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Clinical and molecular characterization of patients with stage 4(M) neuroblastoma aged less than 18 months without *MYCN* amplification

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Abstract

Introduction: The survival of children with stage 4(M) neuroblastoma without *MYCN* amplification and below the age of 18 months is considered better than the still dismal outcome of older high-risk neuroblastoma patients. This study analyzes the impact of clinical and molecular characteristics on the long-term outcome.

Patients and methods: Clinical presentation, survival, and recurrence patterns of patients enrolled onto trials NB90, NB97, and NB2004 were retrospectively analyzed. Gene expression signatures based on RNA microarrays (TH10) were investigated if tumor material was available.

Results: Between 1990 and 2015, 177 patients with stage 4(M) *MYCN* nonamplified neuroblastoma aged less than 18 months at diagnosis were eligible. After a median follow-up of 9.7 years (IQR 5.0, 13.4), the proportions of 10-year event-free survival (EFS) and overall survival (OS) were 73% (95% confidence interval [CI] 67–79%) and 86% (95% CI 80–92%), respectively. Of the 27 neuroblastoma recurrences, 44% occurred in more than one site. Four additional patients presented histologically mature ganglioneuroma at recurrence. Six patients developed a secondary malignancy.

Abbreviations: 95% CI, 95% confidence interval; EFS, event-free survival; LDH, lactate dehydrogenase; mIBG, ^{123}iodine metaiodobenzylguanidine scintigraphy; NSE, neuron-specific enolase; OS, overall survival; RA, isotretinoin (retinoic acid); VMA/HVA, vanillylmandelic acid and/or homovanillic acid in urine

The secondary 5-year EFS and OS of the 27 patients with neuroblastoma recurrence were 44% and 59%, respectively. TH10 gene expression signature was not prognostically predictive in the investigated subcohort.

Conclusion: The outcome of patients with stage 4(M) neuroblastoma aged less than 18 months is favorable when treated with high-risk or otherwise intensive therapy. The development of secondary malignancies and the potential of maturation to ganglioneuroma call for a controlled stepwise reduction of treatment intensity.

KEYWORDS
expression signature, neuroblastoma, secondary malignancy, stage 4 <18 months, TH10 classificator

1 | INTRODUCTION

Metastatic neuroblastoma is a model for contrasting biological features. In infants, metastases confined to liver, skin, and bone marrow, stage 4S(MS),[1] regularly undergo spontaneous regression.[2] Stage 4S(MS) disease may represent a type of multifocal stem-cell proliferation of the developing neural crest and is associated with a good prognosis.[3] Older patients typically suffer from highly malignant, treatment-resistant disease and have a poor prognosis.[4] The key molecular features are telomerase activation comprising *MYCN* amplification.[5] In contrast, infants with stage 4 nonamplified *MYCN* disease show a better outcome even with reduced treatment[6] and may represent a third group of metastatic neuroblastoma. This group is mainly characterized by lacking *MYCN* amplification and an age less than 1 year. Recently, extending the age limit to 18 months has been proposed.[7] Only a few publications so far have reported specifically on patients with stage 4 neuroblastoma patients aged less than 1 year at diagnosis.[6,8,9] Most reports include this group in an intermediate-risk group together with stage 3. Further discriminating features are *DNA* ploidy, *MYCN* amplification, and various clinical criteria differentiating between stage 4(M) and stage 4S(MS).[10–17] This study investigates the long-term outcome of a large, well-defined series of patients, describes the recurrence pattern, and reports the prognostic potential of clinical and selected molecular characteristics.

2 | PATIENTS AND METHODS

2.1 | Patients

The NB90, NB97, and NB2004 trials of the German Pediatric Oncology Society were open-label trials conducted nationwide in 66 pediatric oncology university and community hospitals in Germany and Switzerland. All trials comprised the entire risk spectrum of the disease. The trials were approved by the Ethics Committee of the University of Cologne. Informed consent signed by the parents or legal guardians was a prerequisite to register in the trials. All trials were conducted in accordance with the published principles of the Guidelines for Good Clinical Practice (ICH-GCP), the applicable European and national legislation, and in accordance with the Declaration of Helsinki of the World Medical Association. More than 98% of all patients diagnosed in Germany were registered in the trials.[18] This analysis deals with a defined subpopulation of patients who in earlier periods were generally not discriminated from the high-risk population but are nowadays predominantly attributed to the intermediate-risk group.

The data lock was October 10, 2018.

2.2 | Diagnosis and staging

Diagnosis and staging were performed according to the International Neuroblastoma Staging System (INSS).[1] Throughout all German trials, stage 4(M) in infants was defined by the presence of metastasis to bone with or without manifestations in other metastatic sites. Bone lesions were detected by X-ray or scintigraphic imaging using ^{99m}technetium (bone) or ^{123}iodine-metaiodobenzylguanidine (osteomedullary, diffuse or multiple spot uptake). Large primary tumors (stage 3) and/or metastatic sites to distant lymph nodes, and single small osteomedullary ^{123}iodine metaiodobenzylguanidine scintigraphy (mIBG) spots were attributed to stage 4S and treated as such. The cutoff <547 days (<18 months) was chosen as suggested by London et al. in 2005.[7,19] The age limit of the excluded stage 4S patients was 12 months for the trials NB90 and 97 and 18 months for the trial NB2004.

2.3 | Inclusion and exclusion criteria

Inclusion criteria were patients with (i) newly diagnosed neuroblastoma according to the INSS[1]; (ii) stage 4(M) disease in patients aged <18 months at diagnosis; (iii) treatment according to the guidelines of the national trials NB90, NB97, NB2004[18]; (iv) diagnosis between January 1, 1990 and December 31, 2015; and (v) written informed consent obtained from the parents or legal guardians. Exclusion criteria were (i) amplification or unknown status of the *MYCN* oncogene; and (ii) insufficient diagnostic information.

2.4 | Treatment

A schematic and details are provided in Figure S1 and Table S1. In brief, in trial NB90 the patients were treated according to the high-risk protocol including eight cycles of chemotherapy (alternating cycles N1 [cisplatinum, etoposide, vindesine] and N2 [vincristine, dacarbazine, ifosfamide, doxorubicine] four times), followed by a maintenance regimen consisting of 12 cycles of alternating D1 (melphalan, etoposide) and D2 (vincristine, cyclophosphamide) cycles. Although compliant with the protocol, no patient of this cohort received high-dose chemotherapy with hematopoietic stem cell support.

In the NB97 trial, patients were treated according to the high-risk protocol consisting of six alternating chemotherapy cycles (3 × N5 [same drugs but different dosing as in N1] and 3 × N6 [same drugs but different dosing as in N2]). Infants aged less than 6 months at diagnosis received N4 cycles every 4 weeks until reaching the age of 6 months. The number of received N4 cycles was deducted from the number of N5/N6 cycles (in total six cycles). After induction chemotherapy, all infants received four N7 cycles (oral cyclophosphamide = maintenance chemotherapy). Patients aged >12 and <18 months after induction chemotherapy were randomly attributed to maintenance or high-dose chemotherapy for consolidation. Then anti-GD2 antibody infusions followed over 1 year (six cycles, 1997–2002). During the years 2002 and 2004, oral isotretinoin (retinoic acid [RA], nine courses over 1 year) substituted antibody therapy.

In the NB2004 trial, infants were treated as intermediate-risk patients with six cycles of induction chemotherapy (3 × N5 + 3 × N6), followed by four cycles of maintenance chemotherapy (4 × N7) and isotretinoin for 1 year. Patients aged between >12 and <18 months were treated according to the high-risk protocol with randomizing the induction chemotherapy between the standard arm (six alternating cycles N5 and N6) and the experimental arm (+2 × N8 cycles consisting of topotecan, cyclophosphamide, etoposide followed by six alternating cycles N5 and N6). The consecutive consolidation therapy consisted of high-dose chemotherapy as in trial NB97 and 1 year of isotretinoin (RA).

In all three trials NB90/97/2004, the surgical removal of the primary tumor was recommended provided that the resection did not endanger life or organs. Surgery was performed at diagnosis and/or after two to six courses of chemotherapy. The ambition toward complete surgical removal decreased over time due to data indicating that partial versus complete removal did not demonstrate differences in outcome of stage 4(M) neuroblastoma.[18] Radiotherapy was applied only to active residual tumor after the end of induction chemotherapy and surgical tumor resection(s). Radiotherapy comprised percutaneous irradiation to the primary tumor and ^{131}I-mIBG therapy to primary and metastatic lesions (NB97/2004). In trial NB90, up to four residual metastatic lesions were permitted to be irradiated percutaneously (Table S1).

2.5 | Molecular analyses

Gene expression analysis was performed on fresh frozen primary tumor material. The RNA gene expression profiles were generated using a customized 4 × 44 K oligonucleotide microarray of Agilent Technologies and the raw data analyzed running a classification algorithm. The results were given as favorable or unfavorable as described elsewhere.[20] The TH10 gene expression classifier was reported to be particularly useful within the cohort of patients with stages 1–3 and MYCN nonamplified disease aged ≥18 months for discriminating highly aggressive tumor biology from tumors with a high potential to regress or differentiate.[20]

2.6 | Statistical analysis

IBM SPSS statistic package version 25 was used for statistical analyses. Frequencies were analyzed using the v2 test according to Pearson. For comparison of Kaplan–Meier survival estimations, the log-rank test was applied. Event-free survival (EFS) and overall survival (OS) were calculated from the day of histological diagnosis to an event or to the date of last information if no event occurred. For EFS, event was defined as tumor progression or death of any reason. For OS, death of any reason was counted.[21] All analyses are post hoc analyses and descriptive. Follow-up time was calculated from diagnosis to event or to last follow-up in case of no event.

3 | RESULTS

3.1 | Study cohort (Figure 1)

Of all known German patients, 98.8% participated in the trials according to the German Childhood Cancer Registry (https://www.kinderkrebsregister.de). In the 26-year period between 1990 and 2015, 748 patients with metastatic neuroblastoma aged less than 18 months at diagnosis were enrolled. Four hundred ten patients were classified as stage 4S(MS) (54.8%) and excluded. Of the 338 stage 4(M) patients aged <18 months, 161 had *MYCN* amplification or unknown *MYCN* status or other missing information. One hundred seventy-seven patients were included in this study.

3.2 | Clinical characteristics (Table 1)

The sex ratio was equal (m/f 1.0) in the total group and within 3-month subgroups between 0 and 14 months. Only within the category 15–17 months were more boys than girls observed (ratio 1.3). The number of patients increased with increasing age (Jonkheere–Terpstra test for trend $p = .017$).

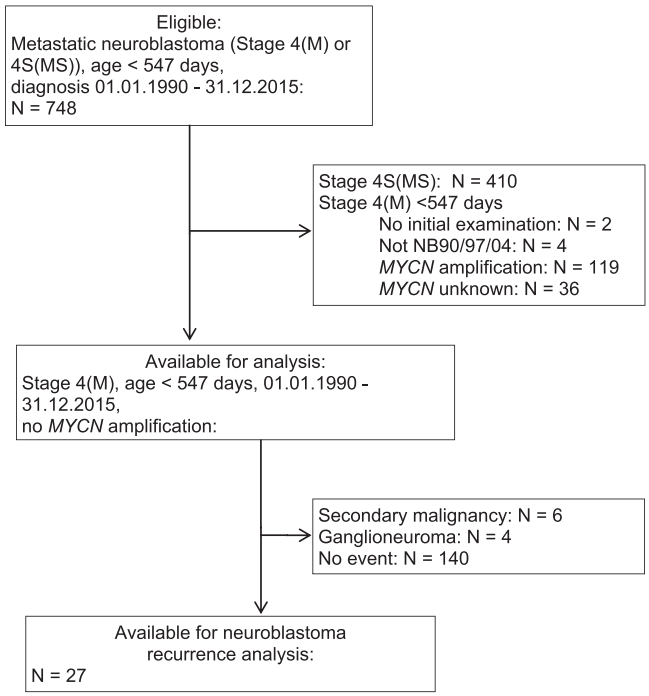

FIGURE 1 CONSORT diagram of patients aged <18 months with metastatic neuroblastoma and without *MYCN* amplification

For 88%, the primary tumors were located in abdominal sites, 9% had large tumors transgressing, for example, from thoracic to abdominal or cervical sites, and an additional 6% demonstrated multiple primaries, for example, left and right adrenal. Osteomedullary sites (96%), liver (42%) and skin (14%) were the most frequently involved metastatic localizations. Elevated levels of the tumor markers urinary catecholamine metabolites (vanillylmandelic acid and/or homovanillic acid in urine [VMA/HVA]) and serum neuron-specific enolase (NSE) were seen in the vast majority (>85%), while the risk markers lactate dehydrogenase (LDH) and ferritin were less frequently increased.

3.3 | Treatment (Figure S1, Table 1)

The majority of patients was treated by surgical resection and by chemotherapy (78%). "Chemotherapy only" was the treatment of 16% and "surgery only" of 5%. Complete or incomplete resection of the primary tumors was achieved in 69%, while biopsy was done in 13%. No surgical tumor resection at all was attempted in further 18%. The frequency of complete resections decreased from 49% (NB90) to 38% (NB2004). Irradiation of residual primary tumor was applied in 14% and ^{131}I-mIBG therapy in 7%. High-dose chemotherapy with autologous hematopoietic stem cell rescue was used in 22% and consolidation with anti-GD2 antibodies in 19%.

TABLE 1 Characteristics of 177 patients with neuroblastoma stage 4(M) aged less than 18 months

Characteristic	Number of patients*N* (%)
All	177 (100)
Sex	
Male	88 (50)
Female	89 (50)
Age at diagnosis (months)	
0–2	12 (7)
3–5	19 (11)
6–8	29 (16)
9–11	29 (16)
12–14	46 (26)
15–17	42 (24)
Primary tumor site[a]	
Abdominal adrenal	111 (63)
Abdominal nonadrenal	45 (25)
Thoracic	30 (16)
Cervical	5 (3)
Unknown	0 (0)
>1 Site (combined regions)	15 (9)
>1 Site (multiple primaries)	10 (6)
Sites of metastasis	
Bone marrow (cytology)	157 (89)
Osteomedullary (mIBG)	169 (96)
Lymph nodes	18 (10)
Liver	74 (42)
Brain/spinal cord	11 (6)
Lung/pleura	11 (6)
Skin	25 (14)
Testicles	4 (2)
Other	14 (8)
Osteomedullary only	82 (46)
Tumor marker	
NSE abnormal	152 (86)
VMA/HVA abnormal	159 (90)
LDH abnormal	118 (67)
Ferritin abnormal	34 (19)
Molecular characteristics	
TH10 classifier, *N* = 39	
Favorable	31 (79)
Unfavorable	8 (21)

(Continues)

TABLE 1 (Continued)

Characteristic	Number of patients*N* (%)
Treatment	
NB 90	39 (22)
NB 97	58 (33)
NB 2004	80 (45)
Surgery[b]	
Complete resection	72 (40)
Incomplete resection	51 (29)
Biopsy only	23 (13)
No OP	31 (18)
Percutaneous radiotherapy	
Given	25 (14)
Not given	152 (86)
mIBG therapy	
Given	12 (7)
Not given	165 (93)
ASCT	
Given	39 (22)
Not given	138 (78)
Antibody therapy	
Given	34 (19)
Not given	143 (81)
Treatment intensity	
Neither surgery nor CT	3 (2)
Surgery only	8 (5)
CT only	28 (16)
Surgery and CT	138 (78)

Abbreviations: ASCT, high-dose chemotherapy with autologous blood stem cell transplantation; LDH, lactate dehydrogenase; mIBG, ^{123}iodine metaiodinebenzylguanidine scintigraphy; NSE, neuron-specific enolase; VMA/HVA, vanillylmandelic acid and/or homovanillic acid in urine.

[a]The numbers exceed 177 and 100%, respectively, as all sites were counted, including multiple primaries and tumors extending to more than one site ("combined" regions).

[b]Best result if >1 operation. Operations for recurrences are excluded.

3.4 | General outcome

The median follow-up time was of 9.7 years (IQR 5.0, 13.4). The 10-year EFS proportion was 73% (95% confidence interval [CI] 67–79%) and the OS was 86% (95% CI 80–92%) (Figure 2). The EFS did not improve over the years (log-rank $p = .313$), but the 10-year OS proportions increased from 69% to 90–93% (NB90: 69% [95% CI 55–83%]; NB97: 93% [95% CI 87–99%], NB2004: 90% [95% CI 72–98%]; log-rank $p = .002$; Figure S2).

Of the 26 patients who died, 16 died due to tumor progression. Death because of toxicity occurred in three cases (all during trial NB90) and in two further cases of tumor progression and/or toxicity (trials NB90 and NB2004). A further five died of secondary malignancy.

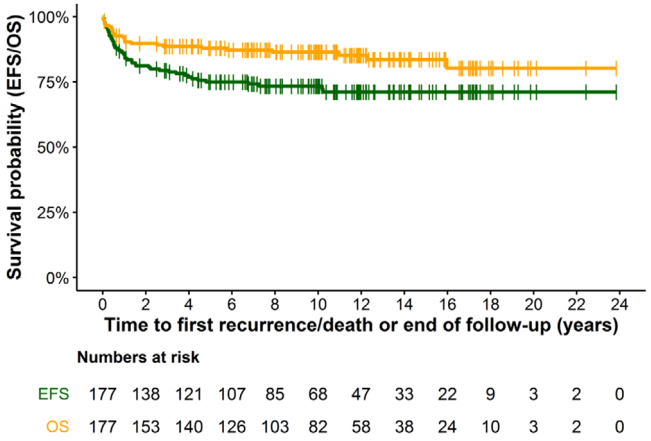

FIGURE 2 Event-free and overall survival of 177 patients with neuroblastoma stage 4(M) aged less than 18 months

3.5 | Characteristics at diagnosis and outcome

The localization of primary tumor had no influence on the recurrence and death, with the exception of an increased risk of death for adrenal primaries (HR[OS] 2.864, 95% CI 1.079–7.603). Elevated levels of serum ferritin indicated a higher risk of recurrence and death (HR[EFS] 2.900, 95% CI 1.526–5.512; HR[OS] 4.674, 95% CI 2.037–10.723), while abnormal levels of the catecholamine metabolites VMA and/or HVA were associated with lower risk (HR[EFS] 0.415, 95% CI 0.194–0.891; HR[OS] 0.333, 95% CI 0.133–0.835).

The localization of metastatic sites, sex, age, NSE, LDH, and TH10 signature had no correlation to outcome (EFS, OS).

3.6 | Molecular characteristics (Table 1, Table S2)

All 177 patients included in this study had no *MYCN* amplification. For 52% of patients (92/177), additional molecular characteristics were available. Gene expression signatures were available for 39 patients and showed an unfavorable outcome prediction in 21%. Of 31 patients with favorable expression, eight had recurrences (26%). Three patients with tumor recurrences initially had multilocular neuroblastoma and a further three recurrences were histologically ganglioneuroma. Of the eight patients with unfavorable gene expression signatures, two presented with recurrences (25%). Two patients of the favorable and none of the unfavorable group died.

3.7 | Therapy-related outcome

More complete resection of the primary tumor was correlated with a better EFS (10-year EFS 91.7% for complete, 74.4% for incomplete, 52.2% for biopsy, and 45.2% for no surgery; log-rank p[EFS] < .001). The benefit of the grade of resectability was less clear for OS: no difference was observed between complete and incomplete resection (p[OS] = .400). A trend for better OS was seen comparing complete

resection versus biopsy (p[OS] = .074) and a significant difference between complete resection versus no operation (p[OS] < .001).

EFS or OS proportions were not associated with the use of high-dose chemotherapy (log-rank p[EFS] = .306, p[OS] = .602, n = 39), antibody application (log-rank p[EFS] = .953, p[OS] = .137, n = 34), external beam irradiation (log-rank p[EFS] = .402, p[OS] = .262, n = 25), or mIBG therapy (log-rank p[EFS] = .285, p[OS] = .068, n = 12).

None of the three patients who were observed only (no chemotherapy, no surgery) experienced a recurrence. Of the five patients who were only operated without any further treatment, three had recurrences.

3.8 | Secondary malignancies

Six patients developed a second malignant neoplasm: thyroid carcinoma, renal cell carcinoma (died), nerve sheet tumor (died), acute myeloid leukemia (died), juvenile chronic myelomonocytic leukemia (died), and myelodysplastic syndrome (died). The diagnosis of the consecutive malignancy was made 3.8–10.4 years after the neuroblastoma diagnosis. The cumulative risk after 10 years was 2.7% (95% CI 1.6–3.8%) (Figure S4). All patients with secondary malignancies were treated with six to eight courses of cyclic chemotherapy. Additional treatments were maintenance chemotherapy (n = 3), antibody therapy (n = 3), high-dose chemotherapy (n = 2), mIBG therapy (n = 2), and isotretinoin (n = 1).

3.9 | Recurrence as ganglioneuroma

In four cases, biopsy of the recurrent tumor demonstrated a mature ganglioneuroma (one at the primary and three at metastatic sites [osteomedullary, lymph node]). All these patients survived with only surgical (3/4) or surgical and antibody therapy (1/4).

3.10 | Secondary EFS and OS of patients

The median time from diagnosis to first recurrence was 279 days (range 41–1510). In 44% of the 27 patients, recurrences presented in more than one site (Table 2).

For all 37 patients with events (neuroblastoma, ganglioneuroma, or secondary malignant disease), the proportions of the secondary 5-year EFS and OS were 51% (95% CI 34.0–67.2) and 62% (95% CI 35.3–77.7), respectively (Figure S3A). The 27 patients with neuroblastoma recurrence had a secondary 5-year EFS of 44% (95% CI 24–64) and a secondary OS of 59% (95% CI 41–77) (Figure S3B).

TABLE 2 Recurrence sites of 27 patients with neuroblastoma stage 4(M) aged <18 months

Recurrence site	Number (%)
Primary site	16 (59)
Osteomedullary	15 (56)
Brain/spinal cord	4 (15)
Bone marrow (cytology)	10 (37)
Soft tissue	2 (7)
Lymph nodes	1 (4)
Liver	1 (4)
Lung/pleura	1 (4)
Skin	0 (0)
Other	1 (4)
Metastatic site(s) only	11 (41)
Primary site only	10 (37)
Primary and metastatic sites	6 (22)
Osteomedullary only	9 (33)

4 | DISCUSSION

Patients aged less than 18 months with stage 4(M) have a much more favorable prognosis than older children. This group is prone to secondary malignancies while treated with high-dose or otherwise intensive chemotherapeutic regimens. Recurrences may show mature histology (ganglioneuroma). Less complete resections of the primary tumor were associated with more primary tumor recurrences, however worse OS was detected only in the small group of patients without surgical approach to the primary tumor.

The strength of this study is the analysis of a comparably large number of stage 4(M) neuroblastoma patients without *MYCN* amplification, below the age of 18 months, and an observation time of nearly three decades.

One limitation is the chosen discrimination of stage 4(M) from stage 4S(MS). The definition was consistent throughout the NB90/97/2004 trials. Stage 3 primary tumors and metastasis to sites other than liver, skin, and bone marrow (e.g., to distant lymph nodes, brain, testes, single mIBG uptake spots over bone marrow) were considered compatible with the stage 4S(MS) biology and its potential to regress spontaneously. Stage 4(M) <18 months was defined by osteomedullary ± other metastases. By this modus operandi, stage 4S(MS) <18 months outnumbered stage 4(M) <18 months (410 [55%] vs. 332 [45%]). When excluding the patients with *MYCN* amplified tumors, the ratio was 289 stage 4S(MS) (62%) versus 177 stage 4(M) (38%). The variability of other reported series is remarkable: The Italian study reported 74% stage 4S(MS) and 26% stage 4(M) patients (age <12 months),[6] while the American studies had more stage 4(M) than stage 4S(MS) patients (85% vs. 15%, 63% vs. 37%, and 65% vs. 35%).[12,22,23] Thus, our strict definition of stage 4(M) <18 months, and wide definition of stage 4S(MS), is less likely to overlook patients with stage 4S(MS) biology. Conversely, during the observation period, 19 stage 4S(MS) cases without *MYCN* amplification progressed to stage 4(M) within a time frame of 2 months to 6 years and 10 months. Further limitations consist of the rather high intensities of chemotherapy throughout the three trials for this group of patients, the inconsistent treatment schemes,

the improving diagnostic capacities, and the timely modifications in the supportive care.

The maintained definition of the cohort by bone metastasis led to the therapeutic "philosophy" to converge rather with high-risk than with stage 4S(MS) strategies. Of the 177 patients, 78% received six to eight courses of intensive induction chemotherapy followed by 3–12 months consolidation treatment (e.g., N7 courses with oral cyclophosphamide/oral isotretinoin). High-dose chemotherapy was given to 22%, antibody therapy to 19%, radiotherapy to 14%, and mIBG therapy to 7% of patients. While the proportions of EFS did not change over time, the OS improved from NB90 to NB97/NB2004. The better outcome may be explained by an improved second-line treatment strategy.

The SIOPEN group reported a 96% 5-year OS (95% CI 89.5–100) of 45 infants with stage 4(M) neuroblastoma achieved with two to four courses of chemotherapy only (trial 99.3).[6] The COG group applied four to eight courses of chemotherapy to 176 infants with stage 4(M) neuroblastoma depending on the "histology" and "DNA ploidy" biological features. The 3-year EFS were 81 ± 3% and 93 ± 2%.[12] Kim and coworkers recently published a 100% 5-year EFS of 20 stage 4(M) patients aged <18 months after surgery and nine cycles of chemotherapy.[8] These and other reports[9,11,14–16] must be interpreted in the context of the varying stage 4(M)/stage 4S(MS) ratios and inclusion criteria. However, an obvious conclusion is that an excellent outcome can be achieved with more limited chemotherapy.

While toxicity-related deaths were rarely observed, the proportion of secondary malignancies was surprisingly high (six of 177 patients) accounting for a 10-year cumulative incidence of 2.7%. The International Neuroblastoma Risk Group Project reported a cumulative risk among the neuroblastoma survivors after 10 years of 1.8% (95% CI 1.0–2.6%) for high-risk and 0.38% (95% CI 0.22–0.94%) for intermediate-risk patients.[24] Thus, the incidence of our series with a conceivably limited biological risk plus intensive cytotoxic therapy was close to the biological high-risk category.

The prediction of the statistically small number of recurrences in this study was not satisfactory with the investigated clinical standard parameters (Table 1). Only high ferritin (19% of cases) and normal VMA/HVA levels (10% of cases) were associated with an increased risk of tumor recurrence and are not considered as useful discriminators in our opinion. While the RNA expression classifier TH10[20] discriminated well between low and high risk in an unselected series of patients, this was not mirrored within the cohort investigated here, which might be due to the relatively small number of patients for which microarray analyses were possible. Only a minority with unfavorable expression characteristics indeed developed progressions. Conversely, none of the few molecularly characterized neuroblastomas progressing to tumor-related death exhibited an unfavorable TH10 expression.

In conclusion, the outcome of patients with stage 4(M) neuroblastoma aged less than 18 months is favorable when treated with high-risk or otherwise intensive therapy. The development of secondary malignancies and the potential of maturation to ganglioneuroma call for a controlled stepwise reduction of treatment intensity. A prognostic impact of the TH10-expression signature could not be detected in this subcohort.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information of this article.

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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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