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RESEARCH ARTICLE

Neuroblastoma stage 4S: Tumor regression rate and risk factors of progressive disease

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Abstract

Background: The clinical course of neuroblastoma stage 4S or MS is characterized by a high rate of spontaneous tumor regression and favorable outcome. However, the clinical course and rate of the regression are poorly understood.

Methods: A retrospective cohort study was performed, including all patients with stage 4S neuroblastoma without MYCN amplification, from two Dutch centers between 1972 and 2012. We investigated the clinical characteristics, the biochemical activity reflected in urinary catecholamine excretion, and radiological imaging to describe the kinetics of tumor regression, therapy response and outcome.

Results: The cohort of 31 patients reached a 10-year overall survival of 84% ± 7% (median follow-up 16 years; range, 3.3-39). During the regressive phase, liver size normalized in 91% of the patients and catecholamine excretion in 83%, both after a median of two months (liver size: range, 0-131; catecholamines: range, 0-158). The primary tumors completely regressed in 69% after 13 months (range, 6-73), and the liver architecture normalized in 52% after 15 months (range, 5-131). Antitumor treatment was given in 52% of the patients. Interestingly, regression rates were similar for treated and untreated patients. Four of seven patients < 4 weeks old died of rapid liver expansion and organ compression. Three patients progressed to stage 4, 3 to 13 months after diagnosis; all had persistently elevated catecholamines.

Conclusion: Patients < 4 weeks old with neuroblastoma stage 4S are at risk of fatal outcome caused by progression of liver metastases. In other patients, tumor regression is characterized by a rapid biochemical normalization that precedes radiological regression.

1 | INTRODUCTION

Neuroblastoma stage 4S (S for "Special") defined patients < 12 months old with primary tumors stage 1 or 2 and dissemination limited to specific sites, such as liver, bone marrow (< 10% invasion), and skin.[1] In the International Neuroblastoma Risk Group Staging System (INRGSS), the age limit was extended to 18 months, and primary tumor stage was not taken into account anymore.[2] In all staging systems, osteomedullary tracer uptake on ^{99}Tc bone scans or ^{123}I-MIBG scans defines stage 4. Stage 4S is characterized by a favorable course of disease and a high rate of spontaneous tumor regression.[1–3] Long-term survival rates are estimated between 65% and 92%.[4–7] In general, neuroblastoma 4S can be managed by active surveillance in expectation of spontaneous tumor regression. In patients with symptoms of organ compression, antitumor treatment (chemotherapy or low-dose radiotherapy to the liver) is advised. Although the tumor regresses in most patients, very young patients are at risk of early and rapid progression of liver metastases, causing life-threatening compression of lungs, kidneys, inferior vena cava, normal liver tissue, and intestines.[8] Tumor progression to true stage 4 or high-risk disease is seen occasionally. This can occur before complete regression and is different from late-onset recurrent disease.

Previously, we explained regression as a process of delayed differentiation of tumor nodules.[9] We consider stage 4S as a multifocal developmental disease with an onset in the early stage of neural crest development. (Pre)migratory neural crest cells suffer from a defect and spread to different target organs of the neural crest (skin, liver, bone marrow, adrenal glands, sympathetic side chain) to form proliferative tumor nodules. The tumor regression reflects a delayed step of cellular differentiation and apoptosis.[9] The process and clinical regression rate have not been studied for the expected time to normalization on different modalities. Also, it is not clear if antitumor treatment (chemotherapy and radiotherapy) has any effect on the initiation of the regression process.

Here, we studied the survival rates, frequency, and rate of tumor regression in a retrospective cohort of patients with neuroblastoma stage 4S. We describe risk factors of progressive disease. Finally, we evaluated the effect of therapy on disease regression.

2 | METHODS

2.1 | Patient cohort

The Erasmus Medical Center's and Amsterdam University Medical Centers' Pediatric Oncology databases were reviewed to identify all patients diagnosed with neuroblastoma stage 4S[1] or MS[2] between 1972 and 2012. Patients diagnosed with stage 4 aged 12 to 18 months were reviewed for MS criteria. The term 4S was used for this study, because all patients met these criteria. Shallow whole-genome sequencing was performed as described previously.[10]

2.2 | Clinical outcome

Tumor response was evaluated according to the International Neuroblastoma Response Criteria (INRC)[1] at last moment of follow-up. For the purpose of this study, we classified three types of progression: (A) fast initial tumor progression with increase of liver mass, (B) tumor progression to stage 4 neuroblastoma < 5 years from diagnosis, (C) late recurrent disease after > 5 years. Initial treatment was according to local protocols; all protocols were based on a wait-and-see approach, unless life-threatening symptoms or complications occurred. Chemotherapy regimens differed over time but in general consisted of cyclophosphamide and vincristine. From 2009 onward, all treated patients are given the combination of cyclophosphamide, vincristine, and doxorubicin. Used chemotherapeutics are listed per patient in Supporting Information Table S3. Patients with progression to stage 4 aged < 1 year at time of progression were upstaged to medium-risk protocols, and patients aged ≥ 1 year to high-risk protocols. To compare the therapy effect on regression, regression kinetics of treated patients were compared with untreated patients. Surgery-only patients were analyzed in the untreated group, because surgery will not have influenced regression of metastases.

2.3 | Radiological evaluation

All radiological and nuclear scan reports were reviewed (MT and BdK). For the liver, both size and architecture were evaluated. Liver size was compared with age-related reference levels.[11] No strict intervals for follow-up were defined until 2009. Ultrasounds in patients with hepatomegaly were performed biweekly or monthly in the first two months, expanding to every two months until six months after diagnosis, followed by undefined regular follow-up. ^{123}I-MIBG and MRI scans were performed every two months from 2009 onward, and without defined follow-up intervals before 2009. CT scans were rarely performed or in low dose in combination with ^{123}I-MIBG scanning. Patients with an event (progression and death) were excluded from the long-term regression analysis.

2.4 | Metabolic evaluation

Urinary homovanillic acid (HVA) and vanillylmandelic acid (VMA) were measured and reported (fold change of the upper limit for age; defined as mean +2 SD) as described previously.[12] Time from diagnosis to last abnormal value was used instead of time to normalization. This probably represented a more accurate time to normalization because the lack of standardized intervals occasionally resulted in long periods

between last abnormal (but slightly elevated values) and first normal values. Additionally, a few patients maintained elevated HVA ($n = 4$) or VMA ($n = 3$) excretion levels even after years of follow-up. By using time to first normal measurement, we would have to exclude these patients, causing information bias.

2.5 | Statistical analysis

Statistical analysis was performed using the statistical program SPSS 25 (IBM Corp., Armonk, NY). Estimated 10-year overall survival (OS) and event-free survival (EFS) rates were calculated according to Kaplan-Meier survival analysis and are reported ±SE. Follow-up time was defined as the time of diagnosis to any event, death, or last follow-up. Fisher exact test and the Mann-Whitney U test were used for comparisons between treated and untreated patients. P values of < 0.05 were considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

We identified 35 patients with the clinical diagnosis of neuroblastoma stage 4S, representing 8% of total neuroblastoma diagnoses. After exclusion of patients with MYCN amplification ($n = 4$), 31 patients were included (Supporting Information Table S1). The median age at diagnosis was 70 days (range, 1-228 days). Seven (23%) patients were < 4 weeks old. The primary tumor was located in the adrenal gland in 23 (74%) (five patients had bilateral adrenal tumors), in the sympathetic side chain in 5 (16%) patients, and remained unknown in 3 (10%) patients. All patients except one had liver metastases, and 5 (16%) had skin metastases. Bone marrow was evaluated in 28 patients and infiltrated in 7 (25%) (Table 1). Antitumor treatment was given in 16 (52%) patients: 12 (39%) patients received chemotherapy, 7 (23%) received Iodine-131-Metaiodobenzylguanidine (^{131}I-MIBG) therapy, 6 (19%) received radiotherapy, and the primary tumor was surgically removed in 5 (16%) patients (Supporting Information Table S1). One patient was presented in a case report previously.[13]

3.2 | Survival and response

The 10-year OS and EFS rates were 84% ± 7% and 69% ± 9% (Figure 1A), respectively. At last follow-up, 18 (58%) patients had reached complete remission (CR), 8 (26%) (very good) partial remission ((VG)PR), and 5 (16%) had died of neuroblastoma. This was similar in treated and untreated patients (Table 1).

3.3 | Tumor regression

Adrenal/sympathetic side chain tumor: Evaluation of primary tumor regression was feasible in 16 of 31 patients. For 15 patients, follow-up was not feasible because of progressive disease ($n = 7$), resection of the primary tumor ($n = 5$), or an unknown primary tumor ($n = 3$). Complete

regression was achieved in 11 (69%) of 16 patients, after a median time of 13 months (range, 6-73 months; Figure 2), while residual lesions persisted in 5 (31%) patients (Table 1). Primary tumor regression was comparable in treated and untreated patients (63% vs. 75%%, 15 vs. 9 months, respectively; Table 1). Interestingly, complete regression was achieved in 92% of the adrenal tumors, while in 0% of the sympathetic side chain tumors ($P < 0.01$).

3.3.1 | Liver

Regression of liver metastases was studied in 23 of 30 patients with liver metastases. For seven patients, follow-up was not possible because of progressive disease. Liver size normalized in 21 (91%) patients, after a median of two months (range, 0-131) (Figure 2). No difference was observed between treated and untreated patients (91% vs 92%; 10 vs 2 months; $P = 0.31$). Liver architecture normalized in 12 (52%) of the patients, after a median time of 14.5 months (range, 5-131 months). Again, no difference was observed between treated and untreated patients (45% vs 58%, $P = 0.68$; 17 vs 14 months, $P = 0.45$). In 11 (48%) patients, both the size and architecture of the liver completely normalized.

3.3.2 | Metabolic regression

Regression of the catecholamines HVA and VMA was studied in 24 of 31 patients. In the other seven patients, excretion levels were not available because of rapid progression ($n = 4$) or before this was standard of care ($n = 3$). HVA levels normalized in 20 (83%) patients and VMA in 21 (88%) patients. Last abnormal values were measured after a median of 2.2 months for HVA (range, 0-158) and 1.6 months for VMA (range, 0-158) (Figure 2), which was comparable between treated and untreated patients ($P = 0.32$ and $P = 0.14$, respectively) (Table 1).

3.4 | Progressive disease

Patients with progressive disease were subcategorized in three types of progression. Four patients died of fast initial tumor progression (type A). Three patients progressed to stage 4 disease < 5 years from diagnosis (type B), one of them died of disease, and two are in CR after additional treatment. Two patients suffered from late relapses (type C): one with stage 4 disease without MYCN amplification who is in CR after high-risk treatment; the other with a localized ganglioneuroma, which has been stable without further treatment.

3.4.1 | Type A progression: fast initial tumor progression with increase of the liver mass

Liver metastases and hepatomegaly were present in 30 and 21 patients, respectively. Six patients (4 patients < 4 weeks old) developed respiratory distress requiring mechanical ventilation (Figure 1B). All four very young patients died within three weeks after diagnosis of multiple organ failure due to organ compression. Two of them were treated with cyclophosphamide and vincristine without effect on liver mass or respiration. The other two patients < 4 weeks old did not receive antitumor treatment because of poor clinical condition; they
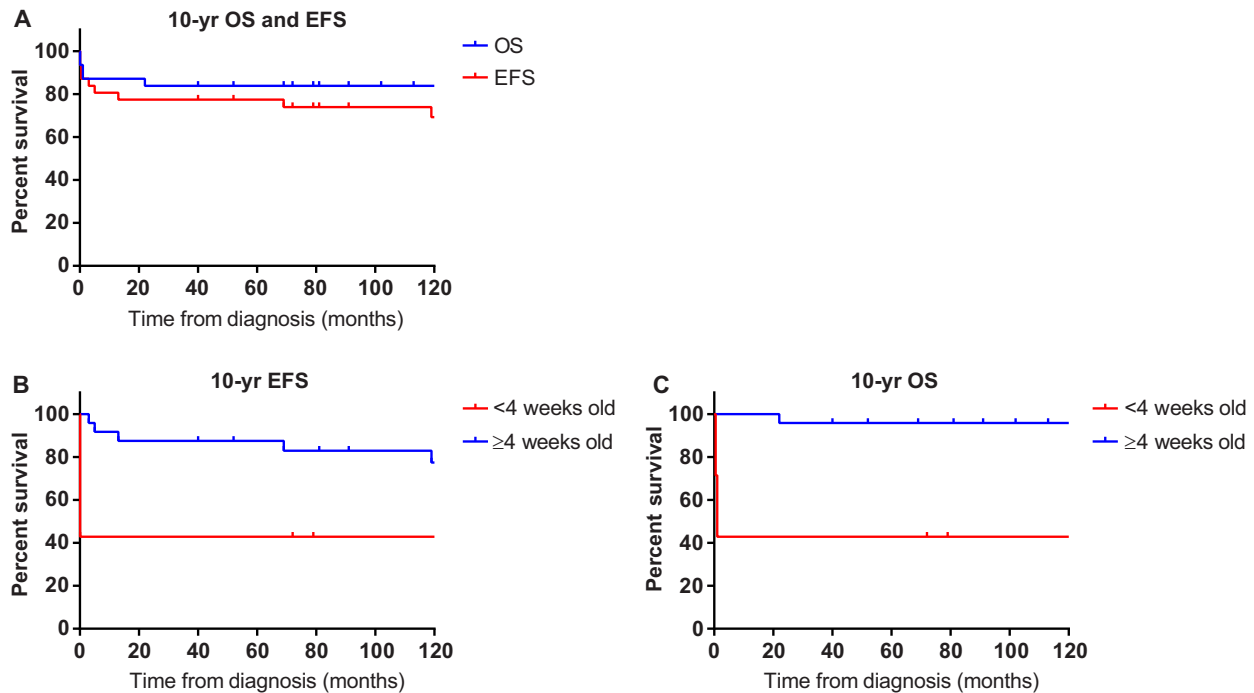
FIGURE 1 Kaplan-Meier estimates of survival of the neuroblastoma stage 4S patients. 10-year EFS and the OS of all patients; (A) 10-year EFS (red line; 69% ± 9%) and OS (blue line; 84% ± 7%). (B) 10-year EFS according to age groups (red line < 4 weeks old at diagnosis [n = 7] 43% ± 19%; blue line ≥4 weeks [n = 24] 77% ± 9%; P = 0.02). (C) 10-year OS according to age groups (red line < 4 weeks old [n = 7] 43 ± 19%; blue line ≥4 weeks [n = 24] 96% ± 4%; P < 0.001)

died within two days after admission. The two older patients, 6 weeks and 6 months old, survived. In total, four of seven patients < 4 weeks old (58%) died of type A progression, resulting in a significant higher risk of dying due to type A progression for younger than for older patients (Figure 1C; log-rank P < 0.001).

3.4.2 | Type B progression: progression to stage 4 disease < 5 years from diagnosis

Type B progression occurred in three patients—3, 8, and 13 months after initial diagnosis—and was fatal in one patient despite high-risk treatment (Table 1). The remaining two patients are in CR, 99 and 108 months after progression. In none of the patients with type B progression, catecholamine excretion normalized prior to the progression. In contrast, patients with no progression and finally CR, catecholamines normalized after 1.2 months (range, 0-8.9 months) for HVA and 0.7 months (range, 0-4.2 months) for VMA (Figure 3; type B progression vs CR: P = 0.02 for HVA, P < 0.01 for VMA).

3.4.3 | Type C progression: late recurrent disease after > 5 years

Type C progression occurred in 2 patients: one suffered from recurrent stage 4 disease, without MYCN amplification, 69 months after initial neuroblastoma 4S diagnosis. This patient is currently, 97 months after progression, in CR after high-risk treatment. The other patient developed a new tumor nodule in a previously unaffected site, 119 months after initial neuroblastoma 4S diagnosis. Biopsy revealed a ganglioneu-

roma, and the tumor remained stable without treatment until last follow-up 143 months later.

3.5 | Copy-number analysis

Twenty tumors were evaluated for numerical chromosomal aberrations (NCA; whole chromosome gains and losses) and for segmental chromosomal aberrations (SCA; partial gains and losses).[14] No tumor material was available for patients with type A progression. Two of three patients with type B progression had isolated SCA, while none of the progression-free patients had isolated SCA (Supporting Information Table S2). The patient with type C stage 4 progression had both NCA and SCA at the time of 4S diagnosis. In this limited cohort, significant differences were observed in EFS when patients were classified in the different genomic pattern groups. Patients with only NCA had a 10-year EFS of 89% ± 11%, patients with both NCA and SCA had a 10-year EFS of 86% ± 13%, and patients with only SCA had a significantly poorer 10-year EFS 0% (log-rank P < 0.01; Supporting Information Figure S1).

4 | DISCUSSION

We performed a retrospective cohort study investigating the regression kinetics and risk factors of progression in patients with stage 4S neuroblastoma. In this cohort of 31 patients, the 10-year OS was 84% ± 7%. Catecholamine excretion and liver size normalization occurred in 83% and 91% of the patients after a median of two

TABLE 1 Patient characteristics at diagnosis and outcome, compared between untreated and treated patients

	Untreated n/N (%)	Treated n/N (%)	Significance (P)
Patient characteristics at diagnosis			
Gender: male	9/15 (60.0)	7/16 (43.8)	0.48
Age < 1 month	5/15 (33.3)	2/16 (12.5)	0.22
Age (median days, range)	70 (1-228)	78 (2-186)	0.29
Primary tumor			NA
Adrenal	11/15 (73.3)	12/16 (75.0)	
Sympathetic side chain	2/15 (13.3)	3/16 (18.8)	
Unknown	2/15 (13.3)	1/16 (6.3)	
Liver metastases	15/15 (100)	15/16 (93.8)	NA
Skin metastases	2/15 (13.3)	3/16 (18.8)	NA
Bone marrow metastases	2/12 (16.7)	5/16 (31.3)	0.66
Fold change of HVA at diagnosis (median)	3.67 (n = 12)	13.35 (n = 10)	0.12
Fold change of VMA at diagnosis (median)	4.61 (n = 12)	13.33 (n = 10)	0.12
MYCN amplification status unknown	5/15 (33.3)	4/16 (25.0)	0.70
LOH1p (n = 21)	2/9 (22.2)	3/12 (25.0)	NA
Outcome characteristics			
Progression			0.60
No progression	12/15 (80.0)	10/16 (62.5)	
Type A	2/15 (13.3)	2/16 (12.5)	
Type B	1/15 (6.7)	2/16 (12.5)	
Type C	0/15 (0.0)	2/16 (12.5)	
INRC at last follow-up			NA
CR	9/15 (60.0)	9/16 (56.3)	
(VG)PR	4/15 (26.7)	4/16 (25.0)	
PD[a]	2/15 (13.3)	3/16 (18.8)	
Primary tumor			NA
Complete regression	6/8 (75)	5/8 (62.5)	
Residual lesion	2/8 (25)	3/8 (37.5)	
Liver			NA
Normalization	6/12 (50.0)	5/11 (45.5)	
Parenchymal aberrations and/or hepatomegaly	6/12 (50.0)	6/11 (54.5)	
Last abnormal HVA (months, median)	1.2 (n = 12)	3.5 (n = 12)	0.32
Last abnormal VMA (months, median)	0.3 (n = 12)	2.2 (n = 12)	0.14
First normal HVA (months, median)	6.7 (n = 11)	6.2 (n = 9)	0.67
First normal VMA (months, median)	5.4 (n = 11)	6.3 (n = 10)	0.62

Abbreviations: CR, complete remission; HVA, homovanillic acid; LOH, loss of heterozygosity, INRC, International Neuroblastoma Response Criteria; NA, not applicable; PD, progressive disease; (VG)PR, (very good) partial remission; VMA, vanillylmandelic acid.
[a]All patients with progressive disease at last follow-up died of disease.

months. Primary tumors and liver architecture normalized in 69% and 52% after a median of 13 and 15 months, respectively (Figure 2). Patients < 4 weeks old are at risk of a fatal outcome due to massive progression of liver metastases and subsequent organ compression.

Normalization of liver architecture has been reported by Levitt et al. and French et al., who describe liver architecture normalization in 42% and 48% of 28 and 15 patients, respectively.[15,16] One study described liver size normalization in < 12 months in two patients.[17] Early expansion of liver metastases caused respiratory distress requir-

ing mechanical ventilation in 19% of patients in the first weeks after diagnosis. It was only fatal in children < 4 weeks old. In our cohort, 58% of the patients < 4 weeks died of type A progression, while none of the patients ≥4 weeks did (P < 0.001). In six previous studies[6,8,18–21] with a total of 506 NB4S patients, 45 patients died of what we describe as type A progression. Of these 45 children, 93% were < 2 months old at diagnosis. A recent report of patients with symptomatic disease and/or unfavorable histology showed a 13 times increased risk of fatal outcome in patients younger than 40 days compared with patients older
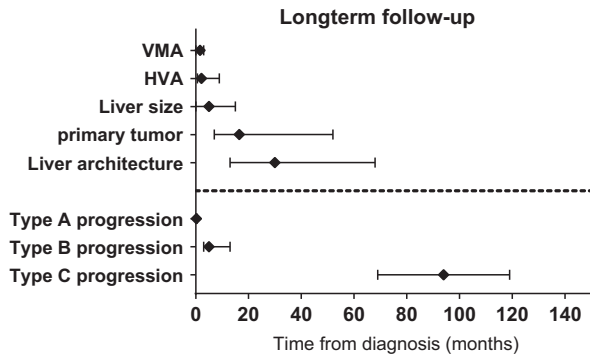
FIGURE 2 Time to normalization according to clinical assessment and events. Median time from diagnosis to normalization or event in months, with 95% confidence intervals, according to urinary catecholamines, radiological assessment, and clinical events, respectively
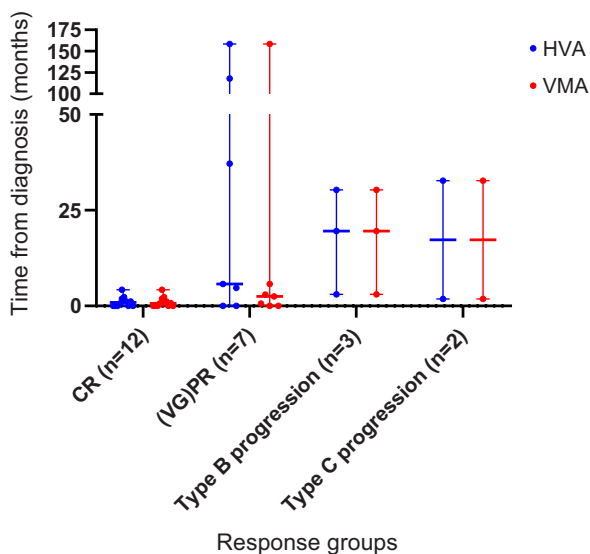

FIGURE 3 Last abnormal HVA and VMA for different response groups. The last abnormal values (measured from diagnosis) for HVA and VMA are depicted in months (y-axis) for the response groups. HVA, red dots/lines; VMA blue dots/lines, whiskers depict the range. CR group: median 1.2 months (range, 0-8.9 months) for HVA and 0.7 months (0-4.2 months) for VMA. (VG)PR group: 5.7 months for HVA (0-159 months) and 2.5 months for VMA (0-159 months). Type B progression: 19.5 months for HVA and VMA (3.0-30.3 months). Type C progression: 17.3 months for HVA and VMA (range, 1.8-32.7 months). CR: complete remission; (VG)PR: (very good) partial remission

than 47 days.[22] These and our study lead to the conclusion that children < 2 months at diagnosis are at risk of dying of type A progression. They should be monitored closely, and starting antitumor treatment should be considered at onset of symptoms. Older children are hardly at risk for a fatal outcome due to type A progression, even if the liver nodules show initial progression.

Antitumor treatment is given in patients with type A progression in an attempt to induce tumor regression to prevent clinical complications of organ compression. However, its effectiveness has never been proven. Here, the commonly used combination of vincristine and cyclophosphamide did not result in arresting the progression in the two treated young patients. Additionally, we observed no difference in the outcome or the regression rate of patients with or without treatment. Although this is a retrospective study with a limited number of patients, which hampers a proper analysis of baseline differences in tumor load, the question is raised whether antitumor therapy influences the outcome or regression in very young children with this type of early progression, and if antitumor treatment is needed in older stage 4S patients. Moreover, a recent large prospective study could not establish an effect of chemotherapy on tumor regression or outcome.[22] Considering the concept of delayed differentiation of early neural crest cells and subsequent differentiation,[9] the question is valid if chemotherapy can accelerate the differentiation and regression process or if it can halt the progression. Therefore, it would be best to study (early) response kinetics in detail in a prospective cohort.

The retrospective design and the long inclusion period are obvious limitations of the study. In this 40-year period, improvements have been achieved in the quality and availability of imaging techniques and other diagnostics. Supportive care and treatment protocols have also been improved; our current treatment protocol contains doxorubicin in addition to cyclophosphamide and vincristine. Still, one of the patients who died of type A progression was diagnosed in 2011, when all modern imaging modalities were present and our current treatment protocol was standard care.

All patients with type B progression to stage 4 disease retained elevated catecholamine excretion until tumor progression was observed, suggesting that these tumors are biologically different from tumors that regress. A different biology is also suggested by the higher number of patients with structural chromosomal aberrations.[23] This is consistent with earlier reports that tumors with segmental aberrations have a more aggressive disease.[14,23,24] Because CNA was tested in only a small number of patients in this study, we cannot draw definitive conclusions. However, in the ongoing European LINES trial, the effect of the CNA in this group is being prospectively studied. Recent research concluded that the combination of telomere maintenance activity and aberrations in the RAS and TP53 pathways can predict unfavorable outcome in low-risk patients.[25] It would be interesting to see if these parameters are helpful in making treatment decisions.

In conclusion, patients with neuroblastoma stage 4S have a favorable outcome as a result of spontaneous tumor regression. Biochemical regression precedes radiological normalization and is usually reached within the first months. Children < 2 months old at diagnosis are at risk of fatal outcome in the first weeks after diagnosis due to tumor progression and it is strongly recommended to watch them closely and consider treatment. The remainder of patients has a small chance to progress to high-risk disease, especially when they have normalized biochemical activity and no segmental gains and losses in their tumor genome.

CONFLICTS OF INTEREST

All the authors declare that they have no conflicts of interest.

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 may be found online in the Supporting Information section at the end of the article.

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