Characteristics and outcome of synchronous bilateral Wilms tumour in the SIOP WT 2001 Study: Report from the SIOP Renal Tumour Study Group (SIOP-RTSG)

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Contributions

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ABSTRACT

Background

Among patients with nephroblastoma, those with bilateral disease are a unique population where maximising tumour control must be balanced with preserving renal parenchyma.

Methods

The SIOP 2001 protocol recommended surgery after neoadjuvant cycle(s) of Dactinomycin and Vincristine (AV) with response-adapted intensification, if needed. Adjuvant treatment was given based on the lesion with the worst histology.

Results

Three hundred and twenty seven patients with stage V disease were evaluable: 174 had bilateral Wilms tumour (BWT), 101 unilateral WT and contralateral nephroblastomatosis (NB) and 52 bilateral nephroblastomatosis. In these three groups, the estimated 5y-EFS was 76.1%, 84.6%, and 74.9%, respectively. AV chemotherapy alone was the successful chemotherapy for 58.7% of all the patients and 65.6% of the non-metastatic patients. Among the 174 patients with BWT, 149 (88.2%) had at least one nephron-sparing surgery. Twenty of 61 bilateral stage I patients were treated with four-week AV postoperatively achieving 94.4% 5y-EFS. At last follow-up, 87% of patients had normal renal function.

Conclusions

This study demonstrates that AV without anthracyclines is sufficient to achieve NSS and good survival in the majority of patients. For patients with bilateral stage I WT and intermediate risk histology, only four weeks adjuvant AV seems to be sufficient.

Clinical Trial Registration

NCT00047138

Introduction

Wilms tumour (WT) is the most common childhood renal cancer and generally has very good survival rates with complete tumour resection. While the vast majority of tumours occur unilaterally, 5–8% of patients present with bilateral disease (stage V). Bilateral Wilms tumour (BWT) may present as synchronous (both kidneys affected at the same time) in about 6–7% cases, or less frequently (<1%) as metachronous disease [1, 2]. Moreover, BWT are nearly always associated with nephrogenic rests. These benign but hyperplastic lesions may be so large that they are detectable as expansile lesions on imaging and are commonly named as nephroblastomatosis (NB). These are often difficult to distinguish from 'true' Wilms tumour until resected.

Management of BWT presents a particular challenge in balancing the aim of maximising survival involving optimal surgical clearance of disease, while preserving sufficient renal parenchyma for lifelong renal function. Thus, determining the optimal timing for NSS and considering how associated genetic features may indicate the risk of future tumour development is crucial. Historically, patients with BWT had significantly worse survival than those with unilateral disease [3]. Previous results from the Renal Tumour Study Group of the "Société Internationale d'Oncologie Pédiatrique"' (SIOP-RTSG) indicated improved tumour volume reduction with prolonged and intensified preoperative treatment, which allowed a greater opportunity for NSS and better survival [4, 5]. Harmonised approaches including standardised preoperative chemotherapy, surgical resection guidelines, and risk-adapted post-operative treatment according to tumour response and histology have evolved over the last three decades in both SIOP-RTSG and the Children's Oncology Group (COG) resulting in improved Event-free and Overall survival (EFS and OS) [5,6,7,8].

The rate of end stage renal disease (ESRD) is reportedly higher in children with BWT than in unilateral WT [9]. In addition to the greater loss of renal parenchyma through tumour surgery, BWT patients have a higher rate of WT1 germline pathogenic variants leading to intrinsic renal disease that can cause progressive loss of renal function at a young age [10]. Nevertheless, the wide use of NSS allows the preservation of satisfactory renal function in the majority of these patients without affecting OS. However, NSS may induce a higher risk of positive resection margins, and the resulting need for radiotherapy to the renal remnant may accelerate loss of intrinsic renal function. In addition, remaining nephrogenic rests spared by NSS may risk local recurrence when compared to unilateral WT treated with complete nephrectomy [11, 12], particularly in the context of genetic predisposition.

Chemotherapy recommendations for the treatment of BWT have been largely based on the success of treating unilateral WT in successive large randomised controlled trials

and prospective registration studies led by the SIOP-RTSG and the COG-RTC. In the randomised SIOP 9 study, one 4-week cycle of AV was compared to two cycles (8 weeks) of AV. No significant further reduction in the proportion of stage III tumours was achieved with an additional 4-week pre-operative treatment cycle (total of 8 weeks), though most patients showed further volume reduction when receiving a second cycle [4]. Thus, the SIOP-RTSG SIOP2001 study approach for bilateral disease consisted of repeated 4-week cycles of AV to achieve response, with addition of anthracycline in case of insufficient response. Likewise, the COG approach to bilateral disease (AREN 0534 - 2009 – 2014) consisted of response adapted one or two cycles of six-week AV, intensified up-front with anthracycline [7].

Here, we present the results of the prospective SIOP 2001 study for patients with synchronous bilateral disease. These included patients with localised bilateral WT, localised unilateral WT and contralateral NB, and localised bilateral NB. The response to AV neoadjuvant therapy was of particular interest. Metachronous diseases will be the subject of a subsequent paper.

Materials and Methods

Study design and enrolment

The SIOP 2001 study was an international, multi-institutional study for all childhood renal tumours that was conducted between November 2001 and September 2017 in 251 hospitals in 26 countries. National and local regulatory and ethical approvals were obtained according to national regulations. It was a prospective protocol with recommendations for treatment of all stages of WT, including BWT and NB, and included a randomised question regarding optimal post-operative therapy for patients with unilateral stage II and stage III intermediate-risk histology WT. The randomisation closed in December 2011 when the experimental reduced therapy arm was adopted as the new standard of care. Following the closure of the randomisation, the study remained open as a prospective registration study in most participating countries. The therapeutic protocol for patients with bilateral tumours was unchanged from 2001 to 2017. The parents or guardians signed a written informed consent for enrolment and treatment of their child in the SIOP 2001 study. All data about clinical characteristics, pathology, surgery, chemotherapy, radiotherapy, and outcome were collected prospectively.

Eligibility

All patients under 18 years at diagnosis with a renal tumour were eligible for enrolment. They were divided in 3 groups:

Localised disease patients

Metastatic disease patients

Synchronous bilateral tumour patients.

Results for localised, metastatic, and selected non-Wilms tumours have already been reported [13,14,15].

The current subgroup-analysis includes all patients with a registered synchronous bilateral disease (stage V), as previously defined, including metastatic stage V.

Treatment for bilateral disease

The overall strategy was to administer response-adapted preoperative chemotherapy with the goal to facilitate bilateral nephron-sparing surgery with negative margins. First line chemotherapy consisted of AV: Vincristine d1/8/15/22, 1.5 mg/m2 body surface and Actinomycin D d1/d15, 45 µg/kg bodyweight, with drug adjustments for age and weight applicable, for 4 weeks followed by imaging reassessment. We assessed treatment response by imaging-defined change in tumour volume between diagnosis and following each cycle of chemotherapy. A subjective surgical assessment of NSS feasibility was additionally carried out. Further 4-week cycles were administered as long as response was observed and deemed likely to facilitate NSS according to a multi-disciplinary team (MDT) or treating physicians' decision. If response to AV cycles was insufficient and/or NSS still not feasible, treatment was intensified with the anthracycline Doxorubicin. Surgery consisted either bilateral NSS if feasible or total nephrectomy (TN) combined with NSS. Bilateral TN was only acceptable in exceptional circumstances (for example in patients with existing end-stage renal disease). There were no specific guidelines concerning the timing of surgery in terms of a one- or two-step approach. Each centre proceeded according to the local surgeon's approach. No detail concerning the surgical rationale for each particular approach was collected in the database.

Surgery was followed by adjuvant chemotherapy and radiotherapy (12–25 Gy) for local stage III cases, and systemic treatment was determined by the lesion with the highest stage and highest risk histology, according to the treatment recommendation for localised disease with at least local stage II. Flow charts and details on treatment approach and schedules are depicted in Supplementary File 1.

Statistical considerations

Data were collected prospectively in the context of the SIOP2001 Trial and Study.

Event free survival (EFS) and overall survival (OS) were calculated from the date of diagnosis to any recurrence or death, and to death for any reason, respectively. Patients who were event-free at the end of follow-up were censored at that time. The survival curves were calculated according to the Kaplan-Meier method. The median follow-up was calculated using the reverse Kaplan-Meier method. Statistical analysis was performed using SAS v9.4 and R v4.02. In statistical analysis comparing patients with NSS and bilateral TN, if patients underwent NSS for at least 1 side, They were classified "NSS".

Results

Patient characteristics

Between June 2001 and September 2017, 4899 children with renal tumours were registered in the prospective SIOP2001 study, of which 327 patients had synchronous bilateral disease, (6.6%). Of these, 174 presented with BWT, 101 with unilateral WT associated with contralateral or bilateral NB, and 52 with bilateral NB without WT. Table 1 shows the patient characteristics and recruiting groups.

Preoperative treatment (Fig. 1)

Of 174 patients with BWT, 2 underwent upfront surgery, 3 had unknown preoperative treatment, 135 had upfront AV, and 34 metastatic patients received upfront AVD. Eighty-five of 135 patients responded sufficiently to the AV regimen, hence facilitating NSS in 76 patients, accounting for 45% of all and 56.3% of the non-metastatic patients. Among these 76 patients, 26 underwent NSS both sides and 50 NSS one side + nephrectomy other side. Following AV, despite volumetric response, 6 patients underwent bilateral nephrectomy due to end-stage renal disease (ESRD) in Denys Drash Syndrome. Among the 50 patients with poor volumetric tumour response, 20 patients were intensified to AVD, and 6/20 received yet another chemotherapy. The remaining 30 received no doxorubicin, but alternative preoperative cytotoxic agents such as etoposide + carboplatin for intensification as described in Supplementary File 1. The median duration of preoperative chemotherapy was 11.6 weeks, ranging from 2 to 48.8 weeks.

Among the 101 patients with unilateral WT and contralateral NB, 4 patients underwent primary surgery and information was missing for two. AV alone was sufficient to achieve NSS for a majority of patients (*N* = 71; 72% of the total and 86% of non-metastatic cases). In 20 patients, doxorubicin was added and alternative chemotherapy was used in only 4 patients. The median duration of preoperative chemotherapy in this group was 9.6 weeks, ranging from 3 to 29.5 weeks.

In cases with bilateral NB, AV was the only chemotherapy given to 36/52 (72%) patients and only 10 received additional doxorubicin [2] or other drugs [8]. Unexpectedly in this group, we observed 4 cases who underwent upfront surgery. Data are missing for 2 patients The median duration of preoperative treatment was longer than in the other groups: 14 weeks, ranging from 3 to 49 weeks. This included 24 patients who never proceeded to surgery (Compare Table 2) because all lesions disappeared with chemotherapy alone.

In summary, among the 327 patients, 276 (135 + 95 + 46) received AV as preoperative chemotherapy. Only 84 patients (30.4%) had an insufficient volumetric tumour response with AV and received intensified chemotherapy (42 AVD and 42 others alternative drugs). AV alone was the successful chemotherapy for 192 patients (58.7% of all and 65.6% of the non-metastatic patients).

Surgical Management (Table 2)

For the 174 patients with BWT, among 169 patients with complete data, 149 (88.2%) had at least one NSS: 48 (28.4%) had bilateral NSS, 101 (59.7%) had one NSS + contralateral TN. 76 patients had at least one NSS after AV alone. Bilateral nephrectomy was performed in 14 children where there was no possibility of nephron salvage by NSS, and in six because of ESRD in Denys Drash Syndrome, making nephron salvage redundant. Bilateral surgeries were performed simultaneously for 97 patients (56%) and sequentially in two separate steps with interval chemotherapy for 77 patients.

Our data did not suggest a relationship between the percentage of NSS, or of bilateral nephrectomy, and treatment with AV alone or treatment with additional drugs (Table 3). In addition, no difference was observed between patients operated before and after 12 weeks of treatment. Moreover, we did not observe a significant change in the frequency of NSS over time from 2001 to 2017. The dataset did not allow correlation of histologic subtype with the type of surgery performed. We did observe a difference according to the treating countries with more bilateral NSS in the GPOH (Gesellschaft für Pädiatrische Onkologie und Hämatologie) group (N = 16/31 patients; 52%), compared to 31% for NOPHO (Nordic Society of Paediatric Haematology and Oncology), 21% for France and 12% for the United Kingdom. We have no data explaining this difference.

For the 101 patients with unilateral tumour and NB, 76 patients had complete data, and 69 (90.7%) of these had at least one NSS: bilateral NSS for 29 (38.1%) and unilateral NSS + contralateral TN for 40 patients (52.6%).

In the bilateral NB group only 15 patients (38%) underwent surgery, while 24 (62%) received chemotherapy only.

Pathology results

In the group of BWT, SIOP staging was obtained for 153/174 patients. The other 21 patients (12%) were classified stage IV without local stage information. The highest local stage where bilateral data was available (147 patients) included 61 (41.5%) stage I, 35 (23.8%) stage II and 51 (34.7%) stage III (without specifying whether it was because of lymphadenopathy, rupture or positive margins). 148 of 174 patients had a documented histological risk group; in most cases, after validation by a national reference pathologist. Four cases were classified as low risk (LR) on both sides. For 106 cases, we observed intermediate risk (IR) as highest risk on one or both sides, while in 38 cases at least one tumour had high-risk (HR) histology. Fifteen (10%) had at least one kidney with diffuse anaplasia (DA). For 69 of148 patients (46.6%), the histology was the same on both sides. The Table 4 shows the correlation of histologic subtypes.

In the 101 patients with unilateral WT and NB, there was also a predominance, 67 of 101 (66%), of stage I: 80 tumours (79%) were intermediate risk, 6 low risk and 15 high risk.

Post-operative treatment

Among 156 BWT patients with complete data, 55 patients received AV (36%) and 48 patients AVD (30%). The more intensive protocol with 4 drugs, as described in the study (etoposide + carboplatin + cyclophosphamide + doxorubicin), was given in 30 patients based on histology. Twenty-three patients underwent another treatment of which the details were unknown. Sixty-one patients had bilateral local stage I and IR histology, and due to ambiguity in the protocol, the adjuvant treatment varied. Treatment delivered comprised 4 weeks AV (AV1 in the protocol) for 20 patients, 27 weeks AV (AV2) for 11 patients, and intensified chemotherapy with doxorubicin (AVD) for 13. The EFS was 94.4%, 78.9%, and 84.6%, respectively ($p = 0.66$; Fig. 2). Eight patients had other combinations without a clear rationale and data are missing for 9 patients, resulting in these 17 patients being excluded from this EFS analysis.

In the group of unilateral WT and NB, complete data were available for 82 patients, of which 38 patients received AV (46.3%) and 23 patients received AVD (28%). The more intensive protocol with 4 drugs was necessary for 13 patients and 8 patients underwent another unknown treatment.

Radiotherapy data was not documented in more than 60% of the patients, precluding further analysis. However, due to omission of the option to state ‘no radiotherapy given’ in the case report form, it is likely that the missing data cases did not receive radiotherapy.

Status at the end of treatment and outcome

At the time of analysis, the median follow-up was 91 months (7.6 years) for the total group (Interquartile range 51-118 months). Among the 174 patients with BWT, the disease status at the end of treatment was available for 163. The majority, 141 patients (87%) were in complete remission (CR). Ten patients were not considered in CR, because of the persistence of stable radiology abnormalities of the renal parenchyma. Twelve patients (7%) presented with progressive disease.

At the time of analysis, 40 patients (23%) had experienced an event. Among these were 34 relapses including 19 cases in the primary site alone, 6 in other abdominal sites, 8 with lung metastases and 1 with unknown location. Histology at the time of relapse was intermediate risk in 18 cases, and high risk in 16 cases (7 DA and 9 blastemal). The 6 non-relapse events were progressive disease for 3 cases and 3 were not disease related. Twenty-two patients (13%) died. The estimated 5 y EFS and 5 y OS was 76.1% and 88.1% respectively. The 10 y OS was 84.6% (Fig. 3). We had data concerning the timing of surgery for 173 patients. Patients who underwent surgery within 12 weeks (n = 78) from diagnosis had similar OS compared to those having surgery after 12 weeks (n = 86) (90.2 vs. 86.2%, p = 0.25, Table 5- Fig. 4). Patients treated with AV have a superimposable event free and overall survival when compared to patients treated with AVD or other combinations (Table 5 and Fig. 5).There was no significant difference in stage, while high-risk histology proved to be significantly worse (p = 0.001) than low and intermediate risk (Table 5).

Among the 101 patients with unilateral WT and NB, the disease status at the end of treatment was available for 88. Seventy patients (79.5%) were in CR. Thirteen (14.8%) patients were not considered in CR, because of the persistence of stable radiology abnormalities of the renal parenchyma. Five patients (5.7%) presented with progressive disease. At the time of analysis, 23 patients (23%) had had an event. Estimated 5 y EFS and OS were 74.9% and 93.7%, respectively, and 10 y OS (Fig. 3) remained the same.

As in BWT, we did not observe a significant difference of EFS and OS by comparing the group of patients operated before 12 weeks and after 12 weeks.

Among the 52 patients with bilateral NB, the status at the end of treatment was available for 48. While 26 patients (54%) were in CR, persistence of stable radiology abnormalities of the renal parenchyma were documented in 18 patients (38%), among whom four (22%) later developed progressive disease (including both progressive nephrogenic rests and WT). At the time of analysis, 12 patients (23%) had had an event. Estimated 5 y EFS was 76.1% and 5 and 10 y OS were 95.4% (Fig. 3).

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Renal function at last follow-up (Table 6)

For the data concerning renal function, the median follow-up was 7.4 years, with evaluation by creatinine level and glomerular filtration estimation according to Schwartz formula. While more comprehensive renal follow-up data, including levels of proteinuria, may have been preferable, the results are nevertheless encouraging with a majority (87%) of patients retaining normal renal function without treatment or transplantation. After bilateral nephrectomy, successful renal transplant was performed in 14 patients and 5 patients were treated with dialysis, with attendant comorbidity and impact on quality of life.

Discussion

Demographic characteristics of our patients with bilateral disease concurred with previous studies, with a similar incidence (6.6%) of bilateral involvement, median age (25.6 months for BWT and younger 14.7 months for NB), female preponderance (51% for BWT and 62% in case of NB), as well as a higher incidence of congenital abnormalities (19%) compared to the population with unilateral tumours [6, 7, 16]. The percentage of familial WT was high (up to 14%), suggesting, as in the paper of Rapley et al., that additional unknown familial WT susceptibility genes are likely to exist and are particularly correlated with bilateral cases [17]. Concerning histology of BWT, 53% had divergent histology in each kidney. We observed a two-fold higher prevalence of DA than reported in unilateral tumours (10%) in line with prior reports [5]. In cases of unilateral WT and NB, a low percentage of NR was found in the kidney carrying the tumour (34%). This is quite surprising given that there is a pathological continuum between isolated NR and hyperplastic NR (nephroblastomatosis).

While the treatment strategy for patients with BWT has renal preservation as one of the main targets, overall survival remains the most important endpoint in treating children

with cancer. Historically, survival for patients with BWT has been lower than for patients with unilateral tumours, but it has improved over time as treatment strategies have become more refined [6, 7, 16, 18].

Treatment guidelines for children with synchronous BWT in the SIOP 2001 study have led to a reasonably good outcome with 5 y EFS and 5 y OS of 76.1% and 88.1% respectively and 10 y OS of 84.6%. The COG recently reported results of the AREN0534 study that achieved a 4-year EFS and OS of 82.1 and 94.9%, respectively, in children with BWT [7]. It is also quite similar to the prospective SIOP93-01 study in France that reported 83.4% 5y-EFS and 89.5% OS and finally to the SIOP-GPOH group, that reported 80.4% 5y-EFS and 93.3% OS between 1989 and 2005 during three consecutive trials [5, 6].

However, the results of the AREN0534 study are based on a significantly shorter median follow-up (4 vs. 10 years) possibly overestimating survival in a group of patients that carry the risk of later relapses and second primary tumours, due to frequently underlying genetic predisposition compared to that of unilateral WT [2]. In our group, 72.5% of all relapses occurred within 2 years after diagnosis, which is less than that of 80% in localised cases. Contrary to stage I-IV unilateral WT, that reach a plateau in EFS after two years, EFS gradually declines beyond 5 years of follow up for BWT, including events even beyond 9 years after diagnosis (Fig. 2). While aiming to maintain two functioning kidneys might be a reason for a higher proportion of early local relapses, the high proportion of underlying congenital abnormalities (19%) identified in our patients may be partially responsible for a higher risk of developing metachronous tumours and late relapses.

In BWT, preoperative chemotherapy has become the internationally accepted gold standard in North America, too, where upfront surgery otherwise remains the preferred strategy for unilateral WT. While AREN0534 introduced 12 weeks of AVD as a standard in North America,SIOP continued the established response-adapted multiple cycles of AV [5,6,7]. 39% of 189 patients treated on AREN0534 retained two kidneys including 35% after bilateral NSS. Our results suggest that response-adapted AV alone as first line pre-operative chemotherapy is comparably effective to achieve NSS. Two functioning native kidneys at the end of treatment were documented in 41% of our patients with documented surgical procedures. Furthermore, 63% of children with non-metastatic BWT underwent NSS, at least in one kidney. We did not observe a significant difference for NSS between patients treated with AV alone versus patients treated with AVD or others drugs during the preoperative treatment. A stepwise treatment escalation

starting with AV minimises the use of possibly cardiotoxic anthracyclines in this comparatively young group of WT patients while maintaining high rates of NSS and survival. AV remains therefore the standard first-line preoperative chemotherapy for the ongoing SIOP-RTSG UMBRELLA 2016 study. Pre-operative Doxorubicin is indicated as standard of care only in case of metastatic disease.

Studies from GPOH and COG suggest that prolonged chemotherapy for more than 3 months increases the risk of DA development as well as stable or progressive disease without facilitating conservative surgery [5, 19, 20]. This led to the recommendation to limit preoperative treatment to 12 weeks if possible in the GPOH group (Furtwängler et al. [5]).

Thus, we investigated whether preoperative treatment for more than 12 weeks had a negative impact (Compare Table 4) but we observed no significant difference of EFS and OS between the children operated on before or after 12 weeks. However, prolonged chemotherapy for more than 12 weeks did not facilitate a greater number of NSS. On the other hand, following a median duration of 81 days for preoperative treatment, 91% of the children benefited from at least one sided NSS. This strong rationale backs the recommendation in the ongoing SIOP-RTSG 2016-UMBRELLA study to give pre-operative chemotherapy in blocks of 6 weeks with a maximum of 2 successive blocks possible in order to prolong pre-surgical chemotherapy to maximise response, but not to do so beyond 12 weeks.

Another important issue in BWT is the choice of strategy to adopt in the event of progressive or non-responsive tumour (PNRT). Failure of response on imaging assessment generally arises in two situations: DA or mature stromal differentiation [5, 21]. In our study, the proportion of DA is significantly higher (10%) compared to unilateral tumours. The same has been previously reported by the National Wilms Tumour Study Group (NWTSG) and the GPOH [5, 16]. Both DA and stromal differentiation respond poorly to chemotherapy, although they are associated with contrasting prognoses [22]. Unfortunately, tissue biopsy is not helpful in this situation due to tumour heterogeneity and frequently patchy pattern of DA [23]. This may be addressed in future with liquid biopsies, as DA is often associated with TP53 mutations that may be detectable in this manner [24]. This may also be addressed with the apparent diffusion coefficient (ADC) on MRI, since a linear relationship between histopathology and ADC has been described with lower ADC strongly related to the percentage of stroma [25]. With regard to PNRT, if these indicators are validated in the future, they may help clinician choose between second-line chemotherapy regimens and earlier surgery.

The current postoperative chemotherapy recommendation for intermediate-risk BWT is AV2 (27 weeks AV) irrespective of local stage [26]. Since BWT kidneys virtually always carry hyperplastic nephrogenic rests, and these might be associated with a higher risk of metachronous relapse in younger children [3], further maintenance therapy for one year according to the NB protocol has been debated [27, 28]. Treatment for unilateral stage I IR WT is, however, significantly short with only 4 weeks (AV1). Due to an ambiguity in the SIOP2001 protocol, AV1 was given in a relevant number of patients, and also in cases of bilateral stage I IR WT. It is thus intriguing that AV1 was administered with apparent safety for patients with bilateral stage I IR tumours, achieving 94% 5 y EFS as compared to 78% in the longer treatment group with 27 weeks of AV2 (Fig. 1). Though this might be biased by selection, it encourages future studies to prospectively compare this AV1 strategy with the historical AV2 strategy in such stage I, IR &LR BWT cases, especially since Actinomycin D has a higher risk of sinusoidal obstructive syndrome in these frequently very young children and infants [29]. This is also a further argument for reducing the burden of treatment in BWT by avoiding anthracyclines for as many patients as possible, at least in these subsets with low risk of relapse.

Optimal surgical management is crucial for preservation of renal function of stage V patients. Currently, it is known to be correlated with increased success rates and thus it is strongly recommended to refer these patients to centres of surgical expertise in order to offer patients the highest chance of bilateral NSS [30,31,32].

With a median follow-up of 7.4 years, 90% of our population have normal renal function, with no medical intervention for 87% and following kidney transplant for 5%. Breslow et al. reported a long-term risk of ESRD in BWT approaching 15% after 15 years of follow-up [33]. The risk of ESRD increased significantly in patients with more than 50% loss of renal parenchyma. Aronson et al. observed that functional outcome after NSS is improved with significantly lower serum creatinine values after bilateral NSS [31] and Hubertus et al. could show a reduced risk of hypertension after bilateral NSS [34, 35]. It is thus debated whether, in order to preserve renal function, the risk of possible stage III disease should be taken through the attempt at NSS. Kieran et al. approached this question in their institution, studying 21 BWT, 5 of which had positive margins. They concluded that local recurrence rates after NSS were not affected by surgical margin status, but all patients with positive margins had received radiotherapy (XRT), which might possibly increase the risk of ESRD. They support the aggressive use of NSS for patients with BWT [36]. The applied dose of XRT was 10.5 Gy and they did not observe

an increased risk for renal insufficiency in patients who underwent focused flank radiotherapy for positive margins. This was supported in a subsequent study with 55 BWT patients where no significant difference was observed between TN and NSS patients in terms of recurrence rate (14.82% vs. 16.36%) [37]. In the experience of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP), 12 of 28 patients classified as having stage III received no focal radiotherapy and 5/12 relapsed locally, accounting for an unsatisfactory DFS of their stage III [8]. Thus, it should be kept in mind during management of BWT that an aggressive approach to NSS with subsequent XRT if required, seems safe and appropriate. In the SIOP RTSG recommendation, the usual radiotherapy dose is at least 14.9 Gy for intermediate risk tumour and 25 Gy for high-risk tumour. In light of the American experience with 10.8 Gy, there may be a rationale to reduce these doses in the situation of BWT with stage III requiring XRT. Eventually, histologic subtype might also be considered. For example, stromal predominant tumours behaving less aggressively and being rather well confined during surgery, as compared to DA, where completion nephrectomy needs to be considered in preference to radiotherapy [30].

In addition to 174 patients with BWT, we analysed patients with WT combined to NB and patients with bilateral nephroblastomatosis (with or without associated unilateral WT). As described by Beckwith in 1990, nephroblastomatosis is defined by the presence of multiple or diffuse nephrogenic rests. It is a pre-neoplastic proliferative process associated with a risk of developing WT [38]. The accurate diagnosis and the choices of therapy for patients with this kind of lesions is often complex, depending on interpretation of a combination of pathologic, radiologic and clinical information [19]. Establishment of clear guidelines for these cases is not easy: Cozzi et al. reported the advantages of conservative management for hyperplastic and multicentric NB, whether associated with WT or not, and they validated the same strategy as in our study of prolonged chemotherapy, with conservative surgery for lesions suspicious for evolving WT [39]. In accordance with this author and others, the good survival observed in patients with NB validates the use of AV alone for a high proportion of patients in this sub-group (at least 50%). Following prolonged chemotherapy, careful response assessment is combined with balanced consideration of an individually tailored surgical approach prioritising conservative management. The total duration of the prolonged chemotherapy remains to be determined. In the ongoing Umbrella study, we will test the option of a maintenance chemotherapy with monthly AV up to 1 year for patients with NB with or without WT.

Limitations of analysis of our results are inherent to the design of the SIOP 2001 study, which was investigating bilateral Wilms tumour management in a single arm prospective observational fashion. Moreover, some information, such as radiotherapy

data, was captured in most cases only if radiotherapy had been applied, resulting in uncertainty in a number of cases as to whether radiotherapy had been given. This hinders an in-depth analysis of radiotherapy's impact on survival and renal outcome. In the end, we don't have data concerning the reason for stage III, preventing analysis of association between margin status and indication of local radiation as a possible surrogate.

In summary, the results of our study demonstrate a favourable outcome of patients with stage V disease receiving a tailored treatment according to the tumour response and histology resulting in 10 years OS of 95.4% (89.3- 100), 93.7% (89-98.7) and 84.6% (78.1-91.7) for NB, WT & NB combined and BWT, respectively. AV proved to be sufficient as pre-operative chemotherapy to induce tumour volume regression in 58.7% of all the patients and in 65.6% of all non-metastatic patients and to achieve NSS in the majority of these. Thus, it is possible to safely avoid cardiotoxicity of anthracyclines in the majority of these very young patients without jeopardising overall survival. Furthermore, 40.7% (115/282) of all patients with documented surgical procedures had two functioning native kidneys after the end of treatment. Preservation of renal function in our cohort is also encouraging with a majority (87%) of patients having normal renal function without treatment or transplantation.

While these results provide a benchmark for future studies, they also inform the strategy currently adopted in the ongoing UMBRELLA protocol of SIOP-RTSG. The key to success for patients with stage V disease is certainly to continue to enhance a multidisciplinary collaboration (oncologist, radiologist, surgeon/urologist, pathologist, radiation oncologist, and nephrologist) from the point of diagnosis with continuing collaborative care well into long-term follow-up.

Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Ethics declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

Ethics approval and consent to participate: national and local regulatory and ethical approvals were obtained according to national regulations.

Consent for publication

The parents or guardians signed a written informed consent for enrolment and treatment of their child in the SIOP 2001 study.