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The Fate (Outcome) of Clinically Apparent Single Lesion and Oligofocal Nephroblastomatosis Treated According to SIOP/GPOH Protocols for Wilms Tumor

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ABSTRACT

Background: The management of clinically apparent single lesions or oligofocal nephroblastomatosis, a facultative precursor of nephroblastoma, remains debated.

Methods: We retrospectively analyzed 37 patients with clinically apparent single or oligofocal nephroblastomatosis (two to three lesions per kidney) among 2347 patients registered between 1993 and 2014 in the SIOP93-01/GPOH and SIOP2001/GPOH renal tumor studies.

Results: Of the 37 patients, 23 had a single lesion, and 14 had oligofocal disease; 65% had a clinically apparent and/or molecularly diagnosed cancer predisposition syndrome, and 27% bilateral involvement. Preoperative chemotherapy was administered to 62%, primary surgery to 32%, and chemotherapy without surgery to 5%. Nephron-sparing surgery was performed in 71%. In oligofocal cases, preoperative chemotherapy led to significant tumor volume reduction. Prognosis was favorable: 10-year event-free, nephroblastoma-free, and overall survival rates were 77.4%, 80.7%, and 92.0%, respectively. Of 35 patients who underwent definitive surgery, 26 received short postoperative treatment (≤4 weeks) or a watch-and-wait approach (W&W). Three patients (11.5%) developed nephroblastoma, two of whom were successfully salvaged. Ten-year nephroblastoma-free survival was 74.1%, 90.0%, and 100% for short, W&W, and long postoperative treatment (>4 weeks), respectively. All 12 patients undergoing primary definitive surgery remained nephroblastoma-free.

Abbreviations: AV, actinomycin D and vincristine; CPS, cancer predisposition syndrome; CR, complete remission; DH-PLNR, diffuse hyperplastic perilobar nephrogenic rest; DWI, diffusion weighted Imaging; EFS, event-free survival; ILNR, intralobar nephrogenic rest; NFS, nephrobastoma-free survival; NR, nephrogenic rest; NSS, nephron-sparing surgery; OS, overall survival; PLNR, perilobar nephrogenic rest; TV, tumor volume; W&W, watch and wait; WT, Wilms tumor.

Conclusion: Short postoperative chemotherapy or W&W is a safe option for patients with single or oligofocal nephroblastomatosis in complete remission, provided they undergo close ultrasound monitoring. The modest relapse risk, manageable with salvage therapy, must be weighed against the toxicity of prolonged treatment, especially in infants. Both primary and delayed surgery are viable strategies.

1 | Introduction

Nephroblastoma or Wilms tumor (WT) is the most common renal malignancy in children [1]. Nephrogenic rests (NR) are frequently identified incidentally in nephroblastoma specimens—particularly in bilateral cases, where prevalence reaches 42%–45% [2, 3]. Histologically, Beckwith et al. 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." He also defined nephroblastomatosis as the presence of multiple or diffuse NR on histology [4]. This is in contrast to the clinical use of the term, where a clinically apparent single lesion might be called nephroblastomatosis too.

Two major NR subtypes—intralobar (ILNR) and perilobar (PLNR)—can be distinguished by histological features and anatomical location within the renal lobe, and they are linked to specific genetic drivers [5, 6]. ILNRs may occur throughout the lobe and hilum, are strongly associated with *WT1* mutations and stromal predominance, and they originate from developmentally earlier tissue. In contrast, PLNRs typically reside at the periphery of the renal lobe, representing remnants of nephrogenic tissue persisting beyond the 36th week of gestation [7, 8].

NRs can be further classified by their developmental and proliferative state into [8]: (i) dormant (microscopic, quiescent foci); (ii) maturing/sclerosing/obsolescent (regressing foci); (iii) cystic (often ILNR, sometimes indistinguishable from renal dysplasia) and mature; and (iv) hyperplastic NR (HNR). HNRs are further subdivided into focal and diffuse forms. The latter typically affects an entire lobe or the whole kidney, enlarging the organ while preserving its architecture [9]. Clinically apparent HNRs typically present with a hypointense signal in contrast-enhanced T1-weighted magnetic resonance imaging (MRI) and low apparent diffusion coefficient values [10]. Small cystic lesions are diagnosed as such. Sclerosing foci usually can be detected in follow-up examinations by a change in the MRI signal. These hyperplastic, cystic, or sclerosing lesions are referred to clinically as "nephroblastomatosis," and they may present as a solitary lesion. However, Beckwith's histopathological definition reserves this term for multiple or diffuse HNRs, even if they are not radiologically apparent. This discrepancy contributes to terminological inconsistencies between clinical and pathological use.

The optimal management of clinically apparent nephroblastomatosis remains controversial and varies widely—from watchful waiting and surgery alone to prolonged maintenance chemotherapy [3, 9, 11–13]. While WT treatment protocols have been extensively refined since 1969, data on NR are largely retrospective and fail to encompass the full spectrum of clinically apparent nephroblastomatosis.

This study presents prospectively collected data from patients treated for clinically apparent nephroblastomatosis within two consecutive renal tumor trials conducted by the Society of Pediatric Hematology and Oncology (GPOH) in Austria, Switzerland, and Germany. Here, we focus specifically on clinically apparent single and oligofocal nephroblastomatosis. Cases of multiple or diffuse nephroblastomatosis are rarely amenable to early nephron-sparing surgery due to extensive involvement of both kidneys. They require a different clinical and therapeutic management and are not covered in this manuscript.

2 | Methods

We retrospectively analyzed 37 patients with clinically apparent unilateral or bilateral, single or oligofocal nephroblastomatosis diagnosed by imaging, with or without histological confirmation. All patients who underwent surgery ($N = 35$) had confirmed intralobar, perilobar, or combined NR. They were selected from a cohort of 2347 WT patients enrolled in the SIOP93-01/GPOH and SIOP2001/GPOH (EudraCT number: 2007-004591-39) renal tumor studies between 1993 and 2014. A detailed description of patient characteristics is given in the patient overview table (Table S1).

The study included patients with nephroblastomatosis present as one or up to three kidney lesions that were clinically apparent—that is, detectable by imaging (ultrasound and/or MRI) at initial diagnosis—and consistent with the radiologic characteristics of ILNR or PLNR. In the SIOP93-01/GPOH and SIOP2001/GPOH studies, radiologic diagnosis was based mainly on contrast-enhanced MRI and, to a lesser extent, on computed tomography (CT). Diffusion-weighted imaging (DWI) was recommended as part of routine diagnostics only in the current Umbrella SIOP-RTSG protocol [10]. All identified lesions were diagnosed and treated accordingly. In 60% of patients, reference radiology was performed at the initial time of diagnosis in addition to local radiological assessment. The term "clinically apparent" was used to distinguish imaging-visible lesions from histologically defined NR, which are identified only microscopically following surgical resection. "Oligofocal nephroblastomatosis" was defined as two to three distinct lesions per kidney, with each side counted separately. Patients with imaging-confirmed additional nephroblastoma were excluded.

"Definitive surgery" was defined as a procedure aimed at achieving complete remission (CR), meaning no residual disease detectable on imaging. The term "delayed surgery" is used throughout the manuscript as a synonym for definitive surgery following neoadjuvant chemotherapy. "First-line treatment" encompassed all therapeutic interventions—surgery, chemotherapy, or both—administered from diagnosis to completion of therapy or disease progression.

Diagnosis followed the SIOP protocols using cross-sectional imaging, with abdominal MRI as the gold standard. Tumor volume (TV) of nephroblastomatosis was calculated using the ellipsoid formula. For oligofocal cases, TV was the sum of individual lesion volumes. In bilateral cases, TV was calculated separately for each kidney and combined for total volume.

Preoperative chemotherapy followed SIOP93-01/GPOH and SIOP2001/GPOH protocols: 4 weeks of weekly vincristine (V) with actinomycin D (A) administered in Weeks 1 and 3. In bilateral disease, AV (actinomycin D and vincristine) chemotherapy could be extended up to 12 weeks to facilitate nephron-sparing surgery (NSS).

Postoperative chemotherapy was guided by histology and treatment response. Regimens included: *short postoperative treatment (AV-1)*: 4 weeks of vincristine with an additional actinomycin D dose in Week 2. Long postoperative treatment (AV-2): 27 weeks of AV combination therapy and/or AV maintenance (vincristine and actinomycin D every 4 weeks for 1 year), used in cases without complete remission (non-CR). *Vincristine monotherapy* was occasionally used as an interim treatment pending final histological diagnosis.

Survival and risk factor analysis were performed using SPSS (Version 27.0, IBM). Survival was calculated via the Kaplan–Meier method (± standard error) and compared using the log-rank test. Nonparametric analyses employed the Mann–Whitney *U* test; categorical variables were assessed using the chi-square test and Fisher–Freeman–Halton exact test. *p*-values were two-sided, with a significance threshold of 5%.

Events for event-free survival (EFS) included progression of nephroblastomatosis, local relapse after CR, progression to nephroblastoma, or death from any cause. Nephroblastoma-free survival (NFS) ended upon development of nephroblastoma, and overall survival (OS) upon death from any cause. Time-to-event metrics were calculated from the date of radiologic diagnosis to the date of first event, nephroblastoma development, or death. Patients were censored at the last documented follow-up.

3 | Results

3.1 | Clinical Characteristics

Of the 37 patients, 23 presented with a single lesion and 14 with oligofocal nephroblastomatosis (Table 1). The median age at diagnosis was 18 months, with no significant difference between groups, although patients with single lesions tended to be younger and more likely to have a cancer predisposition syndrome (CPS). Eighteen patients (46.8%) were female. Lesions were evenly distributed between the left and right kidneys. Bilateral disease was observed in 10 (27%) and CPS in 24 (65%) patients. A CPS was diagnosed clinically in 19, including Beckwith–Wiedemann spectrum (BWSp) (n = 7), lateralized overgrowth and WAGR (n = 4 each), genitourinary anomalies (n = 2), Denys–Drash syndrome (n = 1), and Mulibrey nanism (n = 1). In one of the seven patients with BWSp, the clinical presentation was confirmed by molecular analysis demonstrating a mosaic *11p15* loss of heterozygosity (LOH). An additional five patients were diagnosed with a CPS only after molecular analysis. These patients carried *TRIM28* germline mutations (N = 2), bilateral mosaic loss of imprinting (LOI) of *IGF2*, *CTR9* germline mutation, and *FBXW* germline mutation (one patient each).

Reference radiology was available for 22 patients. Initial imaging identified 27 cases as WT. Of these, seven could not be definitively distinguished and were classified as WT with DD nephroblastomatosis. Another seven were initially diagnosed with nephroblastomatosis, but five of them could not be clearly distinguished and were classified as nephroblastomatosis with DD WT. In three patients, imaging could not establish a clear diagnosis. Median initial tumor volume (TV) was 10 mL (interquartile range [IQR]: 4–24 mL) for single lesions and 21 mL (IQR: 3–77 mL) for oligofocal cases ($p = 0.42$). Initial treatment included preoperative chemotherapy in 23 (62%), primary surgery in 12 (32%), and chemotherapy alone in two (5%) cases. Median follow-up was 7 years (Table 1).

3.2 | Treatment Approach

Among the 23 patients with single lesions, 10 underwent primary surgery (six were <6 months old; three had unclear imaging diagnosis), and 13 received preoperative chemotherapy. No significant differences were noted in initial TV or surgical type (tumor nephrectomy vs. nephron-sparing surgery) between groups. Nephron-sparing surgery (NSS) was more common in the primary surgery group (50%) than in the delayed surgery group (23%).

Postoperatively, 12 (52%) patients received no adjuvant therapy and were monitored, four (26%) received short treatment (≤4 weeks), and five (22%) received long treatment (>4 weeks) with actinomycin D and vincristine (range: 12–47 weeks). Among those receiving postoperative chemotherapy, duration was longer in the primary surgery group (median 16 weeks, IQR: 3–41) than in the delayed surgery (median 4 weeks, IQR: 3–18), though not statistically significant (Table 2).

All 23 patients with single lesions achieved complete remission (CR) after first-line treatment, which had a median duration of 4 weeks (IQR: 0–11). Histology revealed equal distribution of ILNR and PLNR (39% each), with combined ILNR/PLNR in 22%. Four patients relapsed—all initially treated with delayed surgery. Three developed nephroblastoma; one of them died of tumor progression 6 years post-diagnosis. At the last follow-up, 96% of patients were in CR (Table 2).

Among the 14 patients with oligofocal nephroblastomatosis, 10 had bilateral disease. Eight patients had a CPS (clinical Beckwith–Wiedemann spectrum [n = 3], lateralized overgrowth [n = 1], Mulibrey nanism [n = 1], mosaic LOI *IGF2* [n = 1], *CTR9* germline mutation [n = 1], *TRIM28* germline mutation [n = 1]), five of whom had bilateral disease. One patient with a *CTR9* germline mutation had a family history of WT. Initial treatment included preoperative chemotherapy with delayed surgery (n = 10), primary surgery (n = 2), and chemotherapy alone (n = 2). Median initial TV was 21 mL (range: 3–302 mL). The two patients with the largest TV were treated without surgery,

TABLE 1 | Clinical and imaging characteristics of nephroblastomatosis.

	Single lesion	Oligofocal	All
Patient count, *N* (%)	23 (100%)	14 (100%)	37 (100%)
Gender Female, *N* (%)	12 (52%)	6 (43%)	18 (47%)
Median age at diagnosis [months] (IQR)	16 (4–29)	23 (12–30)	22 (7–29)
Localization, *N* (%)			
Left	11 (48%)	3 (21%)	14 (37%)
Right	12 (52%)	1 (7%)	13 (35%)
Bilateral	0	10 (71%)	10 (27%)
CPS, *N* (%)	16 (70%)	8 (57%)	24 (65%)
Ref radiology, *N* (%)	12 (52%)	10 (71%)	22 (60%)
Primary diagnosis on imaging			
NBL	0 (0%)	2 (14%)	2 (5%)
NBL DD WT	1 (4%)	4 (29%)	5 (14%)
WT	15 (65%)	5 (36%)	20 (54%)
WT DD NBL	4 (17%)	3 (21%)	7 (19%)
Unclear	3 (13%)	0 (0%)	3 (8%)
Median TV at diagnosis [mL] (IQR)	10 (4–24)	21 (3–77)	10 (4–36)
Treatment approach			
a) Primary CHT + surgery	13 (57%)	10 (71%)	23 (62%)
b) Primary surgery	10 (44%)	2 (14%)	12 (32%)
c) CHT + no surgery	0	2 (14%)	2 (5%)
Median follow-up time [years] (IQR)	5 (3–10)	10 (7–13)	7 (4–12)

Abbreviations: CHT, chemotherapy; CPS, cancer predisposition syndrome; IQR, interquartile range; NBL, nephroblastomatosis; Ref, reference; TV, tumor volume; WT, Wilms tumor.

while the two patients with the smallest TV underwent primary surgery.

Among the 12 patients with definitive surgery, NSS was performed in nine (75%) and unilateral tumor nephrectomy in three (25%) patients. One patient with primary surgery and seven with delayed surgery achieved early CR within 12 weeks. Histology showed PLNR predominance (67%); combined ILNR/PLNR was found in one case.

Postoperative management in the 12 patients with oligofocal nephroblastomatosis undergoing definitive surgery included watch-and-wait (W&W) or short treatment (≤4 weeks AV/V) in all primary surgery patients and 50% of delayed surgery patients. Long treatment (>4 weeks AV) ranged from 15 to 77 weeks. First-line treatment duration was shortest in primary surgery patients and longest in those without surgery (Table 3).

Twelve of 14 patients achieved CR at the end of treatment. Two patients with bilateral disease had non-CR at the end of treatment: one with residual disease after primary surgery followed by W&W, who progressed during the first year but achieved secondary CR and survived; the other, treated with chemotherapy alone (24 weeks AV), progressed a second time after second-line therapy, developed nephroblastoma 2 years post-diagnosis, and died 1 year later. A third patient, initially treated with chemotherapy alone, relapsed 6 years post-diagnosis but was salvaged and survived. All patients with delayed surgery remained in the first CR. At the last follow-up, 93% were alive and in CR (Table 3).

3.3 | Impact of Preoperative Chemotherapy

In patients receiving preoperative chemotherapy with delayed or no surgery, oligofocal nephroblastomatosis was associated with a significantly longer chemotherapy duration ($p = 0.003$), and significantly greater TV reduction at first reassessment ($p = 0.028$) compared to single lesions (Table 4).

However, no significant correlation was found between chemotherapy duration and TV reduction (Spearman $p = 0.3$), nor between histologic subtype (ILNR vs. PLNR) and TV reduction ($p = 0.3$). Response status at first reassessment and postoperative treatment duration/regimen did not differ significantly between single and oligofocal cases (Table 4, Figure 1).

3.4 | Outcome

Ten-year event-free survival (EFS), nephroblastoma-free survival (NFS), and overall survival (OS) were 77.4%, 80.7%, and 92.0%,

TABLE 2 | Treatment and outcome of single-lesion nephroblastomatosis.

	Single lesions ($N = 23$)						
	Primary surgery		Delayed surgery		Total		*p*-value
Frequency, *N* (%)	10	(100%)	13	(100%)	23	(100%)	
Initial TV [mL]							
Median (IQR)	7	(3–12)	11	(5–33)	10	(4–24)	0.3
Biopsy, *N* (%)	0	(0)	1	(100%)	1	(4%)	
Type of surgery, *N* (%)							
a) TN	2	(20%)	5	(38%)	7	(30%)	0.4
b) NSS	8	(80%)	8	(62%)	16	(70%)	
Definitive histology, *N* (%)							
a) ILNR	2	(20%)	7	(54%)	9	(39%)	0.2
b) PLNR	6	(60%)	3	(23%)	9	(39%)	
c) ILNR+PLNR	2	(20%)	3	(23%)	5	(22%)	
Postop. TTT duration [weeks][a]							
Median (IQR)	16	(3–41)	4	(3–18)	9	(3–24)	0.8
Postop. TTT, *N* (%)							
a) W&W	6	(60%)	6	(46%)	12	(52%)	0.9
b) AV ≤4 weeks or V only	2	(20%)	4	(31%)	6	(26%)	
c) AV >4–27 weeks	1	(10%)	2	(15%)	3	(13%)	
d) >27 weeks AV	1	(10%)	1	(8%)	2	(9%)	
End of first-line TTT, *N* (%)							
CR	10	(100%)	13	(100%)	23	(100%)	
Duration of first-line TTT [weeks]							
Median (IQR)	0	(0–12)	5	(3–13)	4	(0–11)	0.1
Relapse, *N* (%)	0	0	4	(31%)	4	(17%)	0.05
EFS [years]							
Median (IQR)	3	(2–10)	5	(2–11)	4	(2–10)	0.5
WT development, *N* (%)	0	(0)	3	(23%)	3	(13%)	0.1
Status at last visit, *N* (%)							
a) CR	10	(100%)	12	(92%)	22	(96%)	0.4
b) Tumor-related death	0	(0)	1	(8%)	1	(4%)	

Abbreviations: A, actinomycin D; CR, complete remission; ILNR, intralobar nephrogenic rests; IQR, interquartile range; NSS, nephron-sparing surgery; PLNR, perilobar nephrogenic rest; TN, tumor nephrectomy; TTT, treatment; TV, tumor volume; V, vincristine; W&W, watch and wait; WT, Wilms tumor.
[a]Patients with post-op W&W were excluded.

respectively. Seven patients (19%) experienced relapse or progression; five developed nephroblastoma (three at first relapse, two at second), and two died from WT (Figure 2).

The two patients without definitive surgery both progressed, developed WT, and one died 3 years post-diagnosis. The 35 patients undergoing primary or delayed surgery achieved a 10-year EFS of 91.7% and 80.5%, respectively.

Among the 35 patients who underwent definitive surgery, postoperative treatment was not associated with significant differences in EFS, NFS, or OS ($p = 0.54$). EFS was 100% in patients receiving long postoperative treatment (>4 weeks AV), compared to 75.8% in those with short (<4 weeks AV/V) and 77.5% in W&W. Three patients developed nephroblastoma—two after short treatment and one after W&W—resulting in 10-year NFS rates of 100% for long, 74.1% for short treatment, and 90.0% for W&W, respectively. Four of five relapsed patients were salvaged.

4 | Discussion

This study presents a clinical series of 37 patients with clinically apparent single or oligofocal nephroblastomatosis treated within two consecutive nephroblastoma trials conducted in Germany, Austria, and Switzerland over more than two decades, with a median follow-up of 7 years. Despite standardized treatment recommendations, diagnostic and therapeutic approaches varied, primarily due to the inherent difficulty of accurately diagnosing nephroblastomatosis as opposed to diffuse

TABLE 3 | Treatment and outcome of oligofocal nephroblastomatosis.

	Oligofocal (<4/kidney) lesions ($N = 14$)								
	Primary surgery		Delayed surgery		No surgery		Total		*p*-value
Frequency, *N* (%)	2	(100%)	10	(100%)	2	(100%)	14	(100%)	
Bilaterality, *N* (%)	1	(50%)	7	(70%)	2	(100%)	10	(71%)	
Initial TV [mL]									
Median (IQR)	3	n.a.	31	(7–77)	302	n.a.	21	(3–77)	0.1
Biopsy, *N* (%)	0	(0)	3	(30%)	1	(50%)	4	(29%)	
Type of surgery, *N* (%)									
a) TN	0	(0)	3	(30%)		n.a.	3	(25%)	0.1
b) NSS	2	(100%)	7	(70%)			9	(75%)	
Definitive histology, *N* (%)									
a) ILNR	0	(0)	3	(30%)		n.a.	3	(25%)	0.08
b) PLNR	1	(50%)	7	(70%)			8	(67%)	
c) ILNR+PLNR	1	(50%)	0	(0)			1	(8%)	
Postop. TTT duration [weeks][a]									
Median (IQR)	3	n.a.	10	(3–43)		n.a.	4	(3–36)	0.3
Postop. TTT, *N* (%)									
a) W&W	1	(50%)	2	(20%)			3	(25%)	0.7
b) ≤4 weeks AV or V only	1	(50%)	4	(40%)		n.a.	5	(42%)	
c) >4–27 weeks AV	0	(0.0)	2	(20%)			2	(17%)	
d) >27 weeks AV	0	(0.0)	2	(20%)			2	(17%)	
End of first-line TTT, *N* (%)									
a) CR	1	(50%)	5	(50%)	1	(50%)	7	(50%)	0.03
b) CR after second surgery	0	(0)	5	(50%)	0	(0)	5	(36%)	
c) PD	0	(0)	0	(0)	1	(50%)	1	(7%)	
d) Residues	1	(50%)	0	(0)	0	(0)	1	(7%)	
Duration of first-line TTT [weeks]									
Median (IQR)	2	n.a.	18	(6–49)	37	n.a.	18	(6–46)	0.14
Relapse/Progression	1	(50%)	0	(0)	2	(100%)	3	(21%)	0.04
EFS [years]									
Median (IQR)	3	n.a.	10	(7–14)	2	n.a.	9	(4–13)	0.06
WT development, *N* (%)	0	(0)	0	(0)	2	(100%)	2	(14%)	<0.01
Status at last visit, *N* (%)									
a) CR	2	(100%)	10	(100%)	1	(50%)	13	(93%)	
b) Tumor-related death	0	(0)	0	(0)	1	(50%)	1	(7%)	0.04

Abbreviations: A, actinomycin D; CR, complete remission; ILNR, intralobar nephrogenic rest; IQR, interquartile range; NSS, nephron-sparing surgery; PD, progressive disease; PLNR, perilobar nephrogenic rest; TN, tumor nephrectomy; TTT, treatment; TV, tumor volume; V, vincristine; W&W, watch and wait; WT, Wilms tumor.

[a]Patients with post-op W&W were excluded.

hyperplastic perilobar nephrogenic rests (DH-PLNR) based solely on imaging.

Imaging diagnostic criteria for WT typically rely on the presence of a pseudocapsule and heterogeneous contrast enhancement in the solid parenchyma at diagnosis [14], whereas lesion size was not a decisive factor in the SIOP93-01 and SIOP2001 protocols. While DH-PLNR can be identified radiologically, smaller single or oligofocal lesions are challenging to distinguish from WT, and core needle biopsies are often inconclusive. In 2020, Sandberg et al. [15] showed that lesions less than 1.75 cm in diameter are likely to represent HNR.

TABLE 4 | Patients with delayed surgery.

	Single NR ($N = 13$)		Oligofocal NR ($N = 12$)		All ($N = 25$)		p-value
Initial TV [mL]							
Median (IQR)	11	(5–33)	31	(7–77)	16	(5–40)	0.31
Duration pCHT [weeks]							
Median (IQR)	3	(3–5)	13	(5–23)	5	(3–13)	<0.01
Duration pCHT, *N* (%)							
a) ≤12 weeks	13	(100%)	6	(50%)	19	(76%)	
b) >12 weeks	0	(0)	6	(50%)	6	(24)	0.01
Time to first restaging [weeks]							
Median (IQR)	4	(3–4)	7	(5–9)	4	(3–7)	<0.01
Response at first restaging, *N* (%)							
a) near CR	2	(15%)	2	(17%)	4	(16%)	0.6
b) PR	8	(62%)	9	(75%)	17	(68%)	
c) SD	3	(23%)	1	(8%)	4	(16%)	
TV reduction pCHT [%]							
Median (IQR)	50	(21–65)	68	(41–76)	63	(36–72)	0.03
Dur. postop. TTT [weeks]							
Median (IQR)	4	(3–18)	10	(3–43)	4	(3–24)	0.78
Postop. TTT, *N* (%)							
a) Watch and wait	6	(46%)	2	(20%)	8	(35%)	0.58
b) AV ≤4 weeks or V	4	(31%)	4	(40%)	8	(35%)	
c) AV >4–27 weeks	2	(15%)	2	(20%)	4	(17%)	
d) AV >27 weeks	1	(8%)	2	(20%)	3	(13%)	
Dur. of first-line TTT [weeks]							
Median (IQR)	5	(3–13)	22	(7–49)	10	(5–31)	0.07

Abbreviations: CR, complete remission; Dur., duration; IQR, interquartile range; pCHT, preoperative chemotherapy; PR, partial response; SD, stable disease; TTT, treatment; TV, tumor volume.

In our cohort, initial diagnostic accuracy was low: only 19% of lesions were correctly identified as nephroblastomatosis on imaging, and 71% of these could ultimately not be distinguished from WT with definitive certainty. Overall, 73% were misdiagnosed as WT or could not be classified with sufficient certainty, and 8% remained indeterminate after imaging (Table 1). From our previous work, we know that patients with CPS and small tumor volumes at diagnosis are more likely to be diagnosed by ultrasound screening compared to the total cohort of WT patients. However, for this study cohort, we could not assess the route to diagnosis or the influence of CPS [10, 16].

Although histological differentiation can be challenging, as described below, we defined histopathology as the gold standard for our study. Core needle biopsies often fail to capture the lesion's architecture or pseudocapsule, complicating accurate diagnosis. Although open wedge biopsies offer better diagnostic yield, they result in upstaging to Stage III if WT is present. Accordingly, current guidelines strongly discourage biopsy other than cutting-needle biopsy [17–20]. In addition, histopathological differentiation between NR and WT remains difficult due to the variable morphology of NR, which can appear as dormant, maturing/sclerosing, cystic, mature, or hyperplastic [11] and should therefore be assessed by a reference pathologist. HNR after chemotherapy may closely resemble WT and may even present a pseudocapsule. Currently, no definitive histological, immunohistochemical, or molecular markers reliably distinguish the two.

A preoperative treatment strategy modeled after unilateral or bilateral WT protocols aimed at enabling nephron-sparing surgery (NSS) is the most appropriate approach. Outcomes remain favorable with frequent use of NSS and are comparable to those reported in Stage V WT patients [12, 21].

The high prevalence of cancer predisposition syndromes (CPS) in our cohort (65%)—compared to less than 20% in general WT populations—suggests that known CPS significantly increases the likelihood of developing single or oligofocal nephroblastomatosis prior to WT onset [22, 23]. Among oligofocal cases, bilateral involvement was common (71%).

Patients with oligofocal disease received longer preoperative chemotherapy than those with single lesions, which may explain the significantly greater tumor volume (TV) reduction observed

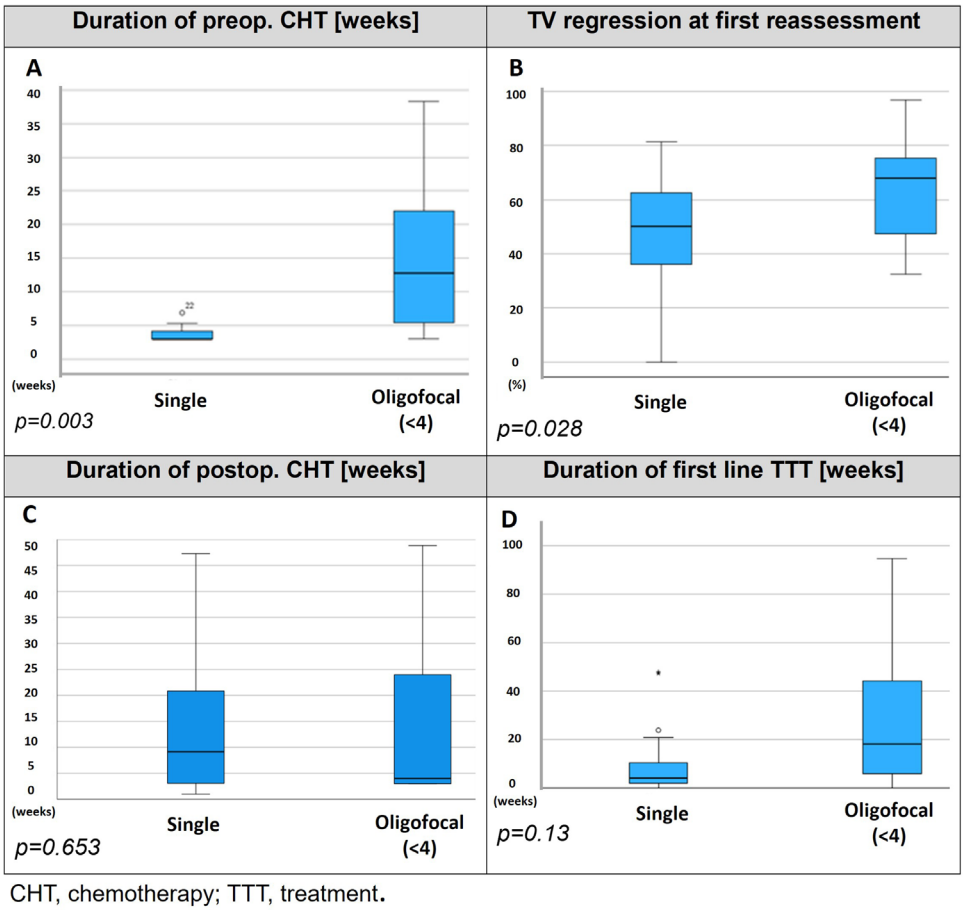


FIGURE 1 | Comparison of single lesion and oligofocal nephroblastomatosis treated with preoperative chemotherapy.

at first reassessment. Similar findings were reported in the SIOP 9 study for WT [24], although statistical significance was not reached in our smaller cohort for the correlation between preoperative TV reduction and the duration of preoperative chemotherapy. It is also plausible that certain single lesions—particularly ILNR, which were more frequent in this group—respond less effectively to chemotherapy.

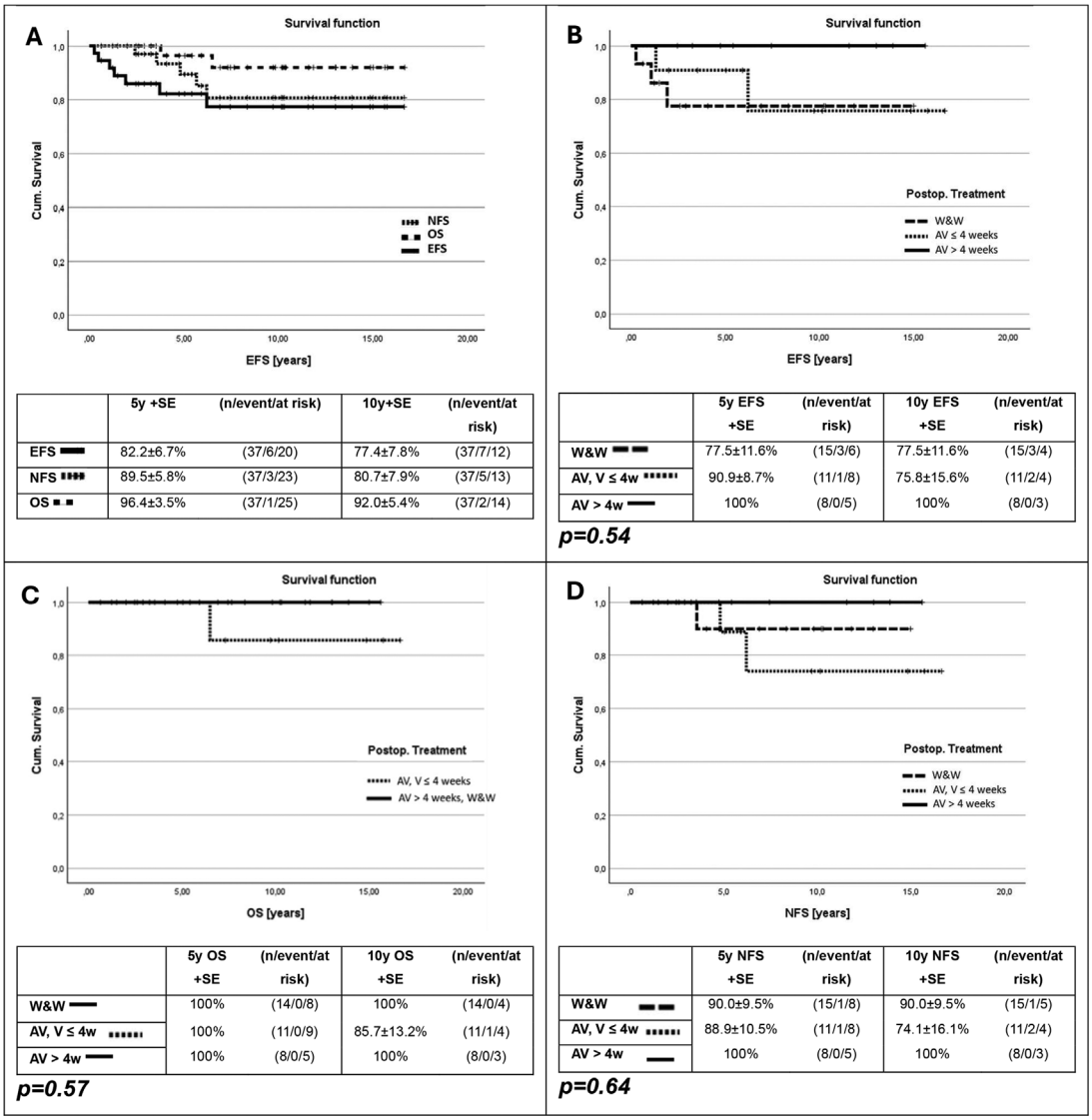
Overall, our findings support preoperative chemotherapy as an effective strategy for oligofocal nephroblastomatosis, facilitating TV reduction, enabling NSS, and preserving renal function. For single lesions, primary surgery followed by watch-and-wait is safe if complete surgical remission is achieved. However, for larger or centrally located single lesions, preoperative chemotherapy should be considered to increase the chances for NSS—especially given the elevated risk of bilateral disease in patients with nephroblastomatosis [23, 25].

Patients with single or oligofocal nephroblastomatosis had excellent outcomes, regardless of treatment duration, with a 10-year OS of 92%. Among the 35 patients who achieved CR at the end of first-line treatment, five relapsed (14.3%), four developed nephroblastoma, and one died.

It is important to know that relapse or progression often resulted in the development of WT, as was observed in five of seven patients in our cohort. Given the histological overlap between HNR and WT, malignant potential may only become evident through lesion progression [17, 21].

Both patients with non-CR at the end of treatment progressed; one was salvaged, while the other developed WT and died. All five relapses occurred in patients managed with W&W or short postoperative treatment (<4 weeks AV), but four of five were successfully salvaged. There is currently no evidence that further treatment can prevent relapses in patients who have not achieved complete remission (CR) at the end of treatment. The question of how such patients should be treated in the event of treatment prolongation also remains unanswered. Current data suggest that the risk of diffuse anaplasia increases with the duration of AV treatment [12]. One possible option is treatment with 13-cis-retinoic acid, which could induce the maturation of nephrogenic remnants into normal kidney cells. However, the evidence is currently weak, and possible side effects must be considered [26, 27]. Therefore, in our opinion, follow-up ultrasound and early detection of recurrence are of utmost importance.

The high chance of cure after relapse aligns with data from very low-risk WT in infants managed with W&W, where salvage was uniformly successful [28]. Recent SIOP 2001 data suggest that 4 weeks of postoperative AV is as effective as 27 weeks in local Stage I bilateral WT [21]. Moreover, prolonged AV therapy carries risks, including neuropathy and veno-occlusive disease, especially in these predominantly infant patients [29].



	5y +SE	(n/event/at risk)	10y+SE	(n/event/at risk)
EFS	82.2±6.7%	(37/6/20)	77.4±7.8%	(37/7/12)
NFS	89.5±5.8%	(37/3/23)	80.7±7.9%	(37/5/13)
OS	96.4±3.5%	(37/1/25)	92.0±5.4%	(37/2/14)

	5y EFS +SE	(n/event/at risk)	10y EFS +SE	(n/event/at risk)
W&W	77.5±11.6%	(15/3/6)	77.5±11.6%	(15/3/4)
AV, V ≤ 4w	90.9±8.7%	(11/1/8)	75.8±15.6%	(11/2/4)
AV > 4w	100%	(8/0/5)	100%	(8/0/3)

p=0.54

	5y OS +SE	(n/event/at risk)	10y OS +SE	(n/event/at risk)
W&W	100%	(14/0/8)	100%	(14/0/4)
AV, V ≤ 4w	100%	(11/0/9)	85.7±13.2%	(11/1/4)
AV > 4w	100%	(8/0/5)	100%	(8/0/3)

p=0.57

	5y NFS +SE	(n/event/at risk)	10y NFS +SE	(n/event/at risk)
W&W	90.0±9.5%	(15/1/8)	90.0±9.5%	(15/1/5)
AV, V ≤ 4w	88.9±10.5%	(11/1/8)	74.1±16.1%	(11/2/4)
AV > 4w	100%	(8/0/5)	100%	(8/0/3)

p=0.64

EFS, event-free survival; NFS, nephroblastoma-free survival; OS, overall survival; A, Actinomycin D; V, Vincristine; W&W, Watch and wait.

FIGURE 2 | Outcome of patients with a single lesion or oligofocal nephroblastomatosis.

Nonetheless, in cases of progression, the likelihood of WT is high, and a history of nephroblastomatosis may increase the risk of anaplasia [12, 30]. Therefore, early detection of relapse is critical. We recommend W&W or short postoperative treatment (<4 weeks) only if CR is achieved at the end of treatment, and only under close and prolonged ultrasound surveillance—similar to Stage V or predisposition WT protocols. Given the higher risk of metachronous and late relapses compared to the unilateral post-nephrectomy population of WT, follow-up should be intensive: every 2–3 months for the first 2 years, then every 3–4 months until 5 years post-end of treatment and at least until the age of 7 years [25, 31].

One limitation of the current study is that the initial radiological diagnosis was based on ultrasound and/or cross-sectional imaging. Although ultrasound followed by MRI was regarded as the gold standard, the choice of imaging modality was determined by local practice at each participating center, and detailed information on the specific modality used was not comprehensively captured in the database. As a result, some patients may have been included based solely on ultrasound findings. While this approach reflects real-world clinical practice, ultrasound may have lower sensitivity for detecting and fully characterizing all renal lesions throughout the kidney.

Our results underscore that achieving CR at the end of treatment is a key prognostic factor. First-line therapy should aim for CR. In bilateral or predisposed patients, preserving renal function is paramount. Surgical decisions should be guided by detailed imaging review and multidisciplinary tumor board discussions involving experts in nephroblastomatosis and pediatric renal tumors to avoid unnecessary invasive procedures.

5 | Conclusions

Given the retrospective design and limited sample size, our findings require validation in larger cohorts.

Patients with single or oligofocal nephroblastomatosis who achieve CR at the end of treatment have an excellent prognosis. In cases where NSS is feasible, short postoperative therapy or W&W is safe—provided close and prolonged ultrasound follow-up is ensured.

Primary surgery is appropriate for typical single or oligofocal lesions if NSS is feasible and a CR can be achieved. For larger or unfavorably located lesions, preoperative chemotherapy is effective in reducing TV and facilitating NSS—thus, taking into account the elevated incidence of CPS and associated risk of bilateral manifestation.

The presence of residual lesions at the end of treatment is associated with progression or relapse, and may indicate an elevated risk for malignant transformation. Patients with progression or relapse should be promptly restaged and discussed in a multidisciplinary tumor board to determine the optimal therapeutic strategy.

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Ethics Statement

Both protocols (SIOP93-01/GPOH and SIOP2001/GPOH) 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.

Conflicts of Interest

The authors declare no conflicts of interest. Nils Welter: consulting or advisory role: Recordati Rare Diseases. Rhoikos Furtwängler: consulting or advisory role: Recordati Rare Diseases.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Table S1: Patient overview table.