasia	10/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	DOD
10	Cooper *et al.* (3)	NR	NR	DDS	VCR, ACD, DOX, CP	Favorable	20/NA	LDR (^{137}Cs/^{192}Ir)	NA	NR	NR	NA	NA	NA	Anephric	NED
11	Nag *et al.* (18)	Female/2y	NR	NR	NR	NR	15/NR	HDR (^{192}Ir)	NA	NR	NR	NA	NA	NA	NR	NED

Mo = months; Y = years; WAGR = Wilms tumor, aniridia, genitourinary, and retardation; DDS = Denys-Drash syndrome; CHT = chemotherapy; VCR = vincristine; ACD = actinomycin-D; DOX = doxorubicin; CP = cyclophosphamide; VP-16 = etoposide; Carbo = carboplatin; IFO = ifosfamide; IR = intermediate-risk; CPDN = cystic partially differentiated nephroblastoma; BT = brachytherapy; Gy = Gray; PDR = pulsed-dose-rate; LDR = low-dose-rate; HDR = high-dose-rate; CTV = clinical target volume; D_{90} = minimum dose received by 90% of the CTV; D_{98} = minimum dose received by 98% of the CTV; $D_{50\%}$ = dose received by 50% of the remaining right kidney; R = right; EQD_2 = equivalent dose in 2 Gy fractions; V = volume; eGFR = estimated glomerular filtration rate; NED = no evidence of disease; DOD = dead of disease; NR = not reported; NA = not applicable.

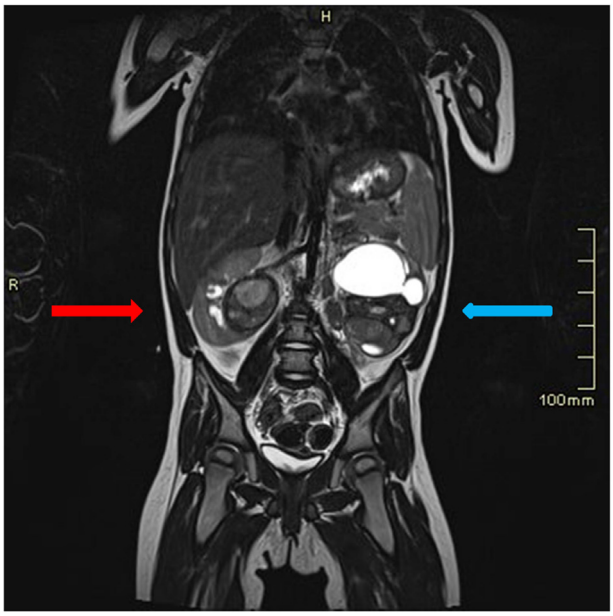

Fig. 1. Tumor extension on MRI (T2W coronal series) at response assessment before surgery (patient 2). Left-sided tumor was surgically treated with total nephrectomy (blue arrow). Right-sided tumor was treated with enucleation and brachytherapy (red arrow).

dose specification that were used for case number one were applied (Fig. 2). The dosimetric parameters CTV D_{90} and $D_{50\%}$ of the remaining right kidney were 13.2 Gy and 1.7 Gy, respectively. The V_{10Gy} of the remaining right kidney excluding the CTV was 1.7%. Patient and brachytherapy details are depicted in Table 1. With the exception of a self-resolving intraabdominal urine leakage after removal of the brachytherapy catheter, no treatment-related complications occurred. Histological examination of the left kidney showed Stage I, mixed-type nephroblastoma (IR). Histological examination of the right kidney showed the presence of a mixed-type nephroblastoma, arising in preexistent intralobar nephroblastomatosis, extending into the resection margins (local Stage III, IR). No pathologic lymph node involvement was histologically assessed. The patient received maintenance chemotherapy for a total of 1 year (VCR-ACD). Five years after the end of treatment, there is no evidence of disease, and the patient has normal renal function.

Case 3

A 9-month-old girl known to have germline WT-1 deletion and gonadal dysgenesis (karyotype 46-XY hypo virilization) with gonadoblastoma in the right ovary (bilateral gonadectomy at 4 weeks of age) (Frasier syndrome), was diagnosed with synchronous bilateral WT. On MRI, the left-sided tumor was located in the upper pole and measured approximately 9 cm in maximum diameter. In the right kidney, there were two centrally located tumors (in close contact with the hilum), with a 1 cm diameter each and showing similar radiological characteristics on MRI as the lesion in the left kidney, as well as three more smaller cystic lesions at the lower pole. The patient received 4 weeks of induction chemotherapy as advised in the SIOP-WT-2001 protocol with minimal radiological response followed by a left-sided partial nephrectomy achieving radical removal of nephroblastoma, mixed-type (local Stage I, IR), and negative lymph nodes. Subsequently, the patient completed 4 weeks of chemotherapy with addition of DOX because of a disappointing radiologic response and underwent subsequent tumor enucleation of both centrally located tumors of the right kidney with intraoperative placing of a brachytherapy catheter for perioperative PDR brachytherapy as described in the previous two cases. After extensive discussions during MTB, the major reason to consider the brachytherapy approach in this patient instead of total nephrectomy of the right kidney was the fact that nearly half of the left kidney parenchyma was removed during initial partial nephrectomy (at time of brachytherapy, the volume of the remaining left kidney was 26 cm^3) which potentially could not preclude renal failure. The CTV D_{90} achieved was 14.6 Gy maintaining a $D_{50\%}$ of 3.1 Gy for the remaining right kidney. The V_{10Gy} of the remaining right kidney excluding the CTV was 4%. Details on patient characteristics and dosimetry parameters are depicted in Table 1. No complications were observed, neither surgery nor brachytherapy related. Histological analysis and central revision revealed mature nephroblastoma (cystic partially differentiated nephroblastoma) (local Stage I, low risk). No additional maintenance chemotherapy was administered. Eight years after the end of treatment, the patient is doing well in continuous complete remission. During the most recent regular follow-up visit, mild hypertension and slight worsening of the renal function were noted (serum creatinine 49umol/L [ref. 30–47] with adequate estimated glomerular filtration rate (Schwartz) 96 mL/min/1.73 m^2 [ref. ≥90 mL/min/1.73 m^2] and no increased albuminuria (9 mg/L) [ref. 0-30 mg/L]). No other signs of chronic treatment–related toxicity have been observed, so far.

Discussion

The management of synchronous or metachronous bilateral WT (Stage V) represents a challenge and, within the context of standard of care, an individualized approach is often inevitable. Although the long-term disease-free survival rate of patients with nonmetastatic unilateral nephroblastoma currently reaches 90%, the cure rate for patients with bilateral disease does not exceed 80% in the most experienced centers (9–13). In this group of patients, mortality is generally related to poor response to chemotherapy and progressive disease but also to ultimate renal

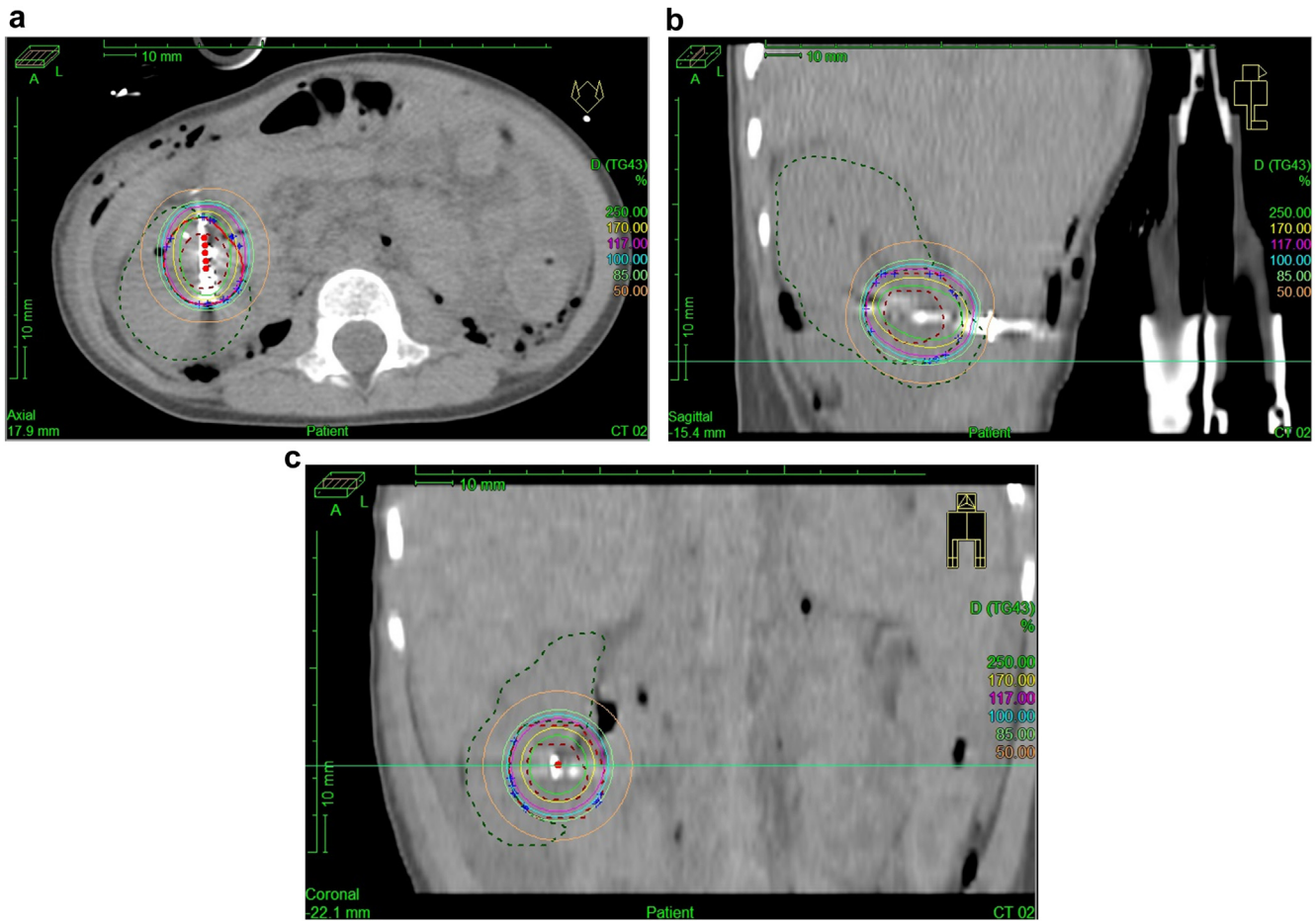

Fig. 2. Brachytherapy isodose distribution after left-sided nephrectomy and tumor enucleation of the right kidney (patient 2). Dark brown dashed line: balloon brachytherapy applicator surface. Red solid (a, axial view) and dashed (b, sagittal view and 2c, coronal view) lines: clinical target volume (CTV). Green dashed line: surface of the remaining kidney. Light blue solid line: isodose area receiving 100% of the prescribed dose. Light orange solid line: isodose area receiving 50% of the prescribed dose.

insufficiency. The latter may be due to underlying predisposing syndromes that intrinsically lead to glomerular sclerosis and subsequent early end-stage renal disease, as well as to the need for aggressive surgery often including sacrificing critical amounts of vital kidney (14–16). Over the past 30 years, all efforts of the medical community were directed toward preservation of the remaining functioning tissue in an attempt to avoid ultimate renal transplantation. Therefore, nephron sparing surgery (NSS) has become, whenever feasible, the current standard local management of Stage V WT (4, 5, 17). However, this surgical approach has its technical limitations, as hilar lesions and centrally located tumors are often considered not suitable for NSS because extensive resection may impair blood supply to the remaining parenchyma. In some cases, tumor enucleation may be considered although it may imply a higher risk of microscopic residual tumor, a fact which is inherent to NSS (7). In such cases, postoperative irradiation of the flank including the remaining kidney with EBRT is indicated.

Brachytherapy is a type of radiotherapy that permits to irradiate the minimal residual tumor (tumor bed) while minimizing the volume of normal renal tissue being irradiated. We considered this technique under strict conditions, and it has been successfully pursued in our three highly selected cases. Including the three patients described in the present article, so far limited experience has been reported in 13 children with WT, 11 in first-line therapy, and two in relapsed setting. 11 patients are alive at time of publication, and two have died with disease; none of them developed a local recurrence (3, 18–20). Details on the published patients with bilateral WT treated with brachytherapy in first line treatment are depicted in Table 1.

Two cases have been reported in which brachytherapy was used in patients with local recurrent WT (19, 20). Flower *et al.* described one patient with unilateral WT who had previously undergone a left-sided nephrectomy followed by whole abdominal EBRT (10.8 Gy in six fractions) because of a Stage III WT at 2 years of age. The patient presented 11 years later with a first locoregional recurrence

(para-aortic) which was treated with chemotherapy, surgery, and whole abdominal/pelvic EBRT (15 Gy in 10 fractions with right kidney shielding, followed by a boost of 10.5 Gy in seven fractions to the tumor bed). Three years later, a presacral recurrence occurred. After macroscopic excision, HDR brachytherapy (Freiburg flap) was administered to a dose of 26 Gy in five fractions followed by hyperthermic intraperitoneal chemotherapy. The patient was free of disease after 12 months (19). Another patient with locally recurrent metachronous WT after partial nephrectomy and previous contralateral nephrectomy was treated with a combination of enucleation, brachytherapy (17 Gy, ^{192}Ir), and EBRT (33 Gy) concomitant to adjuvant chemotherapy. The patient was alive after 10 years without evidence of disease or renal function impairment (20).

There is limited experience about the role of brachytherapy in adults with renal tumors, mainly renal cell carcinoma, but the preliminary results of currently ongoing prospective Phase I and Phase II studies using interstitial ablative brachytherapy in inoperable patients with small tumors suggest good local control and response of the renal cell carcinoma (21).

Careful selection of our three patients for this procedure by an experienced multidisciplinary team in combination with an expert setting for brachytherapy and surgery is essential to make this approach feasible. The relevance of centers of excellence for such rare and challenging pediatric renal cancers has recently been acknowledged by the European Expert Pediatric Oncology Reference Network for Diagnostics and Treatment (22). With a minimum follow-up of 5 years, all three patients have remained in complete remission with preserved renal function. It remains unclear whether the decline in renal function of the third patient with WT-1 germline mutation after 8 years is the consequence of treatment-related damage (chemotherapy, surgery, and brachytherapy) or due to damage in the context of WT-1 deletion (14,16).

The dose received by the remaining kidney in all three patients was remarkably lower than the standard kidney dose constraint considered when applying EBRT (10 Gy), which minimizes the risk of radiotherapy-related renal dysfunction, as illustrated by the dose received by 50% of the remaining kidney ($D_{50\%}$) (Table 1). In addition, because of the dose distribution inherent to brachytherapy, the CTV receives a higher equivalent dose in 2 Gy fractions (EQD_2) in comparison with EBRT while maintaining the remaining kidney dose sparing, highlighted in our case series by the minimum dose received by 90% of the CTV (D_{90}) (Table 1). Dose distribution for patient two is presented in Fig. 2. The prescription dose, 14 Gy, was selected by analogy to the prescription for EBRT as recommended in the SIOP-WT-2001 protocol and was consistently applied in all three patients.

Irradiating patients before definitive pathological findings are available can be considered a disadvantage of this procedure. However, in equivocal cases, after intraoperative placing of the brachytherapy catheter, the brachytherapy administration can be delayed until this information is available. Whether any kind of radiotherapy could have been avoided in the third patient (local Stage I, low-risk histology) remains a matter of debate. In addition, because the patient received intensive chemotherapy after initial left-sided NSS (8 weeks of VCR, ACD, and 4 weeks of DOX), as is often the case in Stage V patients, the definitive histology of the right-sided enucleation is conceivably downstaged. So far, in our series, no major acute complications have been encountered. If correctly applied, no other complications than what is expected after regular partial nephrectomy surgery may be anticipated because no supplementary surgical procedure is required to remove the brachytherapy implant and the overall brachytherapy time is short. For tumors located in the renal pelvis special attention should be made to avoid high-dose areas at the level of the renal vein/artery and ureter to prevent long-term stricture at this level.

Although the current approach is not encouraged in standard practice, a highly selected subgroup of Stage V WT may benefit from available experience with BT. This procedure may be considered for synchronous or metachronous WT, and exclusively being performed by an experienced team, in a dedicated center, under strict conditions: 1. infeasibility of NSS with wide resection margins; 2. NSS resulting in an unacceptable loss of nephron mass, that is, <50% of the initial kidney volume (23); 3. absence of lymph node involvement based on imaging at diagnosis and preoperatively; 4. tumor volume at diagnosis <300 mL because this parameter correlates with very low risk of lymph node invasion (24, 25). The presence of an underlying predisposition syndrome (e.g. WAGR, Denys-Drash syndrome, and Frasier syndrome) may further guide decision-making because these patients are at higher risk of end-stage renal disease, and the overall aim is to preserve as much functional renal tissue as possible for normal growth and development without compromising outcomes.

Conclusion

The standard approach for bilateral WT remains, whenever feasible, NSS with the aim to obtain a complete resection with adequate margins. However, in highly selected cases, tumor enucleation followed by brachytherapy to the tumor bed may be considered to preserve renal function when wider partial nephrectomy is not achievable. Given the rarity and complexity of the procedure, concentration of candidate patients in tertiary pediatric oncology centers that guarantee adequate multidisciplinary care is warranted.

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References

[1] De Backer A, Lamote J, Keuppens F, *et al*. Bilateral Wilms' tumor: in situ cooling of the kidney facilitates curative excision of tumors, with preservation of renal function. *J Pediatr Surg* 1995;30:1338–1340.

[2] D'Angio GJ. *National Wilms' Tumor Study*. Seattle, WA: NWTS Data and Statistical Center; 1991. [Informational bulletin #19].

[3] Cooper CS, Jaffe WI, Huff DS, *et al*. The role of renal salvage procedures for bilateral Wilms tumor : a 15-year review. *J Urol Oncol* 2000;163:265–268.

[4] Fuchs J, Szavay P, Seitz G, *et al*. Nephron Sparing Surgery for synchronous bilateral nephroblastoma involving the renal hilus. *Pediatr Urol* 2011;186:1430–1436.

[5] Wilde JCH, Aronson DC, Sznajder B. Nephron sparing surgery (NSS) for unilateral Wilms tumor (UWT): the SIOP 2001 experience. *Pediatr Blood Cancer* 2014;61:2175–2179.

[6] Smith GR, Thomas PRM, Ritchey M, *et al*. Long-term renal function in patients with irradiated bilateral Wilms tumor. *Am J Clin Oncol* 1998;21:58–63.

[7] Thoms WW, Goldwein JW, D'Angio G. A technique for the use of afterloading 137Cs brachytherapy in renal-sparing irradiation of bilateral Wilms tumor. *Int J Radiat Oncol Biol Phys* 1997;39:1121–1124.

[8] Duckett CP, Zderic S, Goldwein J, *et al*. Brachytherapy for residual intra-renal Wilms' tumor. *Med Ped Oncol* 1997;28:316–320.

[9] Ehrlich PF. Bilateral Wilms' tumor: the need to improve outcomes. *Exper Rev Anticancer Ther* 2009;9:963–973.

[10] Dome JS, Cotton CA, Perlman EJ, *et al*. Treatment op anaplastic histology Wilms' tumor: results from the Fifth National Wilms' tumor study. *J Clin Oncol* 2006;24:2352–2358.

[11] Pritchard-Jones K, Bergeron C, De Camargo B, *et al*. Omission of doxorubicin from the treatment of stage II–III, intermediate-risk Wilms' tumour (SIOP WT 2001): an open-label, non-inferiority, randomised controlled trial. *Lancet* 2015;386:1156–1164.

[12] Dome JS, Graf N, Geller JI, *et al*. Advances in Wilms tumor treatment and Biology: Progress through International Collaboration. *J Clin Oncol* 2015;33:2999–3007.

[13] De Kraker J, Graf N, Van Tinteren H, *et al*. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. *Lancet* 2004;364:1229–1235.

[14] Bache M, Dheu C, Doray B, *et al*. Frasier syndrome, a potential cause op end-stage renal failure in childhood. *Pediatr Nephrol* 2010;25:549–552.

[15] Satín S, Fraga G, Ruíz P, *et al*. WT1 mutations may be a cause of severe renal failure due to nephroblastomatosis in Wilms' tumor patients. *Clin Nephrol* 2011;76:244–248.

[16] Demmer L, Pimack W, Loik V, *et al*. Frasier syndrome: a cause of focal segmental glomerulosclerosis in a 46,XX female. *J Am Soc Nephrol* 1999;10:2215–2218.

[17] Van den Berg RNW, Bierman EN, Van Noord M, *et al*. Nephron-sparing surgery for Wilms tumor: a systematic review. *Urol Oncol* 2016;34:24–32.

[18] Nag S, Tippin D, Ruyman FB. Intraoperative high-dose-rate brachytherapy for the treatment of pediatric tumors: the Ohio State University Experience. *Int J Radiat Oncol Biol Phys* 2001;51:729–735.

[19] Flower E, Ngoc Tran K, Zanjani S, *et al*. Pediatric peri-operative fractionated high-dose-rate brachytherapy for recurrent Wilms' tumor using a reconstructed Freiburg flap. *J Contemp Brachytherapy* 2016;8:429–433.

[20] McMagnus MC, Silliman C, Koyle A. Combined endoscopic resection and brachytherapy for recurrent intrapelvic Wilms tumor. *J Urol* 2002;167:2540.

[21] Wendler JJ, Liehr BU, Damm R, *et al*. Small renal carcinoma: the "when" and "how" of operation, active surveillance. *Ablationpol J Radiol* 2018;83:e561–e568.

[22] Van den Heuvel-Eibrink MM, Hol JA, Pritchard-Jones K, *et al*. Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. International Society of paediatric oncology — renal tumour study group (SIOP–RTSG). *Nat Rev Urol* 2017;14:743–752.

[23] Cozzi DA, Zani A. Nephron-sparing surgery in children with primary renal tumor: Indications and results. *Semin Pediatr Surg* 2006;15:3–9.

[24] Godzinski J, van Tinteren H, de Kraker J, *et al*., SIOP Nephroblastoma Trial & Study Committee. Nephroblastoma: does the decrease in tumor volume under preoperative chemotherapy predict the lymph nodes status at surgery? *Pediatr Blood Cancer* 2011;57:1266–1269.

[25] Godzinski J, Graf N, Audry G, *et al*. Current concepts in surgery for Wilms tumor - the risk and function-adapted strategy. *Eur J Pediatr Surg* 2014;24:457–460.