# The variable clinical spectrum of nephroblastomatosis – results from the German Society of Pediatric Oncology and Hematology (GPOH) childhood kidney tumor group.

**Rhoikos Furtwängler** ( rhoikos.furtwaengler@uks.eu )
Saarland University Hospital
**Jens-Peter Schenk**
University Hospital Heidelberg
**Waltraud Friesenbichler**
St. Anna Children's Hospital, Medical University Vienna
**Manfred Gessler**
Würzburg University
**Stefan Wagenpfeil**
Saarland University Hospital
**Leo Kager**
St. Anna Children's Hospital, Medical University Vienna
**Marina Müller**
Saarland University Hospital
**Nils Welter**
Saarland University Hospital
**Jürgen Fuchs**
Tübingen University Hospital
**Steven Warmann**
Tübingen University Hospital
**Clemens M Meier**
Saarland University Hospital
**Jochen Hubertus**
Ruhr-University Bochum
**Christian Rübe**
Saarland University Hospital
**Christian Vokuhl**
University Hospital Bonn
**Patrick Melchior**
Saarland University Hospital
**Norbert Graf**
Saarland University Hospital

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## Abstract

**Background:** Nephroblastomatosis is defined histologically as ≥2 microscopic foci of nephrogenic rests. In contrast, clinicans' nephroblastomatosis consists of single, multiple or diffuse hyperplastic nephrogenic rests (HNR) apparent on imaging as a renal tumor.

**Methods:** Analysis of 78 patients having clinically apparent uni- or bilateral nephroblastomatosis out of 2347 patients registered in two consecutive International Society of Pediatric Oncology SIOP93-01/GPOH and SIOP2001/GPOH renal-tumor studies (1993 - 2014).

**Results:** Median follow-up and age at diagnosis was 9.2 years and 13 months (0-12.7 years). 59% of patients were female, 57% had bilateral and 53% multifocal or diffuse HNR. Imaging diagnosis was conclusive in 67% when reviewed centrally versus 30% without review (*p=0.015*). 27% of patients developed nephroblastoma(s). 45% had high-risk, 30% intermediate-risk histology and 25% upfront-surgery-blastemal subtype. 5-year-event-free-(EFS), nephroblastoma-free-(NFS) and overall-survival(OS) were 60.7%, 79.8% and 95.5%, respectively. Univariate risk factors for EFS/NFS were female gender (*p<0.001/p=0.031*), bilateral(*p=0.002/p=0.03*), diffuse HNR at diagnosis (*p<0.001/p=0.016*), and non-complete-remission(non-CR) at end of first-line-treatment (*both p<0.001*). Gender and non-CR remained significant in multivariate COX regression analysis for EFS(*p=0.005/p<0.001*), non-CR also for NFS(*p=0.002*). 34 patients achieved CR within 12 weeks from diagnosis: 25 of them were only followed, 9 received further chemotherapy. EFS was 78% and 100%, respectively.

**Conclusion:** Patients having Nephroblastomatosis have an excellent OS but need an extended follow-up for more than a decade. A short treatment is sufficient for those who achieved CR within 12 weeks. Bilateral and diffuse HNR are significant risk factors. Consensus terminology is needed for future trials to facilitate true comparability of results.


## Introduction

Nephroblastoma (WT) is the most common renal tumor of childhood (1, 2). Nephrogenic rests (NR) are its facultative precursor lesions and thus frequently found in nephroblastoma tumor nephrectomy specimens (42-45%), most markedly in case of bilateral WT (3, 4). Beckwith defined NR as "a focus of abnormally persistent nephrogenic cells (after 36 weeks of gestation), retaining cells that can be induced to form a WT" (5). The two main subtypes, intralobar and perilobar NR (ILNR & PLNR), can be discerned by genetic profile, histology and location in the kidney's lobes. ILNR can occur anywhere in the lobe and the hilum, have a strong association to WT1 mutations and stromal predominance and originate from embryologically earlier tissue than PLNR, that occur at the periphery of the renal lobe as remnant of nephrogenic tissue persisting after the 36$^{th}$ week of gestation (6, 7). Depending on the evolutionary and proliferation state of NRs, they can be subdivided in dormant (microscopic, quiescent foci), maturing/sclerosing/obsolescent NR (regressing foci), cystic and mature NR (ILNR hardly to distinguish from renal dysplasia) and hyperplastic NR (HNR)(7). The latter can occur as diffuse (DHNR) or focal HNR. DHNR are usually a lobe surrounding rim of nephrogenic tissue, maintaining the kidney's form but creating gigantic lobes or even entire kidneys. Focal HNR create irregular multicystic (predominantly ILNR) or homogeneous discoid- shaped tumors (predominantly PLNR). HNR can have the same proliferative potential as WT and, unlike non-hyperplastic NR that are found on histology only, may become clinically apparent as a renal tumor on cross-sectional imaging. As a pathologic term, Beckwith defined nephroblastomatosis as presence of multiple or diffuse NR (5). While this includes HNR, it also includes clinically inapparent and not-disease-creating forms. NR apparent on imaging as a renal tumor and thus clinically apparent are always HNR. This is what a clinician terms "nephroblastomatosis". However, this also includes a single HNR which, according to Beckwith, would not qualify for the histologic term according to Beckwith. The optimal treatment of clinically apparent ("clinician's") nephroblastomatosis depends on various factors and is still under discussion. It ranges from "watch and wait", surgery alone, to long lasting maintenance treatment (3, 7-9). While WT treatment trials have been successfully running since 1969 and results published extensively, results on NR are retrospective and have never encompassed the whole spectrum of clinically apparent ("clinician's") nephroblastomatosis. Therefore, here we present the prospectively collected results of all patients treated for clinically apparent nephroblastomatosis in the framework of two consecutive renal tumor trials run in Austria, Switzerland and Germany by the Society of Pediatric Hematology and Oncology (Gesellschaft für Pädiatrische Onkologie und Hämatologie - GPOH) between 1993-2014.

## Methods

For the purpose of this study, diagnoses made by imaging alone as well as by imaging plus histology of diffuse, multi- or unifocal hyperplastic intra-, perilobar or combined nephrogenic rests were included and all were termed "nephroblastomatosis". Patients with combined NR and nephroblastoma were not included in this analysis. Incidental histologic finding of a NR on histology for other reasons, for example in case of kidney transplant, were not included. All 78 patients meeting the above criteria who had been entered for a renal tumor in one of the in two consecutives renal tumor trials of the GPOH between 1993 and 2014 were included in the first dataset. Data were taken from the respective databases. In case of insufficient information on case report forms, data were obtained from treating institutions. Sufficient data for final analysis were available in 75 patients. If imaging had not undergone real-time central review during the initial treatment, imaging was retrieved from the treating institution and reviewed to determine remission status and residual lesions at the end of treatment. Renal involvement by HNR at diagnosis was discerned into single & oligo-focal (<4), multi-focal (≥4) and diffuse nephrogenic rests/nephroblastomatosis. Volume was measured using the ellipsoid formula. For multifocal lesions, the volume of all lesions was summed up. In case of diffuse involvement, the entire lobe or, if applicable, the entire kidney was measured. Response was defined as complete remission (CR) if no visible lesion was present on imaging. CR was termed uncertain (CRu) if residual changes were visible as thin superficial plaques or blurry changes in the parenchyma texture, but there was no measurable lesion left ("residues", "residual changes"). Partial response (PR), stable disease (SD) and progressive disease (PD) were defined as >25% decrease, <25% decrease to 25% of volume increase and >25% increase, respectively. All specimens underwent pathology review by a panel of experienced pediatric pathologists (Ivo Leuschner, Dieter Harms, CV). Classification was carried out according to the revised SIOP working classification of renal tumors of childhood (10).

According to the SIOP 93-01/GPOH and SIOP2001/GPOH protocol for childhood renal tumors, diagnosis was made by means of cross-sectional imaging. WT was assumed in case of WT-typical pseudocapsula and, or tissue inhomogenity in contrast to discoid or diffuse perilobar or unsharply delinated intralobar rest (Detailed in (11)). Preoperative treatment was recommended in patients who are older than six months and younger than 16 years, as explained in detail elsewhere (8). Upfront surgery or cutting-needle biopsy was recommended for all other patients. In case of typical imaging features for diffuse hyperplastic perilobar nephrogenic rests (DHPLNR) upfront chemotherapy was also acceptable for younger children (11). Treatment recommendations for nephroblastomatosis were detailed in the respective treatment protocols SIOP93-01/GPOH (12), SIOP2001/GPOH (13) (Overview Flow Chart in Supplemental File A*)*. It consisted of an induction phase of intensified bimonthly AV for three months (6x) and a maintenance treatment depending on the remission status and protocol. Patients treated on SIOP93-01/GPOH received actinomycin D (1x15µg/kg day 1,2 and 3) and vincristine (1.5mg/sqm day 1) every six weeks in case of PR until CR, followed by every 12 weeks for a total duration of two years. For SIOP2001/GPOH, treatment intervals and duration were shortened to three (PR) and four (CR) weeks and one year, respectively. In case of PD or SD, resection was recommended.

Survival and risk factor analysis was carried out using SPSS (Version 27.0, IBM). Survival was calculated using the Kaplan Meier method and are given with standard error parameter (Survival±SE) and compared using the log-rank test. Cox-regression was used for adjusted multivariate analysis. Non-parametric testing was carried out using Mann-Whitney-U-rank sum test. The chi-square test and Exact Test according to Fisher-Freeman-Halton was used for discrete variables. P-values are two-sided and subject to a significance level of 5%. Progression of nephroblastomatosis, relapse of nephroblastomatosis at local site after complete remission was achieved, progression to nephroblastoma and death for any reason were defined as endpoint for event-free survival (EFS). Development of nephroblastoma was defined as endpoint for nephroblastoma-free survival (NFS) and death for any reason as endpoint for overall survival (OS). Time to event, time to nephroblastoma development and time to death were calculated as the time between date of radiologic diagnosis of a renal tumor and date of 1$^{st}$ event, development of 1$^{st}$ nephroblastoma or death, respectively. Patients were censored at last documented follow-up alive.

## Results

Between 1993 and 2014, a total of 2347 children with a renal tumor were registered in Austria, Switzerland and Germany. 78 (3.3%) of them had nephroblastomatosis at first diagnosis. Median and mean age at diagnosis were one year two months and one year eight months respectively (Range: one day - 12.7 years). 40% (n=30) occurred within the first year of life, only 9% (n=7) were older than three years at diagnosis. 57% (n=43) occurred bilaterally. 59% (n=44) were female. 43% (n=32) had known syndromic features, malformations or syndrome at diagnosis (Supplemental file D). Mean and median follow-up time were 9.2 and 9.7 years, respectively (range: 0.6 – 16.8y). Patients clinical characteristics with respect to presentation and treatment approach are shown in table 1.

**Route to diagnosis:** Radiologic findings were available in 76 patients (98%) at the time of diagnosis. Patients having unilateral tumor(s) had a significantly higher rate of single or oligo-focal tumors (79%), while bilateral tumors were diffuse and multifocal in 88% of cases (*p<0.001*) (Table 1). Being under surveillance for a syndrome was also associated with a higher rate of single or oligo-focal tumors (51%) compared to patients without syndrome (28%) (*p=0.032*).

Overall sensitivity of imaging at diagnosis was low. 37 (49%) patients were diagnosed with nephroblastomatosis, 31 (41%) with nephroblastoma. 8 (10%) had a kidney tumor not further specified. Sensitivity depended on clinical presentation and was 4.5% for single, 83.3% for multifocal and 83.9% for diffuse nephroblastomatosis (p<0.001). 52 patients (68%) had real-time central radiology review. Sensitivity was significantly higher in case of reference radiology: 62% compared to 30% for local radiology findings (Odds-ratio 3.73; *p=0.015*). This was also reflected in clinical decision-making: 62% of patients having reference radiology received upfront nephroblastomatosis-directed treatment compared to 30% having local radiology only.

21 patients underwent biopsy prior to treatment, 13 of whom had reference radiology. Biopsy was conclusive in 5 of 8 (62%) open and 2 of 13 (15%) core-needle biopsies and led to a change in the treatment decision, i.e. to treat as nephroblastomatosis, in 3 of 21 (14%) biopsies.

**Treatment and outcome:** Three patients had insufficient information on outcome and treatment and were excluded from final analysis. 31 (39%) patients had an event, including 10 (13%) who developed nephroblastoma (WT) as their first event and one patient who died due to a treatment-related cardiogenic shock during catheter surgery. 13 of 21 (62%) patients who had a PD of nephroblastomatosis, had multiple PD. 20 of 31 (64%) events were local disease progression of a preexisting, residual lesion. Overall 20 (27%) patients developed a WT, 7 of whom (35%) had further relapse(s) of nephroblastomatosis at a later timepoint. 16 WT occurred unilaterally, two synchronous and two metachronous bilaterally. Histology showed 45% high-risk histology (diffuse anaplasia, n=4; blastemal type after chemotherapy, n=5), and 55% intermediate or non-anaplastic histology (blastemal predominant after primary surgery, n=5; mixed type, n=4; and regressive type, n=2). Four patients ultimately died from nephroblastoma progression, one from treatment-related toxicity. 5-year event-free (EFS), nephroblastoma-free (NFS) and overall survival (OS) were 60.7±5.9%, 79.8±5.1% and 95.5±2.6%, respectively (Figure 1). Events occurred in 70% of the cases within two years, 20% 3 to 5 years after initial diagnosis and 10% later. Mean and median time to nephroblastoma was 4.3 and 3.8 years, respectively (0.6 – 10.8 years). 95% of nephroblastomas occurred between 2.7 and 6.2 years after diagnosis of nephroblastomatosis.

First-line treatment consisted of watch and wait in 7 patients, 13 underwent upfront surgery (not biopsy) and 54 received chemotherapy. One patient died prior to initiation of treatment, three had insufficient information available.

6 of 7 (85%) patients who were only followed, progressed at a median of 6.8 months, including three patients who eventually developed a nephroblastoma (Table 1a).

12 of 13 (92%) patients undergoing upfront surgery achieved a 1$^{st}$ CR. Two patients received short (3 & 9 weeks) and two long treatment of AV (24 & 47 weeks). 9 patients were only followed, including one patient with residual NR who was the only one to experience disease progression 3.1 months after surgery, but then achieved a 1$^{st}$ CR after chemotherapy and surgery and remained disease-free thereafter (Table 1a).

54 (73%) patients received neoadjuvant chemotherapy. 17 of them (31%) had no tumor resection during first-line treatment (Figure 2) including five (29%) achieving a CR at the end of 1st line treatment. 12 of 17 (71%) suffered from progression (n=9) or relapse (n=3) at a median time of 11.8 months after diagnosis and eight developed a nephroblastoma (47%). 37 patients underwent delayed surgery as part of their first-line treatment, resulting in CR in 27 (73%) cases at the end of treatment. 12 of these 37 patients (32%) developed a relapse (n=4) or progression (n=8) 1.92 years after diagnosis (median), including nine patients who eventually developed nephroblastoma (24%) (Table 1a and Figure 22). One patient had a completely necrotic lesion in the final excision after treatment for nephroblastomatosis. She received no further treatment and remained alive for more than five years without relapse.

***Early surgical CR:*** 34 patients (46%), including 12 patients who underwent upfront surgery, achieved a CR by surgery within 12 weeks from imaging diagnosis. 10 had undergone complete (CN), 12 partial nephrectomy (PN) and 12 enucleation (EN). After the histologic diagnosis of nephroblastomatosis, 25 patients had either no further treatment or were treated for less than four weeks, including 15 of 24 patients with nephron-sparing surgery (NSS). Four patients relapsed (1 CN, 1 PN and 2 EN), three of them developed nephroblastoma (1 each CN, PN and EN) and one died of it eventually (PN). No event occurred in the group of nine patients who received a long treatment with AV (median 34 weeks (Range:12 – 93 weeks)). 5-year event-free survival (EFS) and 5-year nephroblastoma-free survival (NFS) were 87 ±6% vs. 100% (*p=0.18*) and 88 ±8% vs. 100% (*p=0.23*) for short and long treatment, respectively *(Figure 3D and 4D)*.

***Risk factor analysis:*** **Diffuse hyperplastic nephrogenic rests** (DHNR) are associated with a significantly inferior EFS compared to single or oligo-focal nephrogenic rests (*p<0.001*), as are multifocal NR but with later events (5-y-EFS: 35.2 ±8.6% vs. 85.1 ±6.1% vs. 63.5 ±17%, respectively; Table 1b, Figure 3A). 5-year nephroblastoma-free survival (NFS) was 68.8±8.7%, 88.7 ±6.2% (*p=0.016*) and 87.5 ±11.7% (not sig.), respectively (Figure 4A). **Bilateral kidney involvement** is associated with inferior survival as compared to unilateral nephroblastomatosis (5-y-EFS: 45.6 ±7.7 vs. 83.5 ±6.8%; *p=0.002*; 5-y-NFS 72.3±7.2% vs. 91.0±6.1%, *p=0.03*). Failure to achieve a **complete remission at the end of 1st line treatment** is associated with significantly inferior event-free and nephroblastoma-free survival, whether achieved by chemotherapy or surgery alone or by a combination of both (5-y EFS: 24.1±7.9% vs. 87.4±5.3%; 5y NFS: 60.7±9.2% vs. 93.6±4.4%, both *p<0.001*; Figure 3B and 4B). Interestingly, not only residual measurable disease but also minimal non-measurable residues, often interpreted as "likely" CR, have a superimposable negative impact on survival, while both surgical and post-chemotherapy CR have a superimposable superior survival (Supplemental File B). **Female patients** had a significantly inferior 5-y EFS of 45.9±7.7% compared to 82.4±7.2% in male patients (*p=0.001*, Figure 3C). 5-year NFS difference was still significant (74.1±7.1% vs. 88.0±6.6%; *p=0.031*, Figure 4C). **Tumor volume** measurements at least at two timepoints were available in 46 patients. Median volume reduction was 43.8% after four weeks, 68% after 8-12 weeks and 69% after longer treatment. A good response to treatment occurred within 12 weeks, while lesions that responded poorly to early treatment rarely achieved a good response later. Response to treatment correlated with survival. Patients who had ≥70% volume reduction at 1st reassessment after a mean treatment duration of 7.2 weeks had significantly superior survival to patients who had lower volume reduction of 30-70% or <30% response (Supplemental File C). This difference remained for the DHNR subset too, when analyzed separately. 5-y-EFS was 100%, 53.3±9.9% and 40±16%, respectively *(p=0.011* and *p<0.001*). ≥70% volume response is also associated with significantly superior NFS (100% vs. 72.2±9% vs. 83.3 ±15%; *p=0.033* and *0.017*). The **duration of maintenance treatment** had no impact on survival. 13 patients had a prolonged "SIOP93-01-like" maintenance treatment (mean: 105 weeks (63-218 weeks), median: 96 weeks), 17 patients had shorter but more intensive "SIOP 2001-like" treatment (mean: 47 weeks (38.1 – 59.9 weeks, median: 48 weeks). 5-y EFS was superimposable (53.8±13.8% vs. 56.6±12.7%; *p=0.77*).

**Multivariate** backward conditional cox-regression for event-free survival including age, bilaterality, diffuse nephroblastomatosis, gender and failure to achieve a CR after 1st line evidenced a relevant impact of the latter two factors. Interestingly, for nephroblastoma-free survival, only failure to achieve a CR after 1st line treatment remained significant, while diffuse nephroblastomatosis, laterality and age were excluded from the final equation (Table 2). Tumor volume response was not part of the model, since it could only be assessed in 46 cases.

13 patients (17%) had only hyperplastic **intralobar nephrogenic rests** (HILNR) on imaging and/or histology, all others had hyperplastic perilobar nephrogenic rests (HPLNR) or combinations. Eleven occurred as single or oligo-focal NR, bilaterally in two cases. Syndromic features were frequent. Four had a Wilms-Tumor, aniridia, genitourinary anomalies, mental retardation (WAGR) syndrome, one a Denys-Drash (DDS), one other syndrome and one urogenital malformation. Two events occurred and led to development of blastemal predominant nephroblastoma. 5-y-EFS was significantly superior compared to HPLNR (91.7±8% vs. 53.4±6.6% *p=0.038*) but 5-y-NFS was similar (88.9±10% vs. 77.5±5.7%, *p=0.44*).

## Discussion

Here we report the hitherto largest clinical series of patients with nephroblastomatosis treated in two consecutive nephroblastoma trials in Switzerland, Austria and Germany over a timespan of more than twenty years with a median follow-up of more than nine years. Even though a uniform treatment was recommended (Supplemental file A) diagnostic approach and treatment varied. This individualization was caused by **difficulties in making a correct diagnosis** based solely on imaging studies for such polymorphous renal lesions (11, 14). In our series, overall diagnostic accuracy was low with only 48.7% of all nephrogenic rests being recognized on initial imaging, while 41% were mistaken for nephroblastoma. Furthermore, both open as well as cutting-needle-biopsies were not able to reliably discern between HNR and nephroblastoma, leading to changes in treatment decision in only 14%. The small sample size of a cutting-needle biopsy does not give a true overview and impression of the pseudo-capsule, rendering it impossible for pathologists to discern NR from blastema reliably. While this is usually possible with open "wedge" biopsies, it would lead to upstaging (stage III) in the case a nephroblastoma is found. Furthermore, even when taking this risk, only 62% were diagnosed of having a NR and it rarely led to change in decision. Thus, in line with current recommendations, biopsy must be strongly discouraged (15). The GPOH offered real-time **radiology review** to all participating sites during SIOP93-01 and SIOP2001/GPOH studies. This increased accuracy from 30 to 62% underlining the importance of radiologic experience in discriminating these rare lesions from other renal lesions (16). However, criteria to discriminate NR from WT are limited, mainly based on the nephroblastoma suggesting presence of a pseudo-capsule and contrast enhancement inhomogeneity in solid parenchyma at diagnosis. Size of a lesion had not been a defining criterion in SIOP93-01 and

SIOP2001. But smaller single or oligo-focal lesions suggest NR. Sandberg et al. found a <1.75 cm diameter cut-off being highly suggestive for HNR, which however does not help with larger lesions (14 ). We found a significantly higher rate of single or oligo-focal nephrogenic rests in predisposed patients (Table 1b), most likely due to successful routine surveillance, as compared to non-predisposed patients having more diffuse and multifocal lesions (Table1b) (17, 18). Decision-making, especially in predisposed patients, should therefore include a thorough review of imaging and multidisciplinary board discussion, including physicians with specific experience in treatment and diagnosis of nephrogenic rests and other childhood kidney tumors to avoid unnecessary invasive procedures.

The **prevention of nephroblastoma** is the main aim of treatment directed at hyperplastic nephrogenic rests (HNR). A gold standard is lacking so far. Acute side effects and long-term effects of different treatment modalities have to be balanced against their efficacy in this non-metastasizing neoplastic disease (9, 19-21). Thus, clinical approach spans from “watch and wait” (W&W) to long-term maintenance treatment and tumornephrectomy. Similar to infant-neuroblastoma, W&W has been suggested as standard approach for HNR (22). This was not successful in our seven patients with six PD (Table 1b). However, all seven had diffuse or multifocal tumors, we can hence only conclude that clinicians need to be aware of the high probability of progression under W&W in this cohort. In contrast, W&W was successfully used in 25 of 34 patients who had undergone early surgery, achieved a 1$^{st}$ CR and were followed up after no or only short treatment (<12 weeks) without maintenance treatment for nephroblastomatosis. Despite 76% nephron-sparing surgeries, only four events (16%) occurred, including three nephroblastoma. Though single or oligo-focal HNR predominated, also a small group of multifocal and diffuse HNR patients (n=4) achieved and maintained an early CR (Table 1a, Figure 3&4D). Contrary, the current SIOP-RTSG Umbrella recommends maintenance of monthly AV for a total duration of one year in case of nephron-sparing surgery if on histology any histologic NR are present, even if the remaining kidneys are in CR (*SIOP-RTSG Umbrella, summarized in* (23)). This recommendation is based on reported association of histologic NR with metachronous relapse and hyperplastic NR’s chemosensitivity (24, 25). However, 42-45% of all WT are accompanied by NR on histology, whether pre-treated or not, suggesting a limited responsiveness of microscopic & histologic NR to treatment (3, 4). One reason might be their wide histologic and biologic spectrum from benign, completely quiescent NR to active, highly proliferative, clinically apparent HNR (6, 7). We provide evidence that even in the latter HNR group, in case of CR, a short response-adapted treatment in combination with NSS followed by W&W is successful, thus challenging the current SIOP-RTSG Umbrella approach of one-year maintenance therapy.

On the other hand, already small residual lesions have a risk of relapse of more than 60% (Supplemental File B). In these cases, a **maintenance treatment** might be justified. Treatment duration varied significantly, ranging from about one (SIOP2001) to two years (SIOP93-01), with no difference in the rate of events or WT. Mean and median time to nephroblastoma was 3.8-4 years, independently whether patients had received a short treatment, a long or a short maintenance therapy. Thus, we could not find evidence of efficacy of the current maintenance treatment. Considering the long time to WT, its duration of up to two years might not be sufficient. A treatment inducing renal cell differentiation such as cis-retinoic acid could be a less toxic alternative. Friesenbichler et al. reported on two patients with residual lesions who had extended maintenance treatment with cis-retinoic acid (biweekly on-off) and achieved sustained CR (26).

Diffuse and multifocal hyperplastic NR (DHNR & MHNR) occur more frequently bilaterally and are usually not amenable to early surgical CR (Table 1). The COG suggested 6-week doxorubicin-intensified AV to induce resectability in bilateral nephroblastomatosis (27). In our cohort, prolonged treatment of ≥12 weeks AV facilitated the achievement of a first-line CR in 60% (32/54) of all upfront CTx patients, including 10 MHNR and DHNR. Interestingly, an early reduction of >70% of the initial tumor volume correlates significantly with superior event- and nephroblastoma-free survival (Supplemental File C). Hence, patients not responding convincingly to initial AV within 6-12 weeks are candidates for treatment escalation. Data on treatment escalation in HNR are lacking. However, data from bilateral nephroblastoma series, which frequently include HNR, suggest that doxorubicin induces a better response. Coppes et al. also found a lower rate of metachronous WT in patients having NR if treated with doxorubicin (24). Alternatively, SIOP recommends carboplatin and etoposide in unresponsive bilateral cases (8, 23, 27). Beside standard cytotoxic drugs, add-on cis-retinoic acid as a differentiation-inducing drug has recently been used successfully in two HNR case series (26, 28). Persistent and thus treatment-resistant nephrogenic rests seem to harbor the origin of nephroblastoma clones. In case of an event, the probability of a nephroblastoma was relevant in our cohort with 29% for the first event. Furthermore, 65% of all patients experiencing an event eventually developed a WT. Similarly, Perlman et al. reported a WT development rate of 39% in their series of 53 DHNR patients (29). Failure to achieve a 1$^{st}$ line CR was significantly and independently correlated with an inferior event-free and nephroblastoma-free survival (Table 2, Figures 3&4B). Furthermore, patients suffering from nephroblastoma had a remarkably higher proportion of 45% high-risk nephroblastoma (blastemal subtype and DA) as compared to 5-7% in the only shortly pre-treated SIOP nephroblastoma population (12, 30, 31). Similarly, Perlman et al. and a report from GPOH indicated a significantly increased risk of 32% and 38% for diffuse anaplasia after long-term pre-treatment for nephroblastomatosis, which is even higher than the 20% in our cohort (8, 29). DA is a late event in nephroblastoma evolution and also in our cohort one more patient developed DA at a later relapse of a nephroblastoma. Prolonged observation of suspicious lesions comes with a significant risk of development of a WT, that has a 45% probability of high-risk histology. It is thus not surprising that three of our patients had pulmonary metastases at first diagnosis of a WT. Early oncologic resection to rule out WT, especially high-risk WT, should hence always be considered for stable or progressive suspicious lesions.

The **relapse and progression pattern** of NR patients differs significantly from WT patients. While 85% of first events after diagnosis of nephroblastomatosis occur within three years, 95% of nephroblastoma occurred 2.7 to 6.2 years after diagnosis of nephroblastomatosis and up to the age of 11. Similarly, Perlman et al. reported a case developing his first WT at the age of 11 years (29). Bergeron and Beckwith et al. stressed the risk of very late metachronous relapse in case of NR or NR-predisposing syndromes (7, 25). Coppes et al. mentioned a late relapse 13.1 years after initial diagnosis even in contralateral NR (24). Similarly, Scalabre et al. reported one metachronous WT after nephron-sparing surgery occurring at the age of 12 years (32).This is in contrast to unilateral nephroblastoma, where typically 95% of relapses occur within two years of initial diagnosis (33). This suggests to continue follow-up at least up to early adolescence. Supplemental file F gives an overview of clinical & diagnostic characteristics and treatment considerations based on published data and our experience (3, 4, 6, 8, 11, 25, 26, 29, 32, 34-37).

Based on different phylogenetic background, **intralobar (ILNR)** and perilobar (PLNR) nephrogenic rests can be distinguished (6, 34). Hyperplastic ILNR are more common in patients with WT1 germline mutation, typically in Denys-Drash syndrome or WAGR patients (3, 6). This was the case in five of 13 patients in our series. While hyperplastic ILNR (HILNR) had a significantly lower risk of an event than hyperplastic PLNR, the risk of nephroblastoma is similar in both groups. Despite of the well-documented association of ILNR with stromal predominant WT, both WT were blastemal predominant (3, 17). In summary, there is no evidence to support a different surveillance or treatment approach for HPLNR and HILNR so far.

Overall, patients having HNR in our cohort had 40% risk of relapse or progression, which is dramatically lower if a CR can be achieved (Figures 3&4B). Although HNR are considered non-metastasizing, benign lesions, the overall survival of the entire cohort of 93.5% is not superior to the 94% for stage I-III WT treated in the GPOH (12). Interpretation of our data could be limited by under-registration of uneventful focal lesions. However, compared to 12% focal HPLNR in the NWTSG cohort, our higher rate of 46% single or oligo-focal HNR supports the representativeness of our dataset (table 1b).

Smaller case series reported homogeneously favorable outcomes and supported prolonged maintenance treatment. Taken together, only two out of 18 patients developed WT (9, 26, 38-40). Contrary, Perlman et al. reported that 46% of their 52 patients developed WT, most likely due to a higher rate of 88% DHPLNR. In our cohort **prevention of nephroblastoma** as the main goal achieved a 5-y-NFS of 78.9%. Risk factor analysis yielded two main risk factors: gender and non-CR after 1$^{st}$-line treatment (Figures 3&4, Table 1). While it is self-explaining that residual HNR tissue harbors the origin of further lesions, it is surprising that females had a higher risk of progression and WT-development. It is known that WT is slightly more common in females, and females were more likely to have bilateral and DHNR, both factors showing a significantly higher risk in univariate analysis. However, when all three were adjusted in a COX-model, female gender remained independently associated with higher risk of event (HR 3.715; *p=0.005;* Table 2) and had a strong trend towards a higher risk of WT (HR 2.575; *p=0.092*). Recently, Vujanic et al. demonstrated a bi-partite peak in females with histologic NR at one and three to four years (3). Interestingly, our cohort with HNR had a single incidence peak in the first year of life. It is furthermore intriguing that all but one patient who later developed WT were younger than 24 months at diagnosis of HNR (Supplemental File E). Coppes et al. found an increased risk of metachronous contralateral WT development in case of histologic NR and age at diagnosis ≤12 months compared to older patients *(p<0.001)* (24). In a recent Children's Oncology Group study of 8 patients treated for DHPLNR, 25% developed favorable histology WT, which is in line with our results (41). Any DHNR and bilateral tumors correlated significantly with inferior event-free survival. DHNR, especially when occurring in both kidneys, limit the surgical options and hence the likelihood to achieve a CR during first line. In contrast, single and oligo-focal HNR are usually amenable to radical surgery and have less frequent events. However, the risk of developing a nephroblastoma was similar in both groups, and underlines the same malignant potential. This underlines the importance of meticulous follow-up at least in the first decade and a half of life, irrespectively of the clinical presentation of HNR.

## Conclusion

In summary, treatment of patients having nephrogenic rests is not a miracle, but requires the experience and knowledge of dedicated pediatric radiologists, oncologists, surgeons and pathologists, who are familiar with the characteristics and pitfalls of histologic and clinically apparent hyperplastic NR (Summarizing table in Supplemental File F). NR have a high risk of misinterpretation at initial diagnosis of a renal lesions. This implies that atypical smaller renal tumors should always be reviewed by reference radiologists. Furthermore, we strongly advise to contact established international collaborative groups reference networks in such situations. Treatment must be adapted to the response and it must be assessed whether an early CR can be achieved without long maintenance treatment. Contrary, for patients having irresectable residual lesions, the current treatment is frequently inefficacious and new treatment approaches, such as retinoids, are needed (26, 28). Due to the rarity of HNRs, international collaboration and harmonized protocols are needed to prospectively explore molecular markers and outcome. However, before embarking on such studies, a consensus-terminology is needed to overcome the often misleading and divergent use of the terms NR and nephroblastomatosis by pathologist and clinicians.

## Declarations

Ethics approval and consent to particapte:

Both protocols had undergone review and approval by institutional ethics committees and had been approved by national authorities prior to patient inclusion (Institutional-Review-Board-Number: EthikKomm./Ls_23/04/93 and 136/01). Informed consent was obtained from all patients, parents or legal guardians as appropriate.

Consent for publication:

Not applicable.

Availability of data and materials:

The anonymized datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

None

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Conflicts of interest statement:

The authors declare no conflict of interest.

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Author contributions:

RF and NG contributed in design of the study, statistical analysis, data collection and writing the first draft and writing and reviewing of the final manuscript.

MM, MG, WF, LK, NW, CR, PM, JF, SW, JH and CMM participated in the collection of data and contributed in writing and reviewing of the final manuscript.

SW contributed in the statistical review and writing & reviewing of the final manuscript.

JPS centrally reviewed imaging, participated in data collection and contributed in writing and reviewing of the final manuscript.

CV centrally reviewed pathologic diagnosis, participated in data collection and contributed in writing and reviewing of the final manuscript.

Conflict of interest statement:

No conflict of interest to declare.

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## Tables

Table 1 Characteristics

| 1a Initial Treatment Approach | Watch and Wait $ | Upfront Surgery | Upfront Chemotherapy | |
|---|---|---|---|---|
| | | | No Surgery | Delayed Surgery |
| n=74° | 7 | 13 | 17 | 37 |
| Gender – Female | 71 % (5) | 46% (6) | 71% (12) | 54% (20) |
| Mean Age (Diagnosis) | 1.1 (0.1-2.9) | 2.4 (0-12.7) | 1.7 (0.01-5.8) | 1.5 (0.8-7.4) |
| Bilateral | 86% (6) | 8% (1) | 100% (17) | 49% (18) |
| Volume (Diagnosis) | 88.2 ±79 ml | 9.9 ±11.8 ml | 468 ±380ml | 148 ±258 ml |
| Initial Presentation<br>Single/ Oligo \| Multi-focal \| Diffuse | 0 \| 1 \| 6 | 12 \| 0 \| 1 | 1 \| 4 \| 12 | 22 \| 4 \| 1 |
| Surgery (nS/CN/PN/EN) | n.a. | (0/2/5/6) | (17/0/0/0) | (0/9/18/10) |
| 1st line treatment duration | 36 ±31w$ | 7 ±14w | 41 ±48w | 50 ±29w |
| CR at the end of 1st line | 0 | 92% (12) | 29% (5) | 72% (27) |
| CR achieved anytime | 57% (4)$ | 92% (12) | 65% (11) | 89% (33) |
| Event | 86 % (6) | 8% (1) | 70% (12) | 32% (12) |
| WT development | 43% (3) | 0 | 47% (8)* | 24% (9) |
| Histology subtype:<br>FH \| IR \| HR \| DA | 1 \| 1 \| 0 \| 1 | 0 | 3 \| 1 \| 3 \| 1 | 1 \| 4 \| 2 |
| Time to WT | 3.2 ±2.8y | n.a. | 4.1 ±1.4 y | 4.9 ±2.7 y |
| Death | 0 | 0 | 12% (2) | 8% (3) |
| | | | | |
| 1b Nephrogenic rests at diagnosis – Initial presentation | Single & Oligofocal | Multifocal | Diffuse | p-value |
| n= 75 | 35 | 9 | 31 | |
| Gender – Female | 46% (16) | 44% (4) | 77% (24) | *0.10* |
| Mean Age (Diagnosis) | 1.9 ±2.3y | 2.7 ±2.0y | 1.1 ±1y | *0.07* |
| Bilateral | 23 % (8) | 78% (7) | 90% (28) | <0.001 |
| Syndrome | 51% (18) | 33% (3) | 36% (11) | *0.17* |
| Only ILNR | 33% (13) | 0 | 3% (1) | <0.001 |
| Volume (Diagnosis) | 58 ±156ml | 77 ±120 ml | 431 ±365 ml | <0.001 |
| Surgery (nS/CN/PN/EN) | 1/ 9/ 13/ 12 | 5/ 1/ 2/ 1 | 18/ 1/ 8/ 3 | <0.001 |
| Neoadjuvant Treatment S - W&W – AV – AVD | 12 \| 0 \| 22 \| 1 | 0 \| 1 \| 8 \| 0 | 1 \| 6 \| 23 \| 0 | 0.001 |
| Adjuvant Treatment nS – W&W – V – AV – AVD | 1 \| 13 \| 6 \| 14 \| 2 | 5 \| 1 \| 0 \| 1 \| 2 | 18 \| 3 \| 0 \| 6 \| 2 | <0.001 |
| 1st line treatment duration<br>Mean ±SD, Median (Range) | 16 ± 21w<br>6 (0-95) | 56 ±40w<br>50 (0-124) | 61 ±49w<br>50 (0-218) | <0.001 |
| Post-surgical CTx Duration | 20 ±22w | 28 ±14w | 47 ±36w | 0.07 |
| CR at the end of 1st line | 94% (33) | 56% (5) | 20% (6) | <0.001 |
| CR achieved anytime | 94% (33) | 67% (6) | 67% (21) | 0.018 |
| Event | 17% (6) | 44% (4) | 68% (21) | <0.001 |
| WT - development | 11% (4) | 33% (3) | 42% (13) | |
| Histology subtype:<br>FH \| IR \| HR \| DA | 1 \| 1 \| 2 \| 0 | 1 \| 1 \| 0 \| 1 | 3 \| 4 \| 3 \| 3 | 0.03 |
| Time to WT | 4.2 ±1.6y (2.4-6.2) | 5.3 ±1y (4.2-6.1) | 4.1 ±2.5y (0.6-10.8) | *0.99* |
| Death | 6% (2) | 11% (1) | 7% (2) | *0.67* |
| | | | | |

°One patient died prior to initiation of treatment; $ Treatment stated after first progression is shown; * p≤0.05; # p≤0.01; § p≤0.001; FH: Favorable Histology -Blastemal Predominant after upfront surgery (Surgery >12 weeks after Chemotherapy); IR: Intermediate Risk - Mixed, Regressive; HR: High Risk - Blastemal Predominant after CTx; DA: Diffuse Anaplasia; WT: Nephroblastoma/Wilms Tumor; nS=no Surgery, PN=Partial nephrectomy, EN=enucleation, CN=complete nephrectomy; ILNR=Intralobar Nephrogenic Rest; w=weeks, y=years, ml=millilitres; SD= Standard Deviation

Table 2 COX-regression analysis Event Free and Nephroblastoma Free Survival:

| EFS | Significance (p) | Exp(B) (HR) | 95% CI lower | 95% CI upper |
|---|---|---|---|---|
| Female Gender | 0.005 | 3.715 | 1.495 | 9.232 |
| non-CR after 1st line | 0.000 | 10.03 | 4.047 | 24.866 |
| | | | | |
| **NFS** | **Significance (p)** | **Exp(B) (HR)** | **95% CI lower** | **95% CI upper** |
| non-CR after 1st line | 0.002 | 5.723 | 1.902 | 17.218 |
| *Female Gender* | *0.092* | *2.575* | *.856* | *7.750* |

## Figures

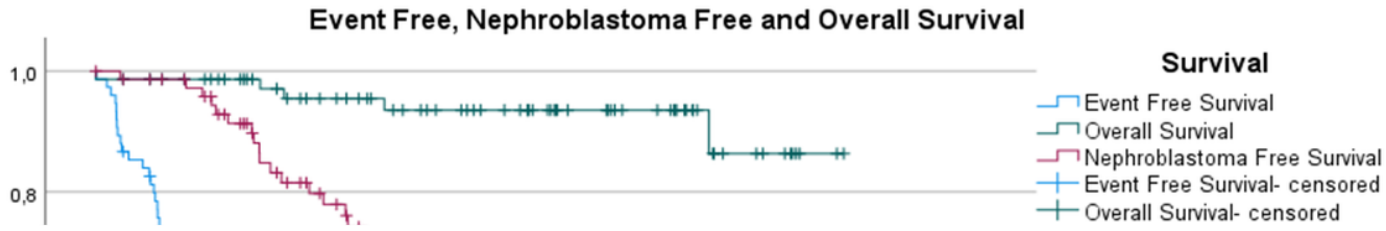


**Figure 1**

Event Free (EFS), Nephroblastoma Free (NFS) and Overall Survival (OS) of all 75 evaluable patients with nephroblastomatosis.

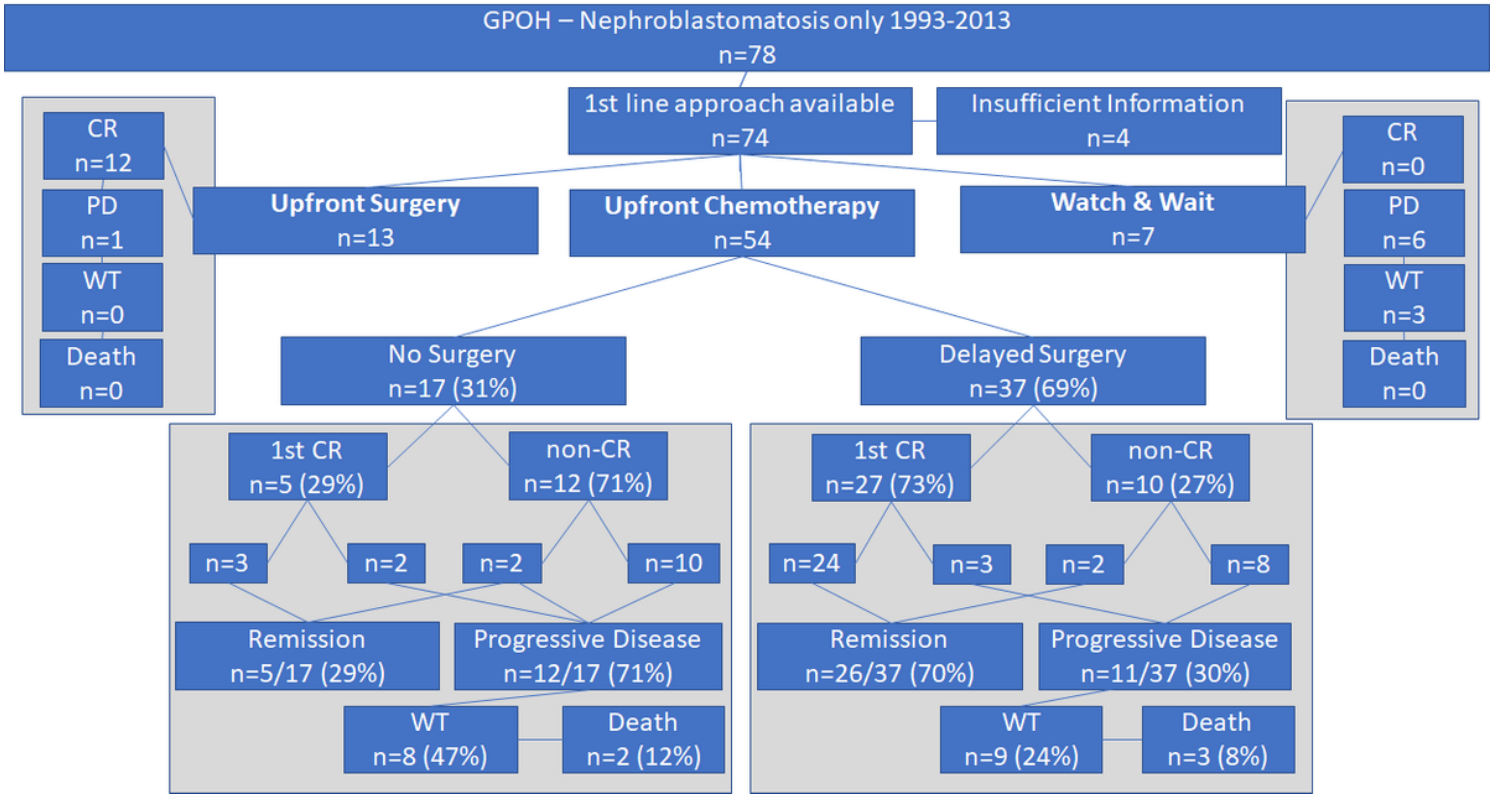


**Figure 2**

Treatment and Outcome Tree – Outcome according to treatment approach of 74 patients having sufficient information on upfront approach. PD= Progressive Disease, WT= Nephroblastoma/Wilms Tumor, CR= Complete Remission.

**Figure 3**

Univariat Risk factors Event Free Survival (EFS)

Survival without event. Graph of survival estimates according to respective factors. Every vertical line represents a censored case at last follow up without event.

a. Initial presentation: single/oligo-focal, multifocal (≥4), diffuse NR (n=75)

b. Complete remission at the end of first line treatment (n=73)

c. Gender (n=75)

d. Patients who achieved early CR after surgery with respect to short or long consolidating treatment (n=34)

**Figure 4**

Univariat Risk Factors Nephroblastoma Free Survival (NFS)

Survival without development of a Nephroblastoma. Graph of survival estimates according to respective factors. Every vertical line represents a censored case at last follow up without nephroblastoma.

a. Initial presentation: single/oligo-focal, multifocal (≥4), diffuse NR (n=75)

b. Complete remission at the end of first line treatment (n=73)

c. Gender (n=75)

d. Patients who achieved early CR after surgery with respect to short or long consolidating treatment (n=34)

## Supplementary Files

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