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Does nephroblastomatosis influence the natural history and relapse rate in Wilms' tumour? A single centre experience over 11 years

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Abstract

The presence of multifocal or diffuse nephrogenic rests (NRs) in one or both kidneys is termed nephroblastomatosis (Nbm). Nbm may be a predisposing factor for Wilms' tumour (WT). The aim of this retrospective study was to evaluate the impact of Nbm on the outcome of WT in children. We assessed the outcome of 81 children with Wilms tumours and practical implications of Nbm in the treatment and follow-up. All the pathology slides have been reviewed in 1997. 63 had WT without Nbm (group A) and 18 had WT associated with Nbm (group B). There was no statistical difference between the two groups according to the age at diagnosis and histology. Clinical abnormalities were more frequent in group B (33 versus 8%). There was no statistical difference between the percentage of stage IV in both groups, but bilaterality (stage V) was present only in the group B. Relapse was observed in 20/81 patients (25%): 11 (17%) in group A and 9 (50%) in group B. Mean delay of relapse was longer (25 months) in group B than in group A (10 months). For the whole population, with a median follow-up of 9 years, the event-free survival (EFS) and the overall survival (OS) probabilities were respectively 74%±10 and 83%±9 at 120 months. The difference in EFS between groups A (82±9%) and B (38%±29) was significant ($P = 0.004$). The discovery of Nbm in the non-tumoral part of the kidney with WT can be an adverse factor and in particular favours the subsequent development of a new Wilms tumour. It justifies separate follow-up guidelines.

Keywords: Wilms' tumour; Nephroblastomas; Nephroblastomatosis; Chemotherapy; Children

1. Introduction

Wilms' tumour (WT) accounts for approximately 8% of childhood malignancies and is a triphasic embryonic renal neoplasm consisting of varying proportions of epithelium, blastema and stroma. The annual incidence is 7–8 per million children under the age of 15 years and the prevalence is 1/8000 live births. The existence of precursor lesions has been recognised for many years. The currently used term is nephrogenic rest (NR). It is characterised by the abnormal persistence of metanephric cells in the part of the normal kidney. In perinatal autopsy series in children without renal tumours NRs have been found in approximately 1% of cases [1], and NRs were seen in 30–44% of kidneys removed for WT [2]. Currently, four categories of NR [3] are described depending on the renal lobe distribution and histological appearance: perilobar; intralobar; combined; and universal NRs. Their natural history is highly variable. Some rests may regress spontaneously, whereas others develop into Wilms' tumours [2,4–7]. The presence of multifocal or diffuse NRs in one or both kidneys is termed nephroblastomatosis (Nbm) [6]. The distinction between NRs and Nbm has practical implications because Nbm in one kidney probably means that Nbm is also present in the contralateral kidney with a risk of WT development later. Nbm can be seen with imaging procedure before the treatment [8] or can be seen only with macroscopic and microscopic examination in the nephrectomised kidney.

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The aim of this retrospective study was to evaluate if the presence of Nbm according to Beckwith's definition associated with WT influenced the outcome of WT in children. We analysed 81 children treated for WT in Centre Léon Bérard from 1983 to 1993.

2. Patients and methods

2.1. Patient population

From January 1983 to December 1993, 83 consecutive, untreated and unselected patients with WT were admitted to the Centre Léon Bérard.

2.2. Diagnosis

After clinical examination, especially to find clinical abnormalities, the clinical diagnosis of renal tumour was assessed with ultrasound examination (US), excretory urography (between 1983 and 1988) and abdominal computerised tomography (CT) (commonly used since 1988). Magnetic resonance imaging was used only during the follow-up for 6 cases with WT and Nbm. A definitive diagnosis was confirmed by histopathological examination after one month of chemotherapy and surgery. Histological tissue was first analysed by local pathologists then reviewed by the Societé Internationale d'Oncologie Pédiatrique (SIOP) committee experts according to the SIOP protocol.

Clinico-pathological stage and histological type of the WT (low grade, standard grade and high grade) were classified according to SIOP classification [9]. When NRs were present they were classified according to their distribution (focal or diffuse) and with regard to their location in the kidney: perilobar NR (PLNR) or intralobar NR (ILNR), combined type or universal. Nbm was defined according to Beckwith as: ''the presence of multifocal or diffuse NRs in one or both kidneys'' [6]. A single NR in a normal part of the kidney was not classified as Nbm.

2.3. Therapeutic regimen

Patients were treated with SIOP 6 and SIOP 9 protocols. In the SIOP 6 protocol [10,11], all patients were given prenephrectomy chemotherapy for 4 weeks with vincristine (VCR) and actinomycin D (AMD), except those with metastases at diagnosis. Patients with metastases at diagnosis were treated with a three-drug preoperative regimen consisting of VCR, AMD and doxorubicin (Doxo). In the SIOP 9 protocol, the prenephrectomy chemotherapy for patients without metastasis, was randomisation to either 4 or 8 weeks duration with the same drugs (VCR, AMD) [12].

Postoperative chemotherapy in SIOP 6 was given according to the local stage and the histological grading: patients with stage I nephroblastoma were randomised to receive VCR and AMD for either 17 or 38 weeks; patients with stage II node-negative nephroblastoma received VCR and AMD for 38 weeks and in addition were randomised to receive either 20 Gy irradiation post-nephrectomy or no irradiation; patients with stage II node-positive and stage III nephroblastoma were randomised to receive either a two-drug regimen of VCR and AMD with intensified VCR or the two-drug regimen with the addition of doxorubicin (Doxo) and in both arms local irradiation with 30 Gy. Postoperative chemotherapy in SIOP 9 was based on the results of SIOP 6. Patients with stage I nephroblastoma had 17 weeks post-operative treatment with VCR and AMD. Patients with Stage II node-negative disease received no radiotherapy, but 27 weeks of VCR, AMD and doxorubicin. Stage II node-positive and stage III patients were treated with radiotherapy (15 Gy) and the same three drug regimen as stage II node-negative patients for 27 weeks. For stage IV patients, the post-surgery chemotherapy was given according to the local stage.

2.4. Study design

Analysed data included: age at diagnosis, clinical presentation (presence of congenital abnormalities and/or syndromes), surgical record, local pathology report and SIOP central review, therapy, relapse and outcome. 'Relapse' means the development of Wilm's tumour whatever its location, after complete remission. Because the precise definition of Nbm was revised [6] all available slides (between 3 and 10 per kidney) of part of the normal kidney were reviewed again in 1997 by two pathologists. For the analyses, we have defined two groups of patients: group A for patients with isolated WT at diagnosis and group B for patients with WT associated with Nbm.

2.5. Statistical analysis

Wilcoxon 2 samples test and Fisher's exact test were used to compare age, sex, favourable or unfavourable histology between groups. Event free-survival probabilities (EFS) and overall survival probabilities (OS) with 95% confidence intervals (CI) were estimated using the actuarial Kaplan–Meier method [13]. EFS probabilities was defined as the time from the date of the beginning of treatment to the date of the first event (death, relapse of WT, development of distant metastases) or last contact. Overall survival probability was defined as the time from the date of the beginning of treatment to the date of death or last contact. The differences in EFS and OS between groups were tested using the log-rank test [14].

Table 1
Patient characteristics in both group

	Group A	Group B	Total
Patients	63 (78%)	18 (22%)	81 (100%)
Mean age (months) (range)	46.6 (10–182)	46 (6–180)	46.6 (10–182)
Sex			
Males	34 (54)	8 (44)	42 (52)
Females	29 (46)	10 (56)	39 (48)
Associated clinical abnormalities	5 (8%)	6 (33%)	11 (14%)
Localised	54 (86%)	11 (61%)	65 (80%)
Bilateral (stage V)	0	3 (17%)	3 (4%)
Metastatic (stage IV)	9 (14%)	4 (22%)	13 (16%)
Histology			
Low risk	19 (30%)	1 (6%)	20 (25%)
Standard	34 (54%)	15 (83%)	49 (60%)
High risk	4 (6%)	2 (11%)	6 (7%)
Unclassified	6 (10%)	0	6 (7%)
Nephroblastomatosis			
PLNRS		14 (78%)	
ILNRS		2 (11%)	
Combined		2 (11%)	
Treatment			
SIOP6[a]	40 (63%)	7 (39%)	47 (58%)
SIOP9[a]	23 (37%)	7 (39%)	30 (37%)
Others	0	4 (22%)	4 (5%)

PLNR, perilobar nephrogenic rest; ILNR, intralobar nephrogenic rest.
[a] See text for details

3. Results

3.1. Diagnosis

Slide review of 83 patients modified the diagnosis for 2 patients in whom WT was changed to Nbm. These 2 patients were initially diagnosed and treated as stage I low grade WT. After 6 years and 11 years of follow-up, respectively, these 2 patients are disease-free. They have not been included in this analysis. Patient characteristics of the whole analysed population (81 patients) according to group and clinical abnormalities are shown in Tables 1 and 2. There were 18 cases with Nbm. In twelve cases Nbm was microscopic and in 6 cases macroscopic. In 2 out of these 6 latter patients Nbm without WT was diagnosed and treated before the development of WT. The evolution of nephroblastomatosis lesions in these 2 patients before the occurrence of WT is summarised in Table 3. Nephroblastomatosis was found in 3 stage V and in 15 unilateral nephroblastoma.

There was no difference between the groups according to age at diagnosis. Clinical abnormalities were more frequent in group B (33 versus 8%). There was no statistical difference between the percentage of stage IV in both groups, but stage V was present only in group B. The different histological grades were fairly equally represented in the 2 groups.

3.2. Treatment

The distribution of treatment according to groups is shown in Table 1. Total nephrectomy was performed in all patients in group A. In group B total nephrectomy was performed in 14 cases and partial nephrectomy in 4 cases (in three cases for stage V WT and in one case because of a previous Nbm in one kidney).

3.3. Outcome

Relapse was observed in 20 out of 81 patients (25%): metastatic relapse in 14 patients (17%) and local or contralateral relapse in 6 patients (7%). Eleven of 20 (55%) relapsed patients died due to progressive disease. Five of 6 patients (83%) with anaplastic nephroblastoma died.

Table 2
Associated physical abnormalities with nephroblastomatosis or Wilms' tumour

Abnormality	Number of patients	Nbm present	Type of Nbm	WT stage
Hemihypertrophy	2	Yes	PLNRs (2 cases)	I (V metachronous) I unilateral
Genitourinary malformations				
Bilateral cryptorchidism	2	Yes	PLNRs (1 case) ILNRs (1 case)	V synchronous V synchronous
Dysplastic kidney	1	Yes	PLNRs	IV
Unilateral undescended testis with inguinal hernia	1	Yes	PLNRs + INLRs	I (V metachronous)
Polycystic kidney	2	No	–	I (both cases)
Aniridia	1	No	–	I
Sotos' syndrome	1	No	–	II N-
Bloom syndrome	1	No	–	IV

PLNR, perilobar nephrogenic rest; ILNR, intralobar nephrogenic rest.

Table 3
Follow-up and treatment of 2 patients with an initial clinical diagnosis of nephroblastomatosis before the development of Wilms' tumour

Age[a] (months)	Nbm subtype	Chemotherapy[b]	CR achieved	Nbm relapse	Chemotherapy at relapse[b]	Time to development of WT	WT stage	Outcome
10	PLNRs	4 courses + surgery	Yes			54 months	IV	Alive
11	PLNRs	3 courses + surgery	Yes	At 6 months from CR	6 courses	26 months	I	DOD

CR, complete remission (imaging); DOD, died of disease.
[a] Age at the diagnosis of nephroblastomatosis.
[b] Treatment of the nephroblastomatosis by vincristine (VCR)/antinomycin D (AMD).

In group A, 11 (17%) relapses were observed: 10 (16%) metastatic relapses and 1 (2%) local renal bed relapse. The mean delay between surgery and relapse was 10 months (range 4–21 months). Six out of the 11 (55%) died of disease.

In group B, 9 relapses (50%) were observed: metastases in 4 (22%) cases and local or contralateral relapse in 5 (28%) cases. Among the four patients with metastatic relapse, one was stage III and 3 were stage IV. Out of 5 non-metastatic relapses, 3 were initially stage I with Nbm and relapsed in the contra-lateral kidney (metachronous stage V). There were 2 local relapses in 2 synchronous bilateral tumours after partial nephrectomy. The mean delay between surgery and relapse in patients in group B was 25 months (range 3–74 months). Five out of 9 (56%) died of the disease. One of them had a first nephroblastomatosis only which, in spite of various treatments, evolved to standard risk WT then to an anaplastic form from which the child died with metastatic disease (case 2, Table 3).

For the whole population, with a median follow-up of 9 years, the EFS and the OS probabilities are respectively 74%±10 and 83%±9 at 120 months. With a follow-up of 120 months, the EFS were 82%±9 and 38%±29 respectively for group A ($n=63$) and B ($n=18$) (Fig. 1), and OS were 88%±8 and 60%±28 for groups A and B, respectively (Fig. 2). The difference in EFS between group A and B was significant ($P=0.004$), but the difference in terms of OS was non-significant ($P=0.07$).

4. Discussion

Nbm as a term was first used in 1961 [15], but a simplified scheme of classification and definition were proposed by Beckwith in 1990 [6]. However, although the definition of Nbm has become clearer, its management remains controversial [3].

The overall outcome of the whole of our unselected population is comparable with previously published

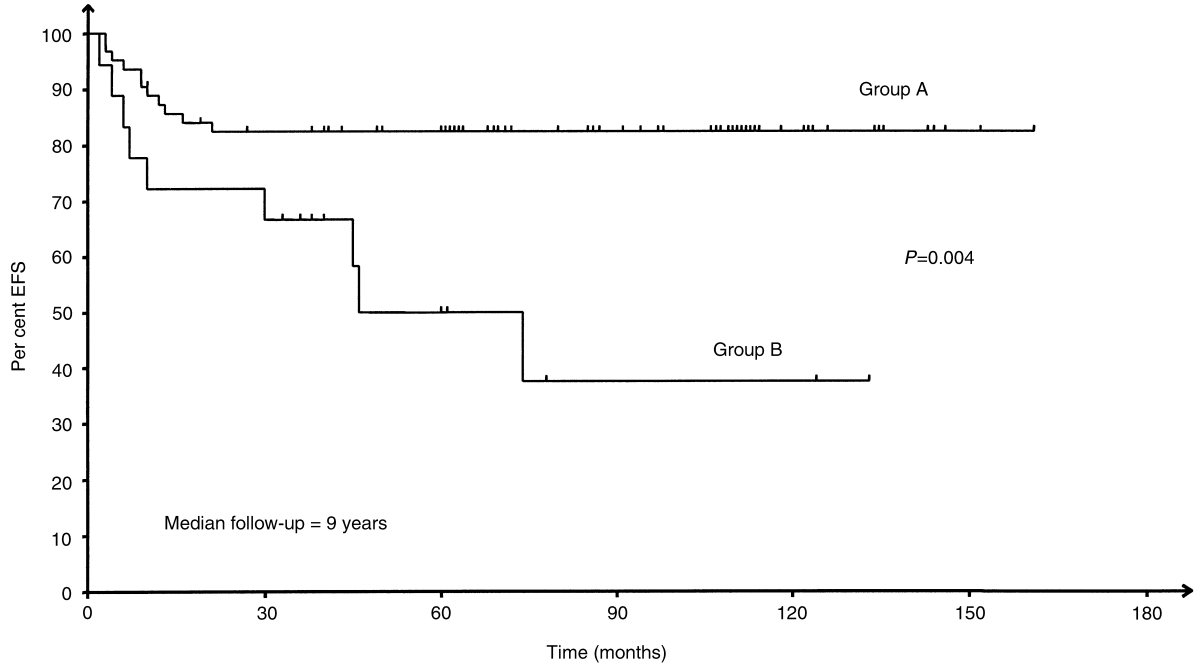

Fig. 1. Event-free survival (EFS) of groups A and B.

outcomes in National Wilms' Tumour Study (NWTS) [16] and in SIOP studies [10,11]. Our retrospective study demonstrates that there is a greater risk of local or contralateral recurrence when the WT is associated with Nbm and that relapses occur later in this group.

The statistical difference in EFS ($P=0.004$) between groups A and B was due to a higher occurrence of non-metastatic relapses in the group with Nbm (28% in group B versus 2% in group A), whereas the frequency of metastatic relapse was similar in both groups. The histology does not seem to be the cause of the difference in EFS since the rate of 'high risk' histology in group B (10.5%) was no different to than that in group A (6%). There is not a statistically significant difference in overall survival between groups A and B, but the number of patients in group B may well be too small.

Two out of 3 patients with synchronous bilateral WT suffered the local relapses. These may be attributed to the partial nephrectomy leaving some Nbm. Indeed in the NWTS experience [17], the rate of local relapse after partial nephrectomy with negative surgical margins is greater for bilateral WT (6.3%) than the rate among children with unilateral WT (1.5–2.5%). Nbm in the remaining part of the kidney could be an explanation for this higher rate of local relapse in spite of apparently adequate surgery. A multivariate analysis is not possible since Nbm is strongly correlated with the bilaterality of the WT and, consequently with the partial nephrectomy. The 3 contra-lateral relapses in the 3 patients with unilateral stage I WT in group B could be related to the presence of contra-lateral Nbm consistent with Nbm as precursor lesions. The three contra-lateral relapses were standard grade. One patient with Nbm at the beginning experienced three relapses, from standard Wilms tumour to high risk (anaplasia form). However, this does not allow any conclusion about the risk increasing to develop an anaplasia form when the kidney has Nbm.

Usually the time to relapse in unilateral WT is less than 2 years [11,16]. We found in our study a mean relapse time of 10 months in group A versus 25 months in group B. The longer relapse time in group B is consistent with the reports of the literature. In the experience of NWTS-3, 39 out of 51 deaths by synchronous bilateral WT were from progressive disease: of the 39 tumour deaths 25 occurred within the first 2 years following diagnosis, 8 between 2 and 3 years of observation, 3 after 3 years and 3 after 4 years of observation [19]. Paulino reported a less than 60 months interval between first and contralateral second tumours in metachronous bilateral WT [20] and Coppes reported the same interval (less than 72 months) but one patient relapsed at 156 months [18]. For the whole population, with a median follow-up of 9 years, the EFS and the OS probabilities are, respectively 74% (95% CI: 64%; 84%) and 83% (95% CI: 74%; 92%) at 120 months (2–156). With a follow-up of 120 months, the EFS were 82% (95% CI: 73%; 91%) and 38% (95% CI: 9%; 67%) respectively for group A ($n=63$) and B ($n=18$) (Fig. 1), and OS were 88% (95% CI: 80%; 96%) and 60% (95% CI: 28%; 92%) respectively for group A and for group B (Fig. 2). The difference in EFS between groups A and B is significant ($P=0.004$), but the difference in terms of OS is not significant ($P=0.07$). Wilms' tumour usually

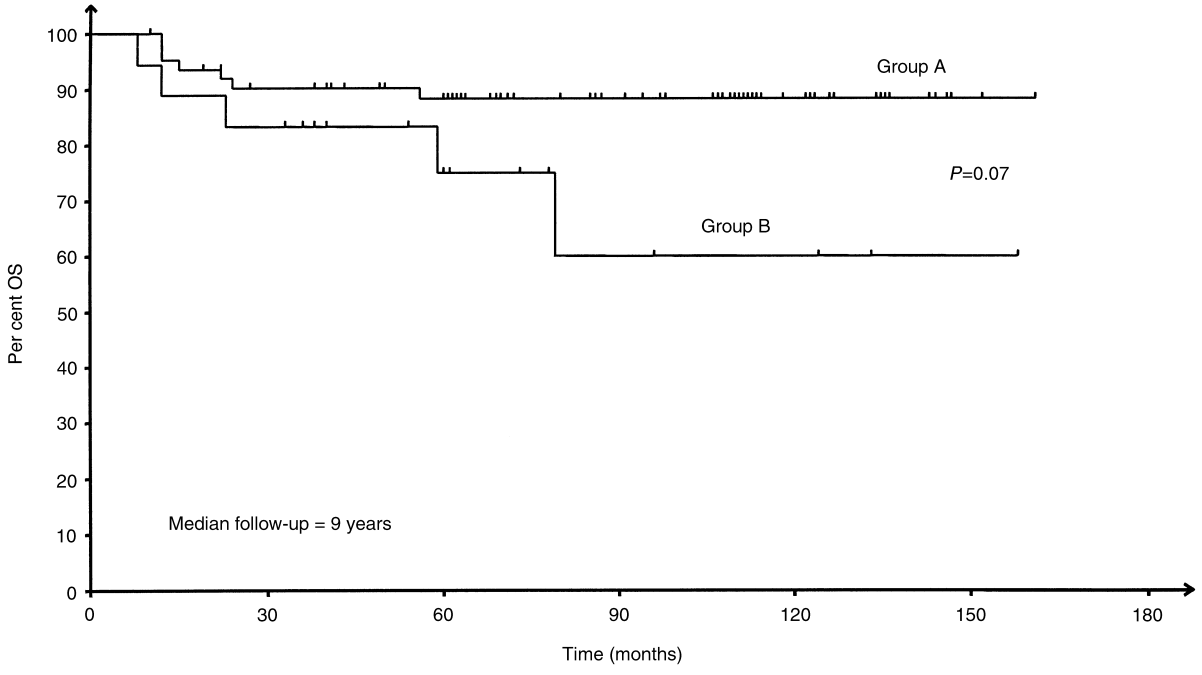

Fig. 2. Overall survival (OS) of groups A and B.

grows rapidly; late relapse might be explained by the slow transformation of NRs into new WT and could explain the absence of difference according to age between groups A and B.

Although these cases are rare, Nbm (according to Beckwith's definition) associated with WT can be considered as a factor which increases the risk of local relapse (in cases of synchronous stage V) or contra-lateral relapse. This raises the possibility that specific management strategies should be determined for Nbm.

If we consider patients with macroscopic Nbm only without WT, few series, with limited numbers of children, have been published giving us information about Nbm treatment. Chadarevian has reported the treatment of 4 cases with massive nephroblastomatosis [21]. Children were 1 newborn, 1 infant of 10 months of age and 2 children of 13 months of age, and 22 months of age. Treatment included vincristine and actinomycin D up to 2 years in 3 cases and for 8 weeks in one, plus doxorubicin in one case. Two patients received irradiation. Surgery was performed in only 1 case. The authors attributed the prompt and dramatic regression to the combination of actinomycin D and vincristine. All of three patients treated without surgery achieved complete remission and remained in complete remission at 10, 30 and 44 months follow-up. Haddy reported a case of bilateral diffuse nephroblastomatosis in a child of 14 months of age who had been treated with vincristine and actinomycin D for 15 months [22]. She achieved complete remission with no other treatment and was in CR 10 months later. Telander reported a similar experience for a child with Nbm treated with actinomycin D and vincristine for 6 months followed by irradiation. Ten months after the end of treatment open renal biopsies were performed and normal kidneys documented [23]. Vincristine and actinomycin D have been effective against nephroblastomatosis in a mouse model [24] and in children [2,25,26].

On the other hand, WT can be associated with Nbm. Bilateral WT (synchronous or metachronous) is associated with Nbm in 90% of cases [6]. In 1978, Kumar [27] reported the St Jude experience of 8 of 118 patients (6.8%) who had WT associated with Nbm. Surgery, irradiation and chemotherapy for 6–18 months (vincristine, actinomycin D and doxorubicin) resulted in the tumour-free survival of these 8 patients for 1–44 months (median 24 months). The report of Heideman [7] concerning 7 patients with Nbm and WT emphasises the therapeutic problems. (1) Is there an advantage in trying to identify a potential patient with Nbm prior surgery to propose a conservative surgical approach? (2) Chemotherapy (short or long) is inadequate in some cases of Nbm or response may be transient, at best. (3) External beam radiation therapy does not appear be more effective chemotherapy alone. Stone [28] reported 2 cases and advocated chemotherapy to treat nephroblastomatosis to avoid transformation into WT. Coppes has reported the NWTS experience of 58 patients with metachronous bilateral WT in whom 42 had NRs at the initial diagnosis. In univariate analysis, the quantity of drugs of the initial treatment (1, 2 and 3 drugs) was a prognostic factor ($P = 0.002$) and Coppes [18] suggests that triple chemotherapy with actinomycin D, vincristine and doxorubicin is more effective in inhibiting the transformation of a NR into WT. In our 3 patients with contralateral relapse the duration of treatment post surgery was short (6, 3 and 1 months) with 2 drugs (vincristine and actinomycin D) since the local stage was I. According to the hypothesis proposed by Coppes and colleagues, patients' cure might have been impaired by the short duration of treatment. In multivariate analysis, age less than 12 months and PLNRs were the two factors which increased the risk of contralateral tumours (relative risk (RR): 8.8) [18]. The strategy for the treatment of Nbm is not yet clear. The role, nature and duration of chemotherapy in Nbm, either isolated or associated with WT should be investigated. This is why we have started a retrospective national study of the treatment of Nbm.

For the follow-up of patients with Nbm, a consensus seems to have evolved. According to the literature, and to our results, the presence of nephroblastomatosis associated with WT is an indication for long-term follow-up by imaging. This is particularly important when the patient is uniphrenic in order to facilitate kidney-sparing surgery in the case of relapse. We agree with D'Angio who has recommended long follow-up (up to 10 years) using abdominal ultrasound for children with NRs identified at initial surgery [29]. We also agree with Beckwith who has recommended prolonged imaging surveillance (with renal ultrasound at 3 months intervals for at least 5 years) for children with a risk of developing WT (Beckwith–Wiedemann syndrome or hemihypertrophy) [30]. More recently, Coppes has suggested a similar follow-up with ultrasound of the remaining kidney every 3 months if NRs were found associated with WT. Ninety-five per cent of metachronous relapses occurred in the first 5 years in Paulino's report [20] and 98% of metachronous relapses occurred in the first 6 years in the NWTS experience [18]. In our experience, the latest relapse occurred approximately 6 years (74 months) after the initial diagnosis. According to estimated doubling times of WT [31,32], we concluded that an abdominal ultrasound every 3 months for at least 6 years should be the standard follow-up for patients in whom Nbm is associated with WT.

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