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Original Research

Neuroblastoma between 1990 and 2014 in the Netherlands: Increased incidence and improved survival of high-risk neuroblastoma

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KEYWORDS
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Abstract ***Purpose:*** Long-term trends in neuroblastoma incidence and survival in unscreened populations are unknown. We explored trends in incidence, stage at diagnosis, treatment and survival of neuroblastoma in the Netherlands from 1990 to 2014.
Methods: The Netherlands Cancer Registry provided data on all patients aged <18 years diagnosed with a neuroblastoma. Trends in incidence and stage were evaluated by calculating the average annual percentage change (AAPC). Univariate and multivariable survival analyses were performed for stage 4 disease to test whether changes in treatment are associated with survival.
Results: Of the 593 newly diagnosed neuroblastoma cases, 45% was <18 months of age at diagnosis and 52% had stage 4 disease. The age-standardized incidence rate for stage 4 disease increased at all ages from 3.2 to 5.3 per million children per year (AAPC + 2.9%, p < .01).

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This increase was solely for patients ≥18 months old (3.0–5.4; AAPC +3.3%, p = .01). Five-year OS of all patients increased from 44 ± 5% to 61 ± 4% from 1990 to 2014 (p < .01) and from 19 ± 6% to 44 ± 6% (p < .01) for patients with stage 4 disease. Multivariable analysis revealed that high-dose chemotherapy followed by autologous stem cell rescue and anti-GD2-based immunotherapy were associated with this survival increase (HR 0.46, p < .01 and HR 0.37, p < .01, respectively).

Conclusion: Incidence of stage 4 neuroblastoma increased exclusively in patients aged ≥18 months since 1990, whereas the incidence of other stages remained stable. The 5-year OS of stage 4 patients improved, mostly due to the introduction of high-dose chemotherapy followed by stem cell rescue and immunotherapy.

1. Introduction

The incidence of neuroblastoma (NB) in developed countries is 11–13 per million children aged <15 years and varies from 65 per million in children <1 year to 1 per million in children of 10–14 years [1–3]. NB is a heterogeneous tumour entity with a variable clinical course. The long-term survival is good to excellent in low-risk disease (5-year OS of >85% in International Neuroblastoma Staging System (INSS) stage 1, 2, 4S [4], or International Neuroblastoma Risk Group Staging System stage L1, MS [5]), but poor in patients with high-risk disease (5-year OS of <50% in stage 4/M in patients ≥18 months old at diagnosis, and/or with MYCN (v-myc avian myelocytomatosis viral related oncogene, neuroblastoma derived) amplification) [6]. Furthermore, patients with a more differentiated histology (ganglioneuroblastoma [GNB]) fare a more favourable course of disease than patients with undifferentiated histology (NB) [7,8]. In the past decades, therapy for high-risk patients has been modified in several ways to increase survival. Induction chemotherapy was intensified, high-dose chemotherapy followed by autologous stem cell rescue and standard radiotherapy were introduced. Most recently, anti-GD2 immunotherapy has been added to the maintenance therapy; this monoclonal antibody is given in combination with alternating GM-CSF or IL-2 to stimulate the immune response [9–12].

Improvements in cancer outcome are often analysed as improvements in survival, but cancer incidence analyses should also be used to monitor changes in outcome by changes in the prevalence of (unknown) risk factors [13]. While survival provides a measure of prognosis and improvement in the treatment, trends in cancer mortality are the result of trends in both incidence and survival. The three analyses together increase the comprehension of the total progress against cancer in a given area over time [14–16].

These epidemiological analyses were used in the evaluations of the NB screening programs, conducted between 1985 and 2000 in Japan and parts of Germany, France, Austria, Canada and the United Kingdom. The rationale behind the screening programs was that detection at an earlier stage of disease would lead to an improved prognosis. Although the screening studies identified more young patients with low-risk NB, this had no effect on incidence of high-risk disease or overall mortality, suggesting overdiagnosis of low-risk patients [13,16–22]. This resulted in the termination of all screening programs. A disadvantage of these screening programs is that change in the incidence over time. In the Netherlands, no screening programs have been performed.

The purpose of this comprehensive, population-based study was to describe the trends in incidence, treatment modalities and survival in NB patients aged <18 years, diagnosed between 1990 and 2014, and to study the effect of changes in treatment on the survival of patients with stage 4 NB.

2. Methods

2.1. Data sources

The Netherlands Cancer Registry (NCR) is a nationwide population-based registry, established in 1989, hosted by the Netherlands Comprehensive Cancer Organization (IKNL). The NCR only registers persons with the Dutch nationality, or people who have been living in the Netherlands for at least three months before diagnosis. Trained registrars of the NCR extracted data on patient and tumour characteristics, and given treatment by retrospective medical record review. Only first-line treatment modalities were registered.

The NCR registers morphology according to the International Classification of Diseased for Oncology (ICD-O-3) [23], currently the ICD-O-3.1 system [24]. Tumour stage was recorded using the TNM classification [25] until 2003 and subsequently according to the Extent of Disease [26] (EoD) classification. Localized disease (TNM/EoD) was converted to INSS stage 1/2, regional disease to stage 3 and metastatic disease to

Table 1
Patient characteristics of patients aged <18 years, diagnosed with a neuroblastoma in the Netherlands between 1990 and 2014.

Characteristics	1990–1994	1995–1999	2000–2004	2005–2009	2010–2014	total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age						
<18 months	45 (45)	54 (48)	56 (45)	57 (45)	53 (41)	265 (45)
≥18 months	55 (55)	59 (52)	68 (55)	69 (55)	77 (59)	328 (55)
Gender						
Male	53 (53)	61 (54)	76 (61)	66 (52)	67 (52)	323 (54)
Female	47 (47)	52 (46)	48 (39)	60 (48)	63 (48)	270 (46)
Histology						
NB	90 (90)	89 (79)	106 (85)	107 (85)	117 (90)	509 (86)
GNB	10 (10)	24 (21)	18 (15)	19 (15)	13 (10)	84 (14)
Stage						
1/2	26 (27)	37 (33)	39 (32)	34 (27)	26 (20)	162 (28)
3	14 (15)	13 (12)	15 (12)	15 (12)	16 (12)	73 (12)
4	47 (49)	52 (46)	63 (52)	67 (54)	77 (59)	306 (52)
4S	9 (9)	10 (9)	5 (4)	9 (7)	11 (8)	44 (8)
Unknown	4	1	2	1	0	8
Localization primary tumour						
Sympathetic side chain	23 (23)	32 (28)	32 (26)	33 (26)	37 (28)	157 (27)
- *Cervical/thoracic*	13 (13)	19 (17)	18 (15)	13 (10)	26 (20)	89 (15)
- *Pelvic*	5 (5)	7 (6)	6 (5)	8 (6)	4 (3)	30 (5)
- *Not otherwise specified*[a]	5 (5)	6 (5)	8 (6)	12 (10)	7 (5)	38 (6)
Adrenal/abdominal	70 (70)	79 (70)	88 (71)	91 (72)	90 (69)	417 (70)
Unknown/no primary tumour	7 (7)	2 (2)	4 (3)	2 (2)	3 (2)	18 (3)

Abbreviations: NB, neuroblastoma; GNB, ganglioneuroblastoma.
Bold fonts indicate characteristics categories, italic fonts indicate subgroups.
[a] Sympathetic side chain tumours, without specified location.

stage 4 or 4S. To validate stage and treatment modalities, hospital-based NB databases were used to cross-check these items and to identify patients with NB stage 4S, according to the INSS staging system [4]. Information on risk stratification, MYCN status and other genetic prognostic factors was not available.

2.2. Patient and data selection

Clinical data from Dutch patients aged <18 years at diagnosis and diagnosed with a NB or a GNB between 1990 and 2014 were extracted from the NCR. Information on vital status (alive, dead, or emigration) was obtained by annual linkage with the Nationwide Population Registries Network that contains vital statistics on all Dutch residents. Last linkage was on February 1, 2018. Because of privacy regulations, no data on cause of death could be obtained. Nationwide disease-specific mortality data were not informative because NB was non-consistently coded as a malignancy of the adrenal gland, the connective and soft-tissues, and the peripheral nervous system [27].

2.3. Statistical analyses

For the NB patient population, the following characteristics were described: age at diagnosis, gender, histology (NB vs. GNB), stage and location of the primary tumour. Differences in these characteristics were tested using χ^2 tests. For analysis over time, five-year periods were defined: 1990–1994, 1995–1999, 2000–2004, 2005–2009 and 2010–2014.

Overall incidence rates were calculated as the average annual number of cases per 1 million person-years, using annual midyear population sizes from Statistics Netherlands, these were provided for the age groups: 0, 1–4, 5–9, 10–14, and 15–17 years. Incidence rates were also calculated for age groups (<18 and ≥ 18 months), stage and stage per age group. The population at risk <18 months was calculated as the population aged 0 years plus 1/8th of the population aged 1–4 years. Similarly, the population at risk ≥18 months was calculated as the population aged 5–17 years plus 7/8th of the population aged 1–4 years. Rates were age-standardized using the age structure of the world standard population [28]. Changes in incidence over time were evaluated by calculating the average annual percentage change (AAPC). AAPC was derived from a regression line fitted to the natural logarithm of the rates, using the calendar year as regressor variable (i.e. $y = ax + b$ where $y = \ln(\text{rate})$ and x = calendar year; then $\text{AAPC} = 100 \times (e^a - 1)$) and calculated for the whole study period 1990–2014 [28].

Traditional cohort-based survival analysis using Kaplan–Meier method with log-rank test was used to calculate overall survival (OS). Survival time was calculated as the time elapsed between the date of diagnosis and the date of death of any cause or date at last follow-up (alive, censored).

For analyses in patients with stage 4 NB, treatment modalities were dichotomized to yes/no (see Table 2). Differences in frequency of applied treatment modalities by period of diagnosis were tested using χ^2 tests.

Time trends in observed 5-year OS were first evaluated by using a parametric survival model. The dichotomized treatment modalities were added to the model to investigate the effect of therapy on the hazard ratio (HR) of period of diagnosis. Age group (<18 and ≥ 18 months), a strong independent predictor of survival, was also entered in the multivariable models. All statistical analyses were two-sided and a p-value <0.05 was considered significant. Analyses were performed with STATA/SE 14.2 (StataCorp LP, College Station, TX, 2015).

3. Results

3.1. Patient characteristics

Between 1990 and 2014, 509 newly diagnosed patients with NB and 84 with GNB were registered by the NCR, of which 583 (98%) were histologically confirmed. Patient and tumour characteristics are presented in Table 1. Median age at diagnosis was 21 months (range 0–16 years), male sex was slightly predominant (54%; male/female ratio = 1.2:1). Seventy percent of the patients had an adrenal or abdominal primary tumour. Most patients were diagnosed with stage 4 disease (52%), followed by stage-1/2 disease (28%), stage 3 (12%), and stage 4S (8%). For 8 patients, no data were available on stage of disease (Table 1). In patients aged <18 months, stage 1/2 was the most common (41%), and stage 4 disease was observed in 26% of the patients. In patients aged ≥18 months, stage 4 dominated (73%; Fig. 1).

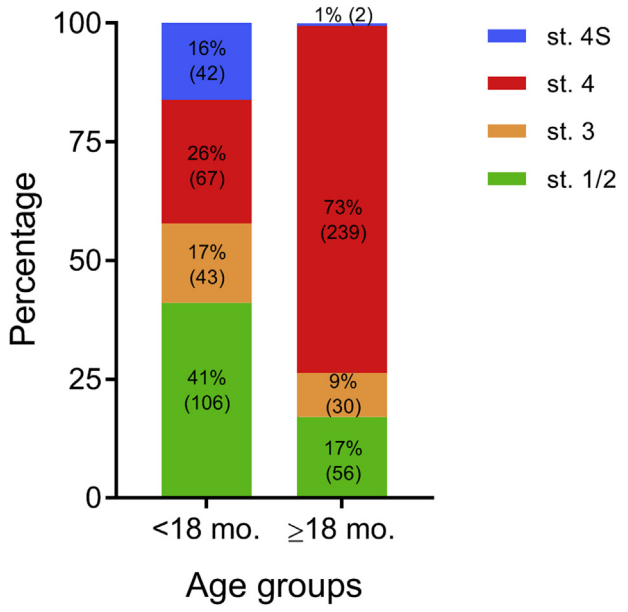

Fig. 1. **Stage distribution of neuroblastoma patients aged <18 and ≥ 18 months at diagnosis.** For patients <18 months and ≥18 months of age, the percentage (number of patients between parentheses) of each stage at diagnosis is given. Blue: stage 4S; red: stage 4; orange: stage 3; green: stage 1/2. Two patients were diagnosed as stage 4S, while they were ≥18 months of age. Stage of disease was unknown in 8 patients, 7 of them aged <18 months and were not included in this graph. Abbreviations: mo.: months; st.: stage. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.2. Incidence

In the time period 1990–1994, on average, 20 new patients per year were diagnosed with NB; this increased to 26 patients per year between 2010 and 2014 (Fig. 2A). The overall incidence rate (all stages, <18 years) significantly increased by 1.6% per year from 6.4 to 9.1 per million between 1990 and 2014 (p = .01; Fig. 2B). Stage 4 NB increased with 2.9% per year (p < .01), while the incidence of all other stages remained stable (Fig. 2B). Incidence rates by age, gender, histological type and stage, as well as the AAPC analyses for NB patients aged <15 years are provided in Appendix Table A1. No other significant changes in these rates were observed.

The age-specific incidence rates for patients aged <18 and ≥ 18 months by stage are shown in Fig. 2C and D. Incidence rates were stable for all stages in patients aged <18 months, whereas an increase in incidence of stage 4 NB was seen in patients aged ≥18 months (AAPC +3.3%, p = .01). For this age group, the number of stage 4 patients almost doubled from 7 patients per year in 1990–1994 to 12 patients per year in 2010–2014. The incidence rates for the other stages in patients aged ≥18 months remained stable.

3.3. Therapy and survival

The 5-year survival rates varied by stage: 93 ± 2% in stage 1/2 disease; 84 ± 6% in stage 4S; 70 ± 5% in stage 3 disease; 35 ± 3% in stage 4 disease (Fig. 3A). Five-year OS of all patients improved from 44 ± 5% in 1990–1994 to 61 ± 4% in 2010–2014 (p < .01) (Fig. 3B). Five-year OS of patients with stage 4 NB improved significantly from 19 ± 6% in 1990–1994 to 44 ± 6% in 2010–2014 (p < .01; Fig. 4A). For patients with the poorest outcome (stage 4 and ≥ 18 months old), 5-year OS significantly improved from 6 ± 4% in 1990–1994 to 43 ± 7% in 2010–2014 (p < .01; Fig. 4B). The 5- and 10-year OS rates over time for gender, age group, histologic type and stage are summarized in Appendix Table A2.

Important changes in the treatment of patients with stage 4 disease were made between 1990 and 2014. High-dose chemotherapy with autologous stem cell transplantation was given in 21% of patients with stage

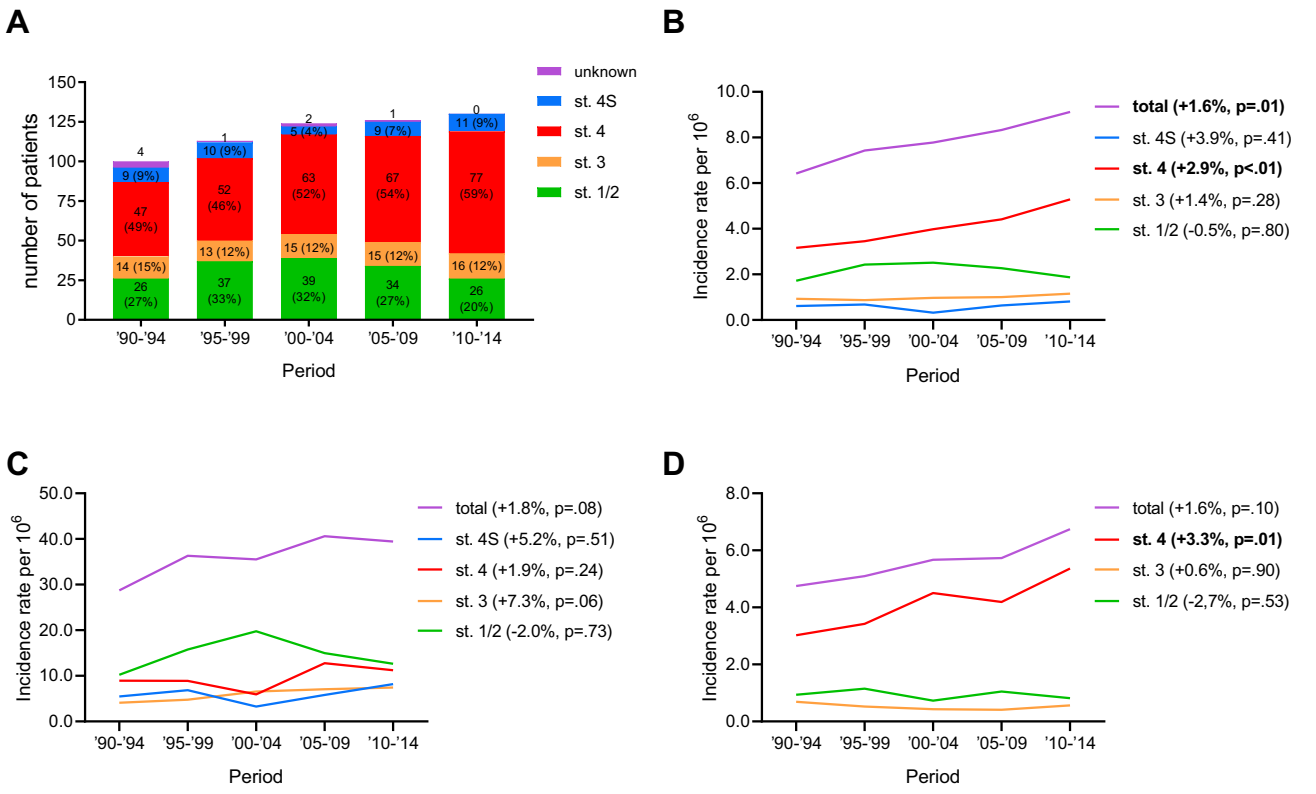

Fig. 2. **Time trends in neuroblastoma incidence per five year period.** The number of newly diagnosed patients (percentage in parentheses) is given by stage and diagnostic period (A); purple: unknown stage; blue: stage 4S; red: stage 4; orange: stage 3; green: stage 1/2, purple: total (in B-D). Time trends of incidence rates according to stage were calculated per million children aged 0–17 years (B); per million children aged 0–17 months (C); and per million children aged 18 months–17 years (D). The average annual percentage change (AAPC) is given in the legends of B-D; bold fonts indicate significant changes over time. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

4 between 1990 and 1999 and in 69% between 2010 and 2014 ($p < .01$); the frequency of primary tumour surgery increased from 58% to 84% ($p < .01$); radiotherapy increased from 16% to 40% ($p < .01$); immunotherapy increased from 0% in 1990–1999 to 4% in 2005–2009 and 53% in 2010–2014 ($p < .01$). The number of patients receiving ^{131}I-MIBG-therapy (39%) and chemotherapy (98%) did not change between 1990 and 2014.

3.4. Multivariable survival analysis for stage 4 neuroblastoma

In univariate analysis, the risk of dying (HR) from stage 4 NB was significantly lower during the periods 2005–2009 and 2010–2014 compared with 1990–1994 (HR 0.54, $p = .01$ and HR 0.50, $p < .01$, respectively). Patients aged ≥18 months had a poorer survival probability (HR 2.12, $p < .01$) than patients aged <18 months (Table 2). Other prognostic factors were the treatment modalities high-dose chemotherapy with stem cell rescue, immunotherapy and surgery. The first multivariable model contained age and period of diagnosis. In this model, the two most recent periods of diagnosis were associated with better outcome (HR 0.52 and 0.44, $p = .01$ and $p < .01$, respectively). Addition of the different treatment modalities to a second multivariable model resulted in the loss of significance for the HRs of these recent periods of diagnosis (HR 0.85 and 1.14, $p = .52$ and $p = .60$, respectively; Table 2). Patients who received high-dose chemotherapy with stem cell rescue (HR 0.46, $p < .01$) and patients who received immunotherapy (HR 0.37, $p < .01$) had a significant reduction of the risk of dying. The changes in the treatment modalities were better discriminants for the changes in survival over time, than the periods of diagnosis (Table 2).

4. Discussion

This is the first report on incidence and survival of children and adolescents with an NB in the Netherlands. Over a 25-year period, we observed a significant increase in incidence of stage 4 disease in patients aged ≥18 months, while the incidence of other stages and ages remained stable. Five-year OS improved for all ages and stages, the most distinct for patients aged ≥18 months with stage 4 NB, where an improvement of 37 percentage points was seen.

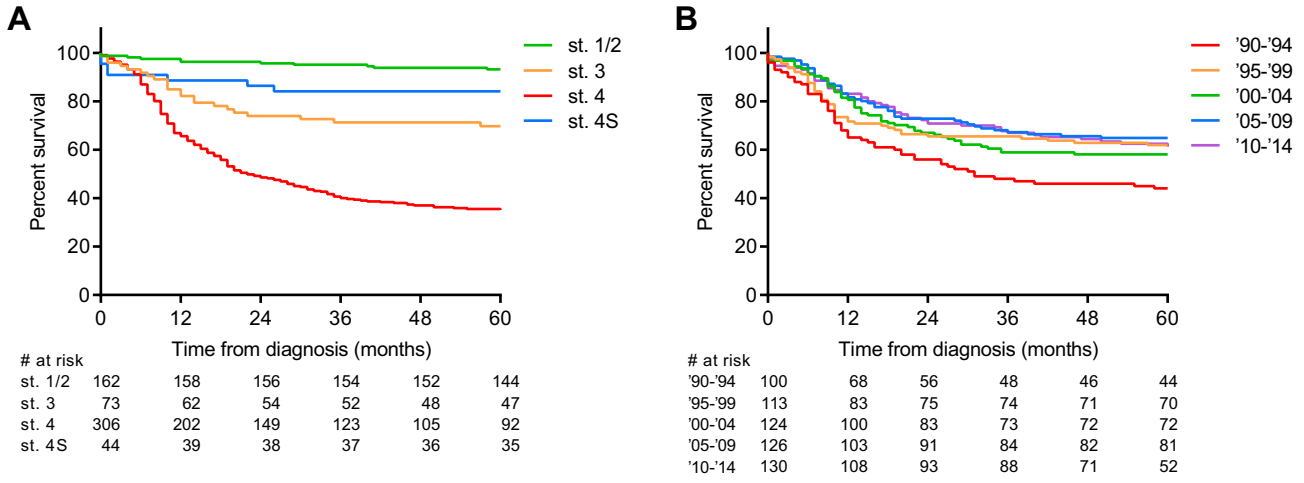

Fig. 3. **Five year overall survival (OS) for neuroblastoma patients.** Five year OS rates are given for different stages (A) and different periods (B). Fig. 3A stage-specific 5-yr OS was 93 ± 2% for stage 1/2 (green), 84 ± 6% for stage 4S (blue), 68 ± 6% for stage 3 (orange), and 35 ± 3% for stage 4 (red). Fig. 3B 5-yr OS for all stages combined was 44 ± 5% in 1990–1994 (red); 62 ± 5% in 1995–1999 (orange); 58 ± 4% in 2000–2004 (green); 65 ± 4% in 2005–2009 (blue); and 61 ± 4% in 2010–2014 (purple). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

The age-standardized incidence rate of around 10.5 cases per million children in 2010–2014 observed in this study is similar to other high-income countries as Canada, USA, and neighbouring European countries (WSR 0–14 years 10.1–15.0) [29,30]. The overall increase in NB incidence of 1.6% per year is in line with the increase in NB incidence in older children (1–4 year) of 1.7% per year in Europe (1978–1997), and of 1.6% per year in Canada (1992–2010) [2,3]. However, in Denmark, NB incidence has been stable between 1981 and 2000 for all stages and age categories [31], whereas in England, a slight decrease in incidence of 0.2% for all stages and age categories was seen between 1993 and 2000 [16]. In Germany, analyses of both tumour stage and age were performed. They found a small (7% per 10 year) increase in overall incidence, but this was attributed to an increase in stage 1–3 and stage 4S and a decrease in stage 4, which is contradicting our data [32]. Etiological factors for NB are largely unknown other than 'it is a developmental tumour of the sympathetic nervous system'. Genetic predisposition is rare (estimated at 1–2%) [33], and no environmental factors have been consistently associated with NB [34]. Improved prenatal ultrasounds only contribute to an increase in patients aged

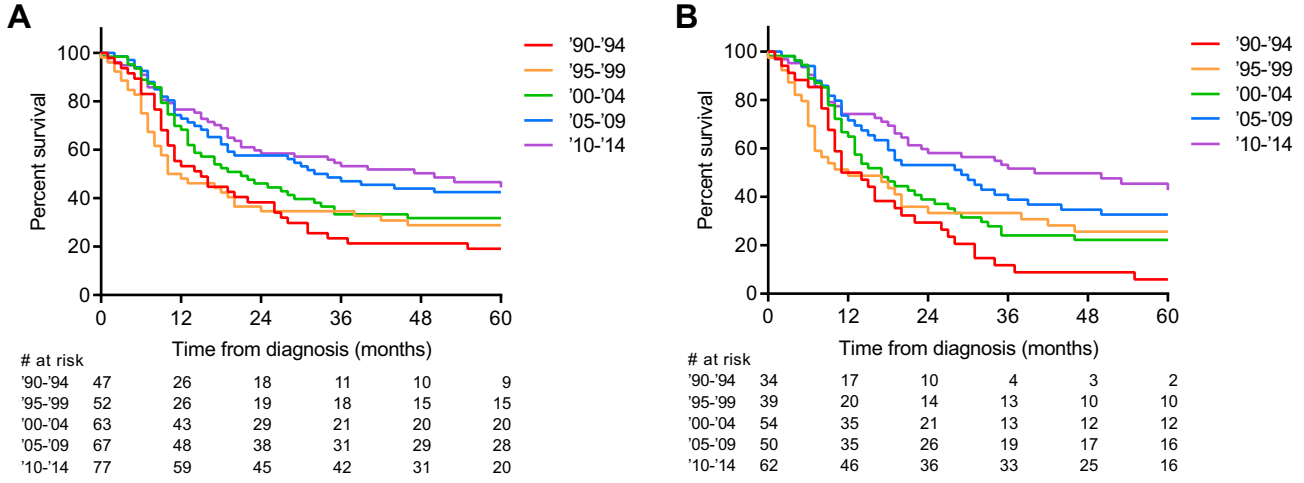

Fig. 4. **Time trends of five year overall survival (OS) for patients with a stage 4 neuroblastoma.** Five year OS rates are given by 5-year periods for all patients with stage 4 neuroblastoma (4A) and for patients with stage 4 neuroblastoma ≥18 months at diagnosis (4B). Fig. 4A 5-yr OS of patients with stage 4 neuroblastoma was 19 ± 6% in 1990–1994 (red); 29 ± 6% in 1995–1999 (orange); 32 ± 6% in 2000–2004 (green); 42 ± 6% in 2005–2009 (blue); and 44 ± 6% in 2010–2014 (purple). For patients ≥18 months old with stage 4, the 5-yr OS was 6 ± 4% in 1990–1994 (red); 26 ± 7% in 1995–1999 (orange); 22 ± 6% in 2000–2004 (green); 33 ± 7% in 2005–2009 (blue) and 43 ± 7% in 2010–2014 (purple). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Univariate and multivariable analyses for 5-year overall survival of patients with stage 4 neuroblastoma by age group, period of diagnosis and treatment modalities.

	n	Univariate analysis					Multivariable analysis, model without treatment modalities					Multivariable analysis, model with treatment modalities				
		HR	95% CI			p	HR	95% CI			p	HR	95% CI			p
Age groups																
<18 months	67	Ref.					Ref.					Ref.				
≥18 months	239	**2.16**	**1.44**	–	**3.25**	**<0.01**	**2.31**	**1.53**	–	**3.48**	**<0.01**	**3.21**	**2.10**	–	**4.91**	**<0.01**
Period																
1990–1994	47	Ref.					Ref.					Ref.				
1995–1999	52	0.89	0.57	–	1.40	0.62	0.84	0.53	–	1.32	0.44	1.03	0.65	–	1.64	0.88
2000–2004	63	0.72	0.47	–	1.12	0.15	0.65	0.42	–	1.01	0.06	0.95	0.60	–	1.51	0.83
2005–2009	67	**0.54**	**0.34**	–	**0.85**	**0.01**	**0.52**	**0.33**	–	**0.82**	**0.01**	0.85	0.53	–	1.38	0.52
2010–2014	77	**0.50**	**0.32**	–	**0.78**	**<0.01**	**0.44**	**0.28**	–	**0.69**	**<0.01**	1.14	0.69	–	1.90	0.60
ASCT																
No	151	Ref.										Ref.				
Yes	155	**0.45**	**0.34**	–	**0.60**	**<0.01**						**0.46**	**0.32**	–	**0.64**	**<0.01**
Surgery																
No	82	Ref.										Ref.				
Yes	224	**0.58**	**0.43**	–	**0.79**	**<0.01**						0.75	0.54	–	1.04	0.09
Immunotherapy																
No	262	Ref.										Ref.				
Yes	44	**0.38**	**0.23**	–	**0.62**	**<0.01**						**0.37**	**0.19**	–	**0.72**	**<0.01**
Radiotherapy																
No	214	Ref.										Ref.				
Yes	92	0.76	0.55	–	1.03	0.08						1.21	0.84	–	1.74	0.30

HRs were corrected for follow-up time.
Abbreviations; ASCT, autologous stem cell transplantation after high-dose chemotherapy; HR, hazard ratio; 95% CI, 95% confidence interval.
Bold fonts indicate characteristics categories.

<18 months at diagnosis. In fact, this has also been shown in NB screening studies based on urinary catecholamine measurements in infants [17,20,35]. Higher registration rates caused by immigration for medical reasons can be ruled out because the Netherlands has a long-standing population-wide cancer registry, covering at least 95% of all newly diagnosed malignancies in Dutch inhabitants [36].

The increase in overall incidence is caused by an increase in the incidence of stage 4 NB in patients aged ≥18 months. In this group, the number of newly diagnosed patients almost doubled. The increase cannot be assigned to higher sensitivity of molecular markers (amplification of MYCN or loss of heterozygosity of chromosome 1p) because these influence risk stratification and not stage of disease. Improved sensitivity of diagnostics and upstaging of patients with lower stage disease can play a small role, but seems to be negligible because only a minimal (non-significant) decrease in lower stage disease was observed, while there was a significant increase in overall incidence and in stage 4 incidence. This leaves the cause of the increased incidence for this subgroup unclear.

The improved survival for patients with stage 4 disease is associated with changes in therapy. Multivariable analysis showed that high-dose chemotherapy followed by autologous stem cell rescue and immunotherapy (HR 0.46, $p < .01$ and HR 0.37, $p < .01$) were the treatment modalities that more adequately predicted the survival improvement than the periods of diagnosis. Berthold *et al.* and Pinto *et al.* [9,37] reported previously of a survival benefit for high-dose chemotherapy in high-risk NB, compared with maintenance therapy. Immunotherapy was introduced in 2009, and in this cohort, only 44 of the 306 patients with stage 4 disease received immunotherapy. Despite this very small number, we observed a significant effect on OS in both the univariate (HR 0.38, $p < .01$) and multivariable analysis (HR 0.37, $p < .01$). This cohort seems to confirm earlier studies demonstrating a benefit for maintenance therapy with immunotherapy [12,38]. In addition, we expect roles for the intensified induction chemotherapy and the improved supportive care over time, but the current data set did not allow these analyses.

The longstanding population-based Netherlands Cancer Registry follows international standards and coding practices, and has, also through its participation in international projects (Eurocare, ACCIS, CI 5), many quality checks. The NCR is one of the few registries that also register stage and initial treatment. A limitation of this study is the lack of data on prognostic markers such as MYCN amplification and on cause of death. However, because the pediatric population in this study is not suspected for other serious underlying diseases or competing causes of death, the observed survival, as reported here, is representative for the NB-specific survival [39]. Another limitation is the relative small size of the Dutch population, resulting in a smaller cohort than

the German, European, or American SEER databases [1,32,39].

5. Conclusions

Our population-based study comprehensively analysed incidence, incidence changes over time, survival, and treatment of NB during a 25-year period in the Netherlands. We observed an increase of 1.6% per year in total incidence and more particularly for patients with stage 4 disease who were ≥18 months of age. Survival for this group improved from 6 ± 4% in 1990–1994 to 43 ± 7% in 2010–2014. The improved survival of stage 4 patients is predominantly associated with the introduction of high-dose chemotherapy with autologous stem cell rescue and immunotherapy.

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Role of the funding source

The funding sources had no role in study design, collection, analysis, and interpretation of data, writing of this manuscript, or the decision to submit the article for publication.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.025.

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