Survival in nephroblastoma treated according to the trial and study SIOP-9/GPOH with respect to relapse and morbidity


1Department of Pediatric Oncology, University of Heidelberg; 2Department of Pediatric Oncology, University of Saarland, Homburg/Saar; 3Institute of Biostatistics, University of Heidelberg, Heidelberg; 4Department of Pediatric Pathology, University of Kiel, Kiel, Germany; 5Department of Pathology, University of Wales College of Medicine, Cardiff, UK; 6Pediatric Nephrology, Children’s Hospital, University of Heidelberg; 7University Children’s Hospital Muenster, Department of Pediatric Hematology and Oncology; 8Department of Pediatric Oncology, University of Erlangen, Erlangen; 9Institute of Human Genetics, University of Düsseldorf, Düsseldorf, Germany; 10Department of Pediatric Oncology, AMC, Amsterdam, The Netherlands

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Background: Recent Wilms’ tumor (WT) trials and studies have tried to determine the minimal therapy needed for cure. The goal was survival without morbidity.

Patients and methods: From January 1989 to March 1994 the German Society of Pediatric Oncology and Hematology registered 440 patients (median age 2.9 years; 231 male, 209 female) with WTs (preoperative chemotherapy 362) for therapy according to the International Society of Pediatric Oncology Trial and Study 9. Therapy for relapse depended on site of relapse and therapy already received. Follow-up included inquiries for morbidity. Prognostic factors for relapse and death were evaluated.

Results: Five-year survival of WTs was 89.5%; 98.2% (385 of 392) of survivors had a follow-up of 5 years (range 0.8–12.6; median 8). In non-anaplastic WTs, young age (<2 years) was of significance (P = 0.026) for a better survival. Non-anaplastic WTs (407 patients) had a 5-year survival of 92.3%, versus 48.5% in anaplastic WTs (33 patients), and a 5-year relapse-free survival of 87.6% versus 42.4%. Survival after relapse was significantly worse for anaplastic than for non-anaplastic WTs (residual 3-year survival 11.8% versus 54.3%; P <0.0001). In preoperatively treated WTs, anaplasia was a strong prognostic factor for death [relative risk (RR) 4.7], followed by poor response to preoperative therapy (RR 3.6), stage IV (RR 3.2) and abdominal stage III (RR 2.2). Low abdominal stages (<III) dominated (280 versus 82). In the 334 unilateral stage I–IV WTs (median age 3.2 years), diffuse anaplasia (21 patients) had a 5-year relapse-free survival of 38.1%, versus 58.4% in blastemal WTs (25 patients); survival was 42.9% in diffuse anaplasia versus 84% in blastemal WTs. None of 46 patients (median age 1.9 years; 91.3% stages I or II) with differentiated WTs (nine epithelial, 37 stromal) relapsed despite their non-response; two died (one therapy related, one due to bilateralization). In the 25 non-anaplastic bilateral WTs, differentiated cases (one epithelial, eight stromal, 33.3% abdominal stage III) were more frequent (P = 0.048) than in unilateral WTs (one stromal, abdominal stage III relapsed). In all, 52.9% of the 5-year survivors had received adriamycin (250–400 mg/m²), 25.7% radiation, 6.4% ifosfamide (24–30 g/m²) and 6.7% carboplatin plus etoposide. Abnormal parameters according to the National Cancer Institute score were seen in 18.9% during follow-up, but only 6.4% were treated for morbidity at the end of follow-up. Three WTs developed renal failure due to Drash syndrome, but none due to tumor therapy. After adriamycin 1.9% of WTs (9% of those receiving 400 mg/m²) required therapy for cardiac toxicity.

Conclusions: Initial therapy should be more individualized, taking the above risk groups (age in non-anaplastic WTs, poor response, anaplasia, etc.) into account, as morbidity even after relapse therapy with ifosfamide, carboplatin and etoposide was not high. Milder therapy in low stages of differentiated and of well responding WTs should be tested.

Key words: late effects, prognostic factors, relapse, survival, Wilms’ tumor

Introduction

The prognosis of Wilms’ tumor (WT) has significantly improved over the last 30 years, and multicenter trials both in Europe and in the USA have been looking for the minimal therapy necessary for cure [1–3]. The goal of all WT trials and studies has been to find...
therapy adapted to the expected risk of the children, i.e. to maximize survival and to minimize remaining or late morbidity in survivors. It is thus an aim of all WT trials and studies to evaluate the impact of prognostic factors for the optimization of future risk-based therapeutic strategies.

During the International Society of Pediatric Oncology (SIOP) No. 9 Trial and Study, the German Society of Oncology and Hematology (GPOH) centers differed in three respects from the other participating centers [4–7]: (i) different criteria were used for defining histological subtypes of non-anaplastic WT; (ii) Adriamycin instead of epiradiamycin was given for therapy in higher end of March 1994. There were 505 patients registered by the GPOH, including October 1991, thereafter 4 weeks), and 6 weeks with additional Adriamycin morbidity during follow-up.

even 3 months after oncologic therapy, or was observed as late subtype as not presented by the SIOP-9, which concentrated on the analysis of prognostic factors and their relative risks in all WT; (ii) prognostic aspects concerning survival. These are as follows: (i) the analysis of hepatotoxicity concerning the adaptation of dosages in the drugs applied for the risk groups have already been taken in subsequent SIOP studies. The response to preoperative therapy of the histological subtypes in unilateral localized WTs and their different age groups has also been published [7]. Thus, this paper focuses on the remaining aspects concerning survival. These are as follows: (i) the analysis of prognostic factors and their relative risks in all WT; (ii) prognostic aspects in stages IV and V, also with respect to the histological subtypes as not presented by the SIOP-9, which concentrated on the unilateral localized WT eligible for randomization; and (iii) therapy morbidity as far as it limited survival or remained even 3 months after oncologic therapy, or was observed as late morbidity during follow-up.

Patients and methods

Patients and treatment

The GPOH joined the SIOP Nephroblastoma Trial and Study 9 in January 1989, and enrolled patients for therapy according to the protocol until the end of March 1994. There were 505 patients registered by the GPOH, including all trial and study patients [6]. Non WTs, including congenital mesoblastic nephroma (CMN), clear cell sarcoma of kidney (CCSK) and rhabdoid tumor of kidney (RTK) were also registered, with differing guidelines for therapy. Preoperative therapy was recommended for patients between 6 months and 16 years of age with characteristic imaging features of WT. Immediate surgery was restricted to patients of a certain age (<0.5>16 years), those with uncertain diagnosis and emergency indications. The duration of standardized preoperative therapy with dactinomycin and vincristine in patients with unilateral localized disease (stage I–III) was either 4 or 8 weeks (randomized until October 1991, thereafter 4 weeks), and 6 weeks with additional Adriamycin [11] for patients with distant metastases (69 patients). The duration and intensity of preoperative therapy in bilateral WT (stage V) was individualized depending on the response and the operability of tumors. The postoperative therapy depended on stage and histology at the time of surgery, and in stage IV patients, additionally on their clinical response to preoperative therapy and their operability thereafter. Patients with stage I had a regimen of two drugs (dactinomycin, vincristine) for 18 weeks. Patients with stage II LN0 (negative lymph nodes) and standard histology had a regimen of additional Adriamycin.

In cases with positive lymph nodes (LN1) and/or in stage III, this therapy was supplemented by an abdominal radiation of 15 Gy on the original tumor bed and an additional boost of 15 Gy on residual disease, or the chain of abdominal lymph nodes in cases of infiltration. Patients with anaplasia and abdominal stage II and III received a radiation with a higher dose (30 Gy) and a more intensified cytotoxic regimen including ifosfamide, similar to that for stage IV patients whose metastases had not adequately resolved. In such cases only, additional radiation of the metastatic site was given. In cases of pulmonary residual disease, the whole lung was radiated with 12–15 Gy. Postoperative therapy of bilateral tumors depended on the abdominal stage and histology of the more involved side, but chemotherapy had to follow the stage II regimen. If no preoperative therapy was given, postoperative therapy had to be prolonged for one cycle.

Maximal cumulative doses of vincristine ranged from 18 mg/m², given 12 times as 1.5 mg/m² bolus injections up to once weekly for stage I (inclusive 4 weeks preoperative therapy), to 36 mg/m², given as 24 bolus injections for stage II and III (inclusive 4 weeks preoperative therapy) or 46.5 mg/m² applied 31 times in stage IV (inclusive 6 weeks preoperative therapy). Cumulative doses of Adriamycin ranged from 250 mg/m² (stage II–III) to 400 mg/m² (stage IV, inclusive preoperative therapy) applied as 4-h intravenous infusions of single doses of 50 mg/m² given up to once monthly. Ifosfamide was applied as a 24-h infusion of 3 g/m² on two consecutive days (with Mesna for uroprotection) up to a cumulative dose of 24 g/m². Dosage of drugs was generally to be reduced to two-thirds, at least in cases of young age (infancy or body weight <12 kg), during radiation and within the first course thereafter, and individually in cases of acute side-effects. Depending on the severity of acute side-effects, therapy could be reduced, omitted or even stopped by the centers.

The guidelines for the therapy of relapse depended on the intensity of prior therapy and the site of relapse. The maximal possible regimen included carboplatin, etoposide, Adriamycin and ifosfamide as intensified for systemic and surgery, plus abdominal, pulmonary or other site radiation for local control. In case of a second complete remission, an additional high dose consolidation therapy with melphalan, carboplatin and etoposide with bone marrow transplantation could be chosen [12, 13].

Histology

In 99.6% (503 of 505) of the renal tumors registered, material was available for histological analysis. Two patients died before surgery after response to preoperative therapy, due to hepatotoxicity [10]. In 99.2% (499 of 503) of the cases, representative material and pathologists’ reports were sent for central review to the Kiel Pediatric Tumor Registry. In addition, a retrospective review of all these cases was carried out by the SIOP panel of pathologists after the closure of the patients registration. There were 63 non-WTs, including 24 cases of CMN, 12 CCSK, 10 RTK and 17 other tumors. These cases were excluded from the present study. Finally, 440 WT constituted the basic sample, including 362 patients with WT who received preoperative therapy and 78 patients who underwent immediate surgery.

Out of 440 WTs, 407 were classified as non-anaplastic and 33 as anaplastic. For histological subtyping of non-anaplastic WTs, the semiquantitative criteria proposed by Beckwith and Palmer [14], with the addition of a subtype with predominant chemotheraphy-induced changes, were used [7]. Thus, the percentage of regressive tissue in the tumor as given by the institutional pathologist was also taken into account. The criteria were based on the percentage of different tumor components (blastemal, epithelial, stromal, regressive), and if one of these comprised more >66% of the tumor sample, the tumor was subtyped accordingly. If there was no predominant component in the viable tumor, the WT was described as mixed. Completely necrotic WT were coded separately. Out of 33 cases with anaplasia, 30 had unilateral WT. For these unilateral stage I–IV WT, the new definitions of focal and diffuse anaplasia were used [15, 16].
Diagnostic imaging of response to preoperative therapy

Tumor volumes had to be measured on ultrasound scan using the ellipsoid formula (length × thickness × depth × 0.523). The measurement had to be performed before preoperative therapy and again before surgery. For tumors that the centers could not adequately measure by ultrasound, the measurement by other multiplanar diagnostic imaging methods, providing the identical method was used initially and for the second measurement, was accepted. The measurement after preoperative therapy was used to calculate the tumor volume reduction in comparison with the initial volume. Two groups of responders were defined as described by us earlier [7] according to the reduction of tumor volume: (i) poor responders (<40% reduction); and (ii) good responders (≥40% reduction). Tumor response could thus be estimated in all WT.

Follow-up

Regular follow-up controls including physical, imaging (abdominal sonography, chest X-ray) and laboratory screening (including urine analysis for proteinuria and glucosuria) were recommended. The monitoring depended on the therapy given (echocardiography and other cardiovascular diagnostic procedures after adriamycin). After radiation, skeletal spine X-ray was recommended 5 years after therapy, or if deformation was seen. Follow-up documentation included reporting relapses, tumor-related events and a questionnaire for side-effects (e.g. hypertension, proteinuria, scoliosis, etc.). If any side-effect was reported, a second questionnaire was sent out to obtain a grading [17]. In this analysis we focus on morbidity that was apparent >3 months after therapy, and was judged to be therapy-related or due to the disabling consequences of the WT and/or the associated syndromes. Side-effects were defined as signs of morbidity if they lead to symptoms or abnormal parameters according to the National Cancer Institute (NCI; Bethesda, MD, USA) score [17] seen at least twice or requiring therapy.

Statistical methods

The variables included in the analysis of potential prognostic factors differed according the initial therapy. In the sample of all WTs, only characteristics known at the start of therapy and not influenced by preoperative therapy were considered. These included sex, age, overall tumor stage and anaplasia. The latter was included because it has recently been shown to be a histological characteristic not affected by chemotherapy [16]. In the sample of patients treated with preoperative therapy, the analysis also included factors possibly influenced by preoperative therapy, such as tumor response, abdominal stage and histological subtypes.

Standard methods were used for the analysis of censored and non-censored data, including the Kaplan–Meier method for estimating survival curves, the log-rank test for comparison of survival curves and Fisher’s exact test for comparing independent proportions [18–20]. Prognostic factors for survival or relapse-free survival were examined with the proportional hazards model. Model building was done by means of backward selection, starting with those factors that were significant (P < 0.05) in the univariate analysis and using the 5% level for exclusion from the model. The zero time point was defined as the first day of treatment. All analyses were carried out using the SAS statistical package system.

Results

Prognostic evaluation of WT concerning survival

All patients. A total of 440 patients (median age 2.9 years, mean age 3.5 years) constituted the basic sample. Of these, 377 had a localized disease, i.e. unilateral (352 patients) or bilateral (25 patients) WT without distant metastases. Three of the 63 patients with initial distant metastases had bilateral WT. The 5-year survival rate was 89.5% [95% confidence interval (CI) 86.6% to 92.4%]. Forty-eight deaths occurred in the study cohort, 40 of which were related to the initial or recurrent WT. Out of six lethal events, four were judged to be related to therapy of the initial tumor and two of the relapse. The causes for the lethal events were as follows: (i) preoperative hypertensive crisis with brain infarction due to a vincristine-related syndrome of inappropriate antidiuretic hormone secretion, stage I completely necrotic WT (girl, 2.5 years old); (ii) respiratory failure due to pulmonary fibrosis following respiratory therapy for postoperative hepatotoxicity for stage I stromal WT (boy, 1 year old); (iii) postoperative pneumonia in drug-induced total pancytopenia, stage III, blastemal WT (girl, 3.4 years old); and (iv) bronchopneumonia and tumor bleeding during preoperative therapy in an aniridia syndrome, stage V with immense bilateral mixed WTs (boy, 1.7 years old). The causes for the lethal events with the relapse were as follows: (i) atypical pneumonia due to pulmonary radiation for pulmonary relapse, initial stage I mixed WT (boy, 2.2 years old); and (ii) sepsis and protein-losing enteropathy after abdominal relapse, initially immediately operated stage I, mixed WT (boy, 0.3 years old).

A further two deaths followed metachronous bilateralizations. No death was clearly attributable to a second malignancy. The lastest death occurred 6.4 years after the initial tumor diagnosis. In multivariate analysis using backwards selection, age was eliminated as a prognostic factor (Table 1). However, further modeling revealed that there was a significant interaction between age and anaplasia (P = 0.014). Subgroup analysis showed that in non-anaplastic WT, but not in anaplastic WT, age was of significant influence on survival (P = 0.026 versus P = 0.27).

In this group, 69 relapses after partial or complete remission occurred. The last relapse was seen 5 years after diagnosis. The 5-year relapse-free survival rate was 84.3% (95% CI 80.7% to 87.5%). The site of first recurrence was a local relapse only (19 patients), a local relapse plus a distant metastasis (16 patients) or a distant metastasis only (34 patients). Table 1 presents the analysis of potential prognostic factors for relapse. Again, age was eliminated from the model. However, there was a significant interaction between age and anaplasia (P = 0.03) and between anaplasia and stage IV (P = 0.03).

Patients treated with preoperative therapy. There were 362 WTs treated with preoperative therapy (median age 3 years, mean age 3.45 years). There were 41 deaths in this group. The 5-year survival rate was 88.6% (95% CI 85.3% to 91.9%). In total, 63 relapses were seen, 36 of which were followed by death. The 5-year relapse-free survival rate was 82.4% (95% CI 78.4% to 86.3%). The site of first recurrent event was either a local relapse only (16 patients), a local relapse plus a distant metastasis (15 patients) or a distant metastasis only (32 patients). Table 2 presents the analysis of potential prognostic factors for relapse and death. In non-anaplastic WT, survival after relapse was significantly longer than in anaplastic WT (Figure 1). Twenty-five of 46 patients with non-anaplastic WTs eventually survived after relapse (15 of 26 patients after a first relapse in distant metastases only, eight of 14 with additional local relapses and two of six with local relapses only at first event).
Patients with unilateral WT treated with preoperative therapy.

The preoperatively treated unilateral WT of stage I–IV (334 patients; median age 3.2 years) had a relapse-free survival rate of 82.5% (95% CI 78.4% to 86.6%). The relapse-free survivals for the different histological types are shown in Figure 2. The group presented as ‘other nephroblastoma types’ comprised the following: (i) differentiated, i.e. stromal and epithelial WT (46 patients), relapse-free survival 100%; (ii) regressive and mixed WT (211 patients), 32 relapses, relapse-free survival 84.8% (95% CI 80% to 89.7%); and (iii) focal anaplasia (six patients), three relapses, relapse-free survival 50% (95% CI 10% to 90%). Figure 3 presents the stage distribution in respect to relapse-free survival.

The overall survival for this group was 88.9% (95% CI 85.5% to 92.3%). The survival of the different histological types is

**Table 1.** Prognostic factors and risks for relapse and death at 5 years in all nephroblastoma treated during the trial and study SIOP-9/GPOH

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<th>Patients</th>
<th>Relapse-free survival, % (95% CI)</th>
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*One death caused by a non-tumor related illness; in complete remission for 3.6 years censored.
*Eliminated in multivariate analysis by backwards selection of the proportional hazards model.
Three patients with bilateral WT.

**Table 2.** Prognostic factors and relative risks for relapse and death in all nephroblastoma treated with preoperative chemotherapy

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*One death due to non-tumor-related illness censored.
*Eliminated in multivariate analysis by backward selection of the proportional hazards model.
Three patients with bilateral WT.

CI, confidence interval; RR, relative risk; WT, Wilms’ tumor.
shown in Figure 4. The group presented as 'other nephroblastoma types' comprised the following: (i) differentiated, i.e. stromal and epithelial WT (46 patients), two deaths, survival rate 95.6% (95% CI 89.6% to 100%); (ii) regressive and mixed WT (211 patients), 16 deaths, survival 92.4% (95% CI 88.8% to 95.9%); and (iii) focal anaplasia (six patients), two deaths, survival rate 66.6% (95% CI 28.9% to 100%). Table 3 and Figure 5 present the stage distributions of the histological types with their median ages with respect to survival.

Patients with stage IV WT at presentation. There were 63 patients with stage IV WTs. The four primarily operated patients had blastemal WTs. The vast majority of the stage IV patients (59 patients; mean age 4.7, median age 4 years) received preoperative therapy with three drugs. Three of them had bilateral WTs. In 57 of 59 patients (96.6%) the lungs were the site of distant metastasis, and four of them also had liver metastases. In another two cases the liver was the only metastatic site. Preoperative therapy was followed by complete abdominal tumor excision in 34 cases (stage I, 18 patients; stage II LN0, 16 patients). Incomplete surgical resection or tumor spread (stage III) and/or abdominal lymph node infiltration (stage II LN1) were diagnosed in 25 cases. Histology of the 59 abdominal tumors after preoperative therapy revealed the following WTs: anaplastic (10 patients), stromal (one patient) blastemal (one patient), mixed (nine patients), regressive (32 patients) and completely necrotic (six patients). The survival rate of non-anaplastic WTs was 82.6%. Figure 6 presents the therapy given to the subgroups of these patients depending on the response of metastases to preoperative therapy and their resectability. In the group of patients who needed more aggressive postoperative therapy, anaplasia was significantly more frequent than in patients who required only the milder therapy without pulmonary radiation (nine of 19 versus one of 40; \( P < 0.001 \)). All 15 patients who relapsed despite the more aggressive postoperative therapy ultimately died. Among them, six patients had anaplastic and nine patients had non-anaplastic WTs (mixed and regressive subtype). Nine out of 15 patients who died had the abdominal tumor stage II LN1 or III. None of the stage IV patients died due to therapy effects.

Characteristics and prognosis of bilateral WTs. All 28 patients with bilateral WTs (mean age 2.3, median age 1.9 years) were treated with preoperative therapy. Three of them presented with distant metastasis at diagnosis. There were 17 patients with completely resected WTs in the more involved side, including 15 patients with stage I and two patients with stage II. Eleven patients had stage III disease due to incomplete resection (10 patients) or lymph node metastases (one patient). Three of the WTs showed focal anaplasia. Histological subtyping in the more involved side of the 25 non-anaplastic cases revealed: eight stromal, one epithelial, eight mixed, seven regressive and one completely necrotic WT. Differentiated WT were significantly more frequent in the cohort of non-anaplastic bilateral WTs (nine of 25; \( P = 0.034 \)) than in preoperatively treated unilateral non-anaplastic WTs (46 of 334). Abdominal stage III was significantly more frequent in the bilateral differentiated (three of nine; \( P = 0.048 \)) compared...
with the unilateral differentiated WT (four of 46). Survival of bilateral WT was 85.1% (95% CI 71.6% to 98.6%; four deaths), and relapse-free survival 80.5% (95% CI 65.2% to 95.8%; five relapses). Two of the five patients with relapses reached complete remission and survived. One of them (local relapse on both sides) occurred in an originally stromal predominant WT of abdominal stage III associated with a WT1 mutation. The other was a local relapse in an original abdominal stage II (LN0) mixed WT. The other three relapses were followed by secondary lethal relapses in the lung. The other two deaths occurred in patients with initial stage IV. The primary abdominal WT had been of regressive (two patients) or anaplastic histology (one patient), and all three had been of an abdominal stage III at least on the more involved side. The fourth death occurred during preoperative therapy in a 20-month-old child with aniridia syndrome and 11p13 deletion.

Metachronous bilateralizations. In one patient, a metachronous bilateralization was seen 9 months after the initial diagnosis (stage I WT, blastemal subtype, age 3 months). This child eventually survived, and was observed in second complete remission for 9.5 years. In contrast, two patients with bilateralizations seen 6 and 38 months after the initial diagnosis of stage I WT (one mixed/one stromal subtype, initially aged 8 and 10 months) died in progressive disease. One of these metachronous bilateralizations with lethal outcome had been a stage II WT with diffuse anaplasia.

Second tumors. Three second malignant tumors occurred during follow-up. One malignant schwannoma in the upper arm and later in the lung concurrent with a second, pulmonary relapse of a stage V WT in a girl with neurofibromatosis was followed by death. One Ewing’s sarcoma in the upper leg and one carcinoma in the left upper bronchus after pulmonary irradiation of recurrence were seen. In addition, one of the WTs was already a second malignancy seen 9 years after an acute lymphoblastic leukemia.

Morbidity of survivors

This analysis is confined to 392 patients without tumor- or therapy-related death (including 365 patients with initial therapy only, and 27 patients with additional therapy for relapse). Of these, 385 (98.2%) survived for at least 5 years after therapy. Only 90 female and 67 male patients had reached 13–14 years of age at last follow-up. Of these 5-year survivors, 204 (52.9%) had received adriamycin (250–400 mg/m²) during initial therapy (194 patients) or at relapse (10 patients). The highest cumulative dose of 400 mg/m² was applied in 44 patients (23 female, 21 male). Eighty-four of 385 patients (21.8%) received abdominal radiation, 73 patients for initial and 11 for relapse therapy (nine for local relapses, two
for abdominal metastases). Pulmonary radiation was applied in 25 survivors (12 initially and 13 at relapse). Thoracic spine was irradiated for epidural metastases during relapse in two patients. Altogether, 25.7% of patients (99 of 385) had received some radiation.

Twenty-five of 385 patients (6.4%) received ifosfamide (12 initially, 13 at relapse: 24–30 g/m²). Carboplatin plus etoposide was given to 6.7% (26 of 385) of the patients (in four of these, the drugs had also been given as high-dose therapy with melphalan in the course of myeloablative therapy). Thoracotomy was performed in 23 patients (5.9%), in 22 for resection of pulmonary metastasis and in one for resection of vena cava tumor thrombus to the heart. Laminectomy was carried out in two patients for resection of epidural metastasis at relapse. Bilateral tumor surgery leading to the loss of >50% of renal tissue was performed in 11 out of 23 with initial or metachronous bilateral WT. Clinical signs of morbidity or abnormal diagnostic parameters, according to the NCI score [17], in at least one organic system were seen in 18.9% (71 of 385) of the long-term survivors (Table 4). In 4.9% (19 of 385), more than one organic system was affected. Four survivors are life-long disabled. The disabling defects in these are due to the WT and its associated syndromes, rather than to cancer therapy (Table 4, a and b). Besides these, 21 survivors (including four patients treated for two organic systems) still receive therapy.

In five (three male, two female) of the 204 survivors (101 male, 103 female) treated with Adriamycin (250–400 mg/m²) cardiac function was diminished, all showing a decline of the left ventricular shortening fraction (to <20% to 28.6%), graded according to the NCI [17] score and partly to further signs (at maximum: a third-degree atrioventricular block after cardiac surgery with an additional, later observed, clinically reduced tolerance to exercise in one). The four (two male, two female) who required therapy [all received at least an afterload reducer, one (male) needed an additional pacemaker (for side-effect of both the cardial surgery for a right atrium tumor thrombus and Adriamycin therapy); another (female) needed additional digitalis] had all been referred to an Adriamycin regimen with the highest cumulative dose (400 mg/m²). Onset of cardioprotective therapy ranged from the first until the seventh year of follow-up.

In nine survivors, esophago-gastro-intestinal morbidity was severe, but curable by a single intervention. One needed esophageal dilatation for fibrosis. This esophageal fibrosis was the side-effect of the multimodality therapy, including high-dose therapy after relapse of stage IV and pulmonary radiation. In the other eight patients, bowel obstructions requiring surgery occurred 3 months to 9 years after therapy. Previous abdominal radiation had been part of therapy in four of these eight patients.

Fifteen (3.8%) of the survivors required therapy for renal or urinary system impairment. Four of these patients needed only a transient therapy, including one who required surgery of a vesico-urethral reflux seen 6 months after the end of therapy, and three patients who needed electrolyte substitution up to 6 years (in these

Figure 3. Relapse-free survival by stage in unilateral nephroblastoma treated with preoperative chemotherapy.
patients proteinuria, glucosuria and electrolyte wasting disappeared). Three other patients developed renal failure due to nephrotic syndrome. Eight survivors still receive therapy for renal or urinary system impairment. The causes for therapy are as follows: hypertension with (three patients) or without (one patient), proteinuria of maximally 3 g/day, and with additional electrolyte wasting (one patient); recurrent infections for vesico-urethral reflux and urinary retention (two patients); and electrolyte wasting

Table 3. Survival in unilateral stage I–IV nephroblastoma treated with preoperative therapy in respect to histology, stage and age

<table>
<thead>
<tr>
<th>Histology</th>
<th>Stage I</th>
<th></th>
<th>Stage II</th>
<th></th>
<th>Stage III</th>
<th></th>
<th>Stage IV</th>
<th></th>
<th>Total</th>
<th></th>
<th>Age, years (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely necrotic WT</td>
<td>1a</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>25</td>
<td>4.1</td>
</tr>
<tr>
<td>Epithelial WT</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
<td>1.0</td>
</tr>
<tr>
<td>Stromal WT</td>
<td>2b</td>
<td>25</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>37</td>
<td>1.9</td>
</tr>
<tr>
<td>Mixed WT</td>
<td>2c</td>
<td>54</td>
<td>0</td>
<td>15</td>
<td>1</td>
<td>6</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>84</td>
<td>3.1</td>
</tr>
<tr>
<td>Regressive WT</td>
<td>2</td>
<td>52</td>
<td>1</td>
<td>21</td>
<td>2</td>
<td>24</td>
<td>7</td>
<td>30</td>
<td>12</td>
<td>127</td>
<td>3.9</td>
</tr>
<tr>
<td>Focal anaplasia</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>4.8</td>
</tr>
<tr>
<td>Blastoernal WT</td>
<td>2</td>
<td>11</td>
<td>0</td>
<td>8</td>
<td>2d</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>25</td>
<td>2.8</td>
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<tr>
<td>Diffuse anaplasia</td>
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<td>4</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>4</td>
<td>7</td>
<td>12</td>
<td>21</td>
<td>5.2</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>167</td>
<td>4</td>
<td>62</td>
<td>9</td>
<td>49</td>
<td>13</td>
<td>56</td>
<td>37</td>
<td>334</td>
<td>3.2</td>
</tr>
</tbody>
</table>

aNOne therapy-related death.

bOne therapy-related death, one after bilateralization.

cOne death after bilateralization.

dOne therapy-related death.

WT, Wilms’ tumor.

Figure 4. Survival by histology in unilateral nephroblastoma treated with preoperative chemotherapy.
with glucosuria and proteinuria (one patient). Finally, five survivors required an electrolyte substitution, at least for a certain length of time, two after therapy with ifosfamide, two after the loss of >50% of renal tissue by surgery and one after renal irradiation. Besides the three Drash syndrome patients, two further survivors showed an increase in renal impairment (proteinuria and hypertension) during follow-up. These two patients had lost >50% of renal tissue by surgery.

Five of the 90 girls who had already passed puberty at the end of follow-up showed an insufficiency of their gonadal system after

Figure 5. Survival by stage in unilateral nephroblastoma treated with preoperative chemotherapy.

Figure 6. Nephroblastoma patients with distant metastases treated with preoperative chemotherapy.

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th># deaths</th>
<th>5-year survival</th>
<th>95%-CI</th>
<th>years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>167</td>
<td>11</td>
<td>93.4%</td>
<td>89.6 - 97.2</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>62</td>
<td>4</td>
<td>93.5%</td>
<td>87.4 - 99.7</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>49</td>
<td>9</td>
<td>81.6%</td>
<td>70.7 - 92.4</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>56</td>
<td>13</td>
<td>78.6%</td>
<td>67.8 - 89.3</td>
<td></td>
</tr>
</tbody>
</table>

Log rank trend test: $p = 0.0002$

STAGE IV

preoperative chemotherapy with ACT D, VCR, ADR, N = 59

Complete response of meta. on diagnostic imaging
N = 34/59 (57.6 %)

Incomplete response of meta. on diagnostic imaging
N = 25/59 (42.4 %)

metastases totally excised
N = 6

Viable metastases, subtotally excised
N = 10

Inoperable metastases
N = 9

A Postoperative chemotherapy: ACT D, VCR, ADR
N = 40/59 (67.8 %)

B Postoperative chemotherapy intensified at least with additional Ifosfamide and irradiation of the metastatic site
N = 19/59 (32.2 %)

Relapses: 13/40; relapse-free survival: 67.5% (52.9-82.0) $P = 0.13$

Deaths: 5/40; survival: 87.5% (77.2-97.7) $P = 0.0003$

Relapses: 10/19; relapse-free survival: 47.4% (24.9-69.8)

Deaths: 10/19; survival: 47.4% (24.9-69.8)
Neurological morbidity after therapy was seen in 16 survivors. In 13 it was a prolongation of an acute vincristine toxicity, despite the SIOP-9 guidelines for therapy modifications, and in three it was related to carboplatin given for relapse (one of the three was additionally paralyzed). The hearing loss due to carboplatin was diagnosed by audiometry only. Vincristine toxicity was obvious in all cases as peripheral neuropathy of the legs. Four patients showed only mild to moderate neurosensory and/or neuromotoric deficiency, which disappeared within 0.5–2 years. Longer-lasting moderate to severe alterations resulting in tip and hollow feet were observed in six survivors. These symptoms vanished within 7.5 years. However, surgery was required in three patients to facilitate residual contractures. Patients with vincristine-related neurological morbidity after therapy tended to be older at start of therapy (median age 5.8 years) than the non-affected survivors (median age 2.8 years), and had been referred to a therapy with more repeated vincristine doses. Only one of 181 (0.5%) stage I survivors with no later relapse therapy was affected, in contrast to 12 out of 204 patients (6.8%) treated initially or at relapse according to a stage II–IV regimen. All four severely affected survivors (minimal age at start of vincristine therapy 3.8 years), but only two of the nine less affected survivors had also received abdominal radiation.

Impairment of the musculoskeletal system was observed in 20 survivors during follow-up. In 12 cases, scoliosis was seen between 3 and 9 years after radiation (median 5 years). Only one patient required invasive orthopedic intervention (modified Boston brace for a 25° scoliosis). In four further cases, scoliosis was due to either thoracotomy or a Beckwith–Wiedemann syndrome. Growth retardation leading to a final height smaller than the third percentile was seen in another four patients, who had all received radiation with an abdominal bath.

In none of the survivors was any deficiency of the hepatic function reported on the follow-up questionnaires by the participating centers.

Discussion

To assess a therapeutic concept in WT, the measurement of both survival and morbidity is helpful. While toxicity criteria for acute side-effects are well defined for all therapy modalities, the measurement of late effects is more problematic, and defined criteria are only available for radiation [21]. We thus had to use the actual score of the NCI [17]. Although in our study follow-up has been sufficiently long to judge determinants of survival in WT, it is too early to analyze all side-effects of therapy. In particular, the late effects of radiation on the bones [22, 23] and gonads [24] will only be evaluable when all children have passed puberty, reached their final height and their reproductive age.

The publication of SIOP-9 has mainly presented survival results for patients older than 6 months, with unilateral localized tumors, who had received preoperative therapy with two drugs (i.e. patients eligible for the randomized trial) [4]. In this analysis, we focused on prognostic factors of all patients with WT. As Tables 1 and 2 show, there is a slight difference in outcome between preoperatively treated WT and the whole sample. Note that the preoperatively treated WT in our study was a significantly (P = 0.003) selected one with respect to age, the percentage of patients <2 years being 26.5% versus 43.6% in the total sample. In multivariate analysis of all WT, age was eliminated by backwards selection, but further modeling revealed that there was a significant interaction between age and anaplasia. In the subgroup of patients with non-anaplastic WT, age turned out to be of significant influence. Note that in the National Wilms’ Tumor Study Group (NWTS) 1, 2 and 3, children <2 years old with favorable small WT were observed to have a better prognosis [25]. The United Kingdom Children’s Cancer Study Group (UKCCSG) Wilms’ Tumor Working Group has recently reported a similar observation of

<table>
<thead>
<tr>
<th>Organic system</th>
<th>Patients</th>
<th>%</th>
<th>NCI grade according to score [17]</th>
<th>Therapeutic intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>5/385</td>
<td>1.3</td>
<td>Mild 2 2 2 0</td>
<td>None 0 0 0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>1/385</td>
<td>0.2</td>
<td>Moderate 2 0 0 0</td>
<td>Transient 0 0 0</td>
</tr>
<tr>
<td>Lung</td>
<td>2/385</td>
<td>0.5</td>
<td>Severe 2 0 0 0</td>
<td>Persistent 0 0 0</td>
</tr>
<tr>
<td>Small/large intestine</td>
<td>11/385</td>
<td>2.8</td>
<td>1 2 8 0</td>
<td>Persistent 3 8 0</td>
</tr>
<tr>
<td>Renal/urinary system</td>
<td>28/385</td>
<td>7.2</td>
<td>13 7 5 3</td>
<td>Persistent 13 4 11</td>
</tr>
<tr>
<td>Gonadal system</td>
<td>5/385</td>
<td>1.3</td>
<td>0 2 3 0</td>
<td>None 0 0 5</td>
</tr>
<tr>
<td>Neurological system</td>
<td>16/385</td>
<td>4.2</td>
<td>5 6 8 4</td>
<td>Persistent 5 7 4</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>20/385</td>
<td>5.2</td>
<td>6 13</td>
<td>None 6 9 5</td>
</tr>
</tbody>
</table>

*Renal failures due to nephrotic syndrome (Drash syndrome) followed by renal transplantations in three patients.

*Scoliosis due to hemihypertrophy as part of a Beckwith–Wiedemann syndrome in four of them.

NCI, National Cancer Institute.
a better prognosis in stage I favorable histology WT in children <2 years old [26]. The median age at diagnosis was 2.9 years in our whole sample, similar to 3.1 years in the NWTS series [27]. The minimal difference of ~3 months could be explained by the slightly differing sex ratios of the samples.

Anaplasia has been recognized as an unfavorable histological feature of WT, implying a poor prognosis [14, 28]. It is neither induced nor obscured by chemotherapy [16]. It had been anticipated by Beckwith that focal anaplasia could be more easily spotted in cases treated by preoperative chemotherapy, as it is chemotherapy resistant; however, the SIOP study of anaplastic cases has not confirmed this. In the literature, the percentage of anaplasia in WTs varies between 5.05% [29] and 6.37% [28], but the latter proportion may be biased by selection of stages. In our sample, anaplasia constituted 7.5% (33 of 440) of all WTs, and 6.2% (27 of 334) of preoperatively treated unilateral WTs of stage I–IV only. Presumably our sample is representative for WTs in Germany, as our data represent 95% of WTs registered in Germany during the study period [6]. By comparison, only 78% of WTs documented in the National Cancer Register of Childhood Tumors were included in the UKCCSG Wilms’ Tumor Study 1 [29]. Worldwide comparisons of the frequency of anaplasia in WT are crucial, as significant ethnic differences have been described [28]. Our sample may be roughly comparable to UKCCSG and NWTS with respect to the proportion of anaplasia. However, both relapse-free survival and overall survival of focal anaplasia in preoperatively treated patients, stage I–IV, were distinctly worse in our study than in NWTS. Faria et al. [15] stated that prognosis with focal anaplasia was no worse than that of non-anaplastic WT. This observation could not be confirmed in our sample of preoperatively treated unilateral stage I–IV WT with focal anaplasia, nor in a larger sample of SIOP data [16]. As in our series, in the NWTS data for primarily operated WTs diffuse anaplasia showed a worse prognosis than focal anaplasia. In preoperatively treated patients, more than half of the relapses with non-anaplastic WT survived, but only a few with anaplasia. Therefore, adaptation of the initial therapy to the high risk for death appears inevitable, at least in diffuse anaplasia.

Further strong prognostic factors in preoperatively treated patients were stage IV and poor response of the abdominal tumor to preoperative therapy. This shows that reaction to preoperative therapy is an early indicator for further prognosis and a key to an adequate postoperative therapy. Only 32.2% of all preoperatively treated stage IV patients received radiation of their metastases at initial therapy and intensified postoperative therapy including ifosfamide. Nevertheless, 61% survived relapse-free, and 76.3% had a 5-year survival. In non-anaplastic WT, 82.6% survived. Similar results for favorable histology were achieved by the NWTS 3 [30] using a four-drug regimen (dactinomycin, vincristine, adriamycin and cyclophosphamide) and radiation of the metastatic site in all cases. But interstitial pneumonitis was a significant cause of morbidity and mortality among these patients [31]. Recently, the additive effects of pulmonary irradiation and anthracycline therapy concerning cardiac long-term consequences [32], especially together with cyclophosphamide and ifosfamide [33], have been outlined. NWTS 2 had shown before that half of favorable stage IV patients could be cured without any anthracycline [30], but only with pulmonary radiation. Our data, together with other presentations [34], have shown that none of the completely necrotic WT recurred. In the SIOP-9, completely necrotic stage IV WT was treated postoperatively with anthracyclines, as other non-anaplastic WTs. The on-going SIOP 2001 trial will try to identify stage IV WTs that could be cured without any postoperative anthracycline, as in NWTS 2, and without radiation of the metastatic site. If confirmed, it would mean that with respect to our data, 10% of stage IV WT would require only 100 mg/m² adriamycin of preoperative therapy, instead of the 400 mg/m².

In our sample, 6.36% of WT had a synchronous bilaterality (stage V), which is a percentage well in accordance with the observations of the NWTS [27]. Further analysis showed a high percentage of stromal WT (36%) among non-anaplastic stage V cases. In unilateral WT, this histology was mainly associated with low stages (stage I and II N0), and presented as a very favorable entity [7] despite non-responsiveness to preoperative therapy. Moreover, abdominal stage III was significantly more frequent among stromal stage V patients than in the unilateral stromal WT. The only relapse of a stromal WT in the whole SIOP-9/GPOH sample occurred in one of these abdominal stage III patients of stromal histology in bilateral WT. Stromal WT histology can cause a great problem because of its unresponsiveness to preoperative therapy, especially as our data and earlier analyses [35] have shown that the loss of renal tissue due to bilateral excisions is the most important reason for later impairment of renal function in bilateral WT, leading even to renal failure. The preservation of as much renal tissue as possible is therefore necessary. An early genetic analysis of stage V patients may in future help to identify patients at-risk for non-responsiveness to chemotherapy due to stromal histology WT [36].

The three patients who developed metachronous bilateralizations were all originally stage I WT, i.e. 1.58% (three of 189) [7] of our non-anaplastic stage I WT presented with the latter complication. This percentage of metachronous bilateralizations was similar to the percentage of synchronous bilateral WT in our group, in accordance with the amount in other WT series [37]. The rate of metachronous bilaterizations was three out of 25, notably higher in the primarily operated young patients with small stage I WT of the NWTS, who received no chemotherapy postoperatively [23].

Although post-therapy morbidity of survivors was low, neurotoxicity due to vincristine was an impressively long-lasting one, found in 3.37% of patients after therapy. The acute vincristine toxicity observed during therapy and leading to therapy modifications was 5.8% [38], comparable to the even higher 7% described by the UKCCSG Wilms’ Tumor Study 1 [29]. Vincristine toxicity in WT therapies has been described previously, but the risk groups for long-lasting toxicity have not yet been analyzed. From our data, older patients, often with repeated vincristine as in the therapy for stage II–IV, were more at risk. Abdominal radiation seemed to increase the severity of symptoms. Older patients (>3 years) with an additional radiation, which is a small group in WT, therefore require principally early reductions of vincristine to
two-thirds, similar to the general reductions in dose recommended in infants. Our observation that older patients are especially at risk for vincristine toxicity potentiated by radiation has also been confirmed by other childhood tumor regimens [39]. Our data on the long-term morbidity of survivors showed that the fear of severe renal impairment, especially due to ifosfamide tubular toxicity [40] in patients who underwent nephrectomy, could not be confirmed. The greatest danger for the renal function remains Drash syndrome in unilateral WT [41], followed by the bilateral loss of renal tissue due to surgery in either synchronous or metachronous bilateral WT [35].

Cardiotoxicity due to adriamycin was the third important long-term side-effect. However, it is too early for final conclusions on our data. Recent publications have focused on the possible latency of congestive heart failure of up to 20 years, if anthracyclines were applied in childhood [32, 33].

A later follow-up in the adulthood of all our survivors will have to control again for these results concerning late morbidity, which seem now so encouraging for the future life of WT patients.

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