Stage 4 s neuroblastoma: features, management and outcome of 268 cases from the Italian Neuroblastoma Registry

Bruno De Bernardi 1*, Andrea Di Cataldo 2, Alberto Garaventa 1, Elisabetta Viscardi 3, Marta Giorgia Podda 4, Aurora Castellano 5, Paolo D’Angelo 6, Elisa Tirtei 7, Fraia Melchionda 8, Simona Vetrella 9, Francesco De Leonardis 10, Carmelita D’Ippolito 11, Annalisa Tondo 12, Antonella Nonnis 13, Giovanni Erminio 14, Anna Rita Gigliotti 14, Katia Mazzocco 15 and Riccardo Haupt 14†

Abstract

Background: Infants diagnosed with stage 4 s neuroblastoma commonly experience spontaneous disease regression, with few succumbing without response to therapy. We analyzed a large cohort of such infants enrolled in the Italian Neuroblastoma Registry to detect changes over time in presenting features, treatment and outcome.

Methods: Of 3355 subjects aged 0–18 years with previously untreated neuroblastoma diagnosed between 1979 and 2013, a total of 280 infants (8.3%) had stage 4 s characteristics, 268 of whom were eligible for analyses. Three treatment eras were identified on the basis of diagnostic and chemotherapy adopted. Group 1 patients received upfront chemotherapy; Group 2 and 3 patients underwent observation in the absence of life-threatening symptoms (LTS), except for Group 3 patients with amplified MYCN gene, who received more aggressive therapy.

Results: The three groups were comparable, with few exceptions. Ten-year overall survival significantly increased from 76.9 to 89.7% and was worse for male gender, age 0–29 days and presence of selected LTS on diagnosis, elevated LDH, and abnormal biologic features. Infants who underwent primary resection ± chemotherapy did significantly better. On multivariate analysis, treatment eras and the association of hepatomegaly to dyspnea were independently associated with worse outcome.

Conclusions: Our data confirm that stage 4 s neuroblastoma is curable in nearly 90% of cases. Hepatomegaly associated to dyspnea was the most important independent risk factor. The cure rate could be further increased through timely identification of patients at risk who might benefit from surgical techniques, such as intra-arterial chemoembolization and/or liver transplantation, which must be carried out in institutions with specific expertise.

Keywords: Neuroblastoma, Infants, Stage 4 s, Prognostic factors

Background

The intriguing subset of neuroblastoma named stage IV-S was described by D’Angio et al. in 1971 and referred to patients who would otherwise be stage I or II, but who had remote disease confined only to one or more of the following sites: liver, skin, or bone marrow. Subsequently the International Neuroblastoma Staging System (INSS) introduced the age limit of 1 year and the degree of bone marrow infiltration less than 10% and reclassified such cases as stage 4 s [2]. Finally, in 2008, the International Neuroblastoma Risk Group Staging System (INRGSS) raised the patient age limit to 18 months [3]. The typical natural history of stage 4 s is characterized by an initial phase of tumor progression lasting a variable number of days/months, usually followed by spontaneous regression, the mechanism of which has not yet been clarified. [4] In a minority of patients, however, stage 4 s disease progresses independently of any therapy, leading to death. This outcome has
been recorded in several studies, which have reported survival rates ranging from 60 to 90% [5–14]. The outcome of infants diagnosed with stage 4 s disease has been seen to be negatively affected by several factors: age < 2 months [9, 11], life-threatening symptoms (LTS) [15, 16] and some biologic features of tumor cells [11, 13, 17–22]. However, several issues remain poorly defined, i.e., which patients may benefit from chemothera-apy, the timing and effect of primary tumor resection, the management of patients with unfavorable biologic features, and the feasibility and benefit of some surgical procedures in the case of massive liver enlargement.

In this study, we aimed to describe the modifications in presenting features and survival probabilities that occurred over a 34-year period in a cohort of stage 4 s in- fants enrolled in the RINB [23], and to define the impact of presenting features on patient outcome.

**Methods**

Between January 1979 and December 2013, a total of 3355 subjects aged 0–18 years with previously untreated neuroblastoma were diagnosed in 27 AIEOP (Italian Association of Pediatric Hematology-Oncology) institutions and registered in the RINB. Of these, 280 (8.3%) had stage 4 s characteristics and were eligible for this study. Patients’ clinical records were reviewed to obtain details regarding the LTS arbitrarily defined as “major symptoms”: i) hepatomegaly, ii) dyspnea, and iii) organ dysfunctions.

**Diagnosis and diagnostic work-up**

Tumor diagnosis was based on the combination of clinical and biochemical data and adequate imaging. After 1985, the diagnosis was usually confirmed by histopathology. From 2000 onwards, histology was centrally reviewed on the basis of the INPC (International Neuroblastoma Pathology Classification) criteria [24]. The diagnostic work-up included imaging studies, local assay of urinary catecholamine metabolites, LDH and ferritin serum levels, and at least one bone marrow aspirate. After 1985, tumor specimens were evaluated for biologic features at a single reference laboratory.

**Treatment**

All patients received supportive care. Early resection of the primary tumor was encouraged, while late resection of a residual mass after tumor shrinkage was based on institutional decision. In this study, the term resection refers to radical resection of the primary tumor [25, 26]. Liver irradiation usually consisted of a total dose of 1.5 Gy divided over 3 consecutive days. The chemotherapeutic approach varied during the study period. Three treatment eras were identified (Additional file 1: Table S1). In the first era (1979–84), chemotherapy was administered independently of clinical presentation. In the second era (1985–1999), treatment was based on symptoms on presentation: in children without LTS a wait-and-see policy was encouraged, while patients with LTS received 2–4 courses of various drug associations. In the third era (2000–2013), patients were treated in accordance with the therapeutic guidelines of an ad hoc SIOPEN (International Society of Pediatric Oncology Europe Neuroblastoma) protocol; those with amplified MYCN were candidates for an intensive therapeutic approach [27].

**Statistical analyses**

Descriptive statistics are reported as absolute frequencies and percentages for qualitative variables, and as median values with their related interquartile range (IQR) for quantitative variables. To compare proportions between groups, Pearson’s chi-square and Fisher’s exact test, when appropriate, were applied. In the univariate analysis of each risk factor, progression-free survival (PFS) and overall survival (OS) were estimated by means of the Kaplan-Meier method, and differences between groups were assessed by means of the log-rank test. Survival estimates referred to the 10 years following diagnosis, and the related 95% confidence intervals (95%CI) were obtained by means of the Kalbfleisch and Prentice method. Finally, a multivariable Cox regression model was fitted in order to evaluate the combined effect of variables. In this analysis, only variables found to significantly affect PFS or OS were included in the model. All tests were two-tailed and a P value <.05 was considered statistically significant. All analyses were performed by means of Stata Statistical Software (Release 13.1, Stata Corporation, College Station, TX, USA).

**Results**

On reviewing the records of the 280 stage 4 s infants enrolled in the RINB, 12 were excluded because of insufficient data (n = 10) or unconfirmed stage (n = 2). Of the 268 patients evaluable for analyses, 26 were enrolled in the first, 116 in the second, and 126 in the third era (accounting for 7.2, 9.2 and 7.3% of patients diagnosed in the respective periods).

**Demographic and clinical features on presentation**

Patient features in the entire cohort and during the 3 eras are listed in Table 1. The prevalence of the main features in the three treatment eras were roughly comparable. Male sex prevailed (58.2%). Median age on diagnosis was 3 months (IQR range, 2–5) with 22.4% of patients diagnosed in the first month of life, followed by a gradual decrease (Fig. 1 plot A).

Seventeen patients (6.3%) were asymptomatic, as the tumor was detected by ultrasound examination performed in late pregnancy (n = 2) or during post-natal screening.
Table 1 Presenting features of 268 stage 4 s neuroblastoma patients

| Feature                                      | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|----------------------------------------------|--------------|-----------|-----------|-----------|---------|
| No. (%)                                      | 268 (100)    | 26 (9.7)  | 116 (43.3)| 126 (47.0)| 0.0501  |

Demographic and clinical features

Gender

|                  | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|------------------|--------------|-----------|-----------|-----------|---------|
| Male             | 156 (58.2)   | 17 (65.4) | 70 (60.3) | 69 (54.8) | 0.0501  |
| Female           | 112 (41.8)   | 9 (34.6)  | 46 (39.7) | 57 (45.2) |         |

Age, days. Median (IQR)

| Age, days | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|-----------|--------------|-----------|-----------|-----------|---------|
| 0–29      | 60 (22.4)    | 6 (23.1)  | 31 (26.7) | 23 (18.3) | 0.619   |
| 30–59     | 40 (14.9)    | 4 (15.4)  | 15 (12.9) | 16 (12.7) |         |
| 60–89     | 37 (13.8)    | 6 (23.1)  | 10 (8.6)  | 12 (9.5)  |         |
| 90–119    | 40 (14.9)    | 3 (11.5)  | 11 (9.5)  | 18 (14.3) |         |
| 120–365   | 91 (33.9)    | 7 (26.9)  | 37 (31.9) | 47 (37.3) |         |

Age, days

| Age, days | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|-----------|--------------|-----------|-----------|-----------|---------|
| 0–29      | 60 (22.4)    | 6 (23.1)  | 31 (26.7) | 23 (18.3) | 0.286   |
| 30–365    | 208 (77.6)   | 20 (76.9) | 85 (73.3) | 103 (81.7)|         |

Symptoms at presentation

| Symptoms at presentation | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|--------------------------|--------------|-----------|-----------|-----------|---------|
| None                     | 17 (6.3)     | 0         | 4 (3.5)   | 13 (10.3) | 0.039*  |
| Yes, minor               | 51 (19.0)    | 3 (11.5)  | 19 (16.4) | 29 (23.0) |         |
| Yes, major               | 200 (74.6)   | 23 (88.5) | 93 (80.2) | 84 (66.7) |         |
| Major symptoms           | 200 (74.6)   | 23 (88.5) | 93 (80.2) | 84 (66.7) | 0.107   |
| Hepatomegaly, yes        | 186 (69.4)   | 21 (80.8) | 85 (73.3) | 80 (63.5) | 0.073*  |
| Dyspnea, yes             | 52 (19.4)    | 4 (15.4)  | 25 (21.5) | 23 (18.2) | 0.699   |
| Organ dysfunction, yes   | 34 (12.7)    | 3 (11.5)  | 9 (78)    | 22 (17.5) | 0.073*  |

Combinations of major symptoms

| Combinations of major symptoms | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|--------------------------------|--------------|-----------|-----------|-----------|---------|
| No major symptoms or no symptom | 68 (25.4)    | 3 (11.5)  | 23 (19.8) | 42 (33.3) | 0.033*  |
| Organ dysfunction only         | 2 (0.8)      | 1 (3.9)   | 0         | 1 (0.8)   |         |
| Dyspnea ± Organ dysfunction    | 12 (4.5)     | 1 (3.9)   | 8 (6.9)   | 3 (2.4)   |         |
| Hepatomegaly ± Organ dysfunction | 146 (54.5)  | 18 (69.2) | 68 (58.6) | 60 (47.6) | 0.753*  |
| Hepatomegaly + Dyspnea ± Organ dysfunction | 40 (14.9) | 3 (11.5) | 17 (14.7) | 20 (15.9) |         |

Minor symptoms

| Minor symptoms | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|----------------|--------------|-----------|-----------|-----------|---------|
| Skin nodules, yes | 42 (15.7)    | 4 (15.4)  | 28 (24.1) | 10 (7.9)  | 0.002*  |
| Abdominal mass, yes | 34 (12.7)    | 1 (3.8)   | 12 (10.3) | 21 (16.7) | 0.139*  |
| Cervical mass, yes | 11 (4.1)     | 0         | 5 (4.3)   | 6 (4.8)   | 0.814*  |
| Neurologic symptoms, yes | 12 (4.5)  | 0         | 6 (5.2)   | 6 (4.8)   | 0.753*  |

Primary site

| Primary site | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|--------------|--------------|-----------|-----------|-----------|---------|
| Adrenal^     | 175 (65.3)   | 16 (61.5) | 77 (66.4) | 82 (65.1) | 0.272*  |
| Retroperitoneal ganglia | 49 (18.3)   | 4 (15.4)  | 16 (13.8) | 29 (23.0) |         |
| Thorax       | 22 (8.2)     | 3 (11.5)  | 11 (9.5)  | 8 (6.3)   |         |
| Neck         | 9 (3.4)      | 0         | 5 (4.3)   | 4 (3.2)   |         |
| Not identified | 13 (4.9)    | 3 (11.5)  | 7 (6.0)   | 3 (2.4)   |         |

Liver infiltration, yes

| Liver infiltration, yes | All patients | 1979–1984 | 1985–1999 | 2000–2013 | p       |
|------------------------|--------------|-----------|-----------|-----------|---------|
| yes                    | 230 (85.8)   | 22 (84.6) | 102 (87.9)| 106 (84.1)| 0.689*  |
(n = 15). This occurred in an increasing number of patients over the 3 eras (0, 3.5, and 10.3%, respectively; P = .039) (Table 1). Two hundred patients (74.6%) presented with at least one major symptom, the most frequent being hepatomegaly (n = 186; 69.4%), with decreasing incidence over the 3 eras (not significant), followed by dyspnea (n = 52; 19.4%), and at least one organ dysfunction (n = 34; 12.7%). (Table 1).

Other symptoms were: i) skin nodules (42 patients = 15.7%), with different incidence in the 3 eras (15.4% vs. 24.1% vs. 7.9%; P = .002); ii) abdominal mass (in the absence of hepatomegaly) (34 patients = 12.7%), with decreasing incidence over the study period (not significant); iii) cervical mass (11 patients = 4.1%); and iv) neurological abnormalities (12 patients = 4.5%) (Table 1).

The primary tumor site was most often identified in the adrenal (n = 175; 65.3%), including 9 bilateral cases (3.4%), followed by retroperitoneal ganglia (n = 49; 18.3%), thorax (n = 22; 8.2%), and neck (n = 9; 3.4%). In 13 patients (4.9%), a primary tumor was not identified. Hepatic involvement was documented in 230 patients (85.8%). Bone marrow infiltration was detected on light microscopy examination in 111 patients (41.4%) (Table 1).

**Table 1 Presenting features of 268 stage 4 s neuroblastoma patients (Continued)**

| Feature | All patients | Treatment era | p |
|---------|--------------|---------------|---|
|         | No. (%)      | 1979–1984     | 1985–1999 | 2000–2013 |
| Positive bone marrow cytology, yes | 111 (41.4) | 8 (30.8) | 42 (36.2) | 61 (48.4) | 0.082* |
| Biochemical, biologic and histologic features | | | | |
| Urine VMA (222 tested) | | | | |
| Normal | 59 (26.6) | 2 (8.3) | 22 (22.9) | 35 (34.3) | 0.019 |
| Elevated | 163 (73.4) | 22 (91.7) | 74 (77.1) | 67 (65.7) |  |
| Urine HVA (112 tested) | | | | |
| Normal | 18 (16.1) | 0 | 2 (6.1) | 16 (21.0) | 0.149* |
| Elevated | 94 (83.9) | 3 (100) | 31 (93.9) | 60 (79.0) |  |
| Serum LDH (227 tested) | | | | |
| Normal | 131 (57.7) | 7 (87.5) | 78 (75.7) | 46 (39.7) | <0.001* |
| Elevated | 96 (42.3) | 1 (12.5) | 25 (24.3) | 70 (60.3) |  |
| Serum ferritin (193 tested) | | | | |
| Normal | 116 (60.1) | 5 (100) | 55 (61.1) | 56 (57.1) | 0.176* |
| Elevated | 77 (39.9) | 0 | 35 (38.9) | 42 (42.9) |  |
| MYCN gene (183 tested) | | | | |
| Normal | 168 (91.8) | 0 | 61 (91.0) | 107 (92.2) | 0.776 |
| Amplified | 15 (8.2) | 0 | 6 (9.0) | 9 (7.8) |  |
| 1p chromosome (138 tested) | | | | |
| Normal | 110 (79.7) | 1 (100) | 32 (76.2) | 77 (81.1) | 0.603* |
| Deleted | 28 (20.3) | 0 | 10 (23.8) | 18 (18.9) |  |
| DNA index (121 tested) | | | | |
| Aneuploid | 80 (66.1) | 0 | 24 (60.0) | 56 (69.1) | 0.318 |
| Di-tetraploid | 41 (33.9) | 0 | 16 (40.0) | 25 (30.9) |  |
| Histology by INPC (75 tested) | | | | |
| Favorable | 69 (92.0) | 0 | 0 | 69 (92.0) | – |
| Unfavorable | 6 (8.0) | 0 | 0 | 6 (8.0) |  |

Abbreviations. IQR interquartile range, VMA vanillylmandelic acid, HVA homovanillic acid, LDH lactate dehydrogenase, INPC International Neuroblastoma Pathology Classification
# patients may have more than one symptom
* Fisher exact test
^, 9 (3.4%) bilateral adrenal primary
Biochemical, biologic and histopathologic data
Vanillylmandelic acid (VMA) urinary excretion was found elevated in 163 of 222 patients tested (73.4%); the number of cases with abnormal values decreased significantly over the 3 eras \( (P = .019) \). Homovanillic acid (HVA) excretion was found elevated in 94 of 112 patients tested (83.9%). The serum level of LDH was found elevated in 96 out of 227 patients (42.3%), with significant differences among the 3 groups (12.5% vs. 24.3% vs. 60.3%) \( (P < .001) \). Serum ferritin was found elevated in 77 out of 193 patients (39.9%).

Biologic features were evaluated in patients in the second and third eras only. MYCN gene was amplified in 15 out of 183 tumors (8.2%). Chromosome 1p was found deleted in 28 of 138 tested tumors (20.3%) and DNA index was di- or tetraploid in 41 of 121 tumors tested (33.9%). In the third era, histopathology of 75 tumors was centrally evaluated with 69 being rated favorable (92.0%) (Table 1).

Treatment, clinical course and outcome
Details of clinical course and outcome in the 3 patient groups are reported in Fig. 2.

First treatment era (1979–1984)
Twenty-five/26 patients (96.2%) received upfront chemotherapy. One patient underwent hepatic irradiation plus primary resection. Eight patients (all treated with chemotherapy) showed disease progression 2–18 months (median, 7) after diagnosis, yielding a 10-year PFS of 69.2% (95% CI, 47.8–83.3). Six patients died at
4–24 months (median, 9), yielding a 10-year OS of 76.9% (95% CI, 55.7–88.9) (Fig. 3, plot A and B).

**Second treatment era (1985–1999)**

Of 116 patients, 74 (63.8%) presented without LTS. The wait-and-see approach was adopted in 37 (31.9%), 18 of whom developed disease progression; 11 of these died, including 3 with MYCN gene amplification. The other 37 patients (31.9%) underwent resection of the primary as the only therapy: 2 died of surgery-related complications, and 9 developed disease progression, one of whom died (Fig. 2). A Silastic patch to allow abdominal enlargement was positioned in 3 patients, and was successful in two.

The remaining 42 patients (36.2%) presented with LTS. Thirty-six (31.0%) underwent upfront chemotherapy (plus primary resection in 8), 17 of whom developed disease progression (11 died); the remaining 6 (5.2%) were treated with hepatic irradiation (plus resection of the primary in one); 4 of the 6 showed disease progression and 3 died (Fig. 2). Three/42 patients (7.1%) with amplified MYCN, who were treated with chemotherapy \( (n = 1) \) or tumor resection \( (n = 2) \), are alive.

Overall, disease progression occurred in 43 patients 0–43 months (median, 3) after diagnosis, yielding an estimated 10-year PFS of 62.3% (95% CI, 52.7–70.5) (Fig. 3, plot A). A total of 26 deaths
occurred after 0–115 months (median, 4), including 2 surgery-related, yielding a 10-year OS of 77.2% (95% CI, 68.3–83.9) (Fig. 3, plot B).

**Third treatment era (2000–2013)**

Of 126 patients, 9 (7.1%) had MYCN gene amplification. Of the 117 (93.4%) without MYCN amplification, 71 (56.3%) had no LTS on diagnosis; 32 (25.4%) of these underwent observation; disease progression ensued in 13 patients, 2 of whom died. The remaining 39 (31.0%) underwent primary resection, which was followed by disease progression in 5 cases (1 died). The 46 patients (30.9%) with LTS received upfront chemotherapy (plus tumor resection in 7); 3 died of chemotherapy-related complications, and 12 suffered disease progression, 6 of whom died (total: 9 deaths). Of the 9 patients with amplified MYCN gene, two received standard chemotherapy (with one fatal progression), and 7 intensive chemotherapy (with one fatal progression) (Fig. 2).

In summary, 32 patients suffered progression, yielding a 10-year PFS of 74.9% (95% CI, 66.2–81.6) (Fig. 3, plot A) and 11 patients died. Another three chemotherapy-related deaths occurred, bringing the overall death count to 14 (10-year OS = 89.7%; 95% CI, 82.9–93.9) (Fig. 3, plot B).

**Patient outcome and prognostic factors**

Table 2 reports the 10-year PFS and OS for the entire study population, by era and clinical and biologic risk factors. PFS was 68.2% (95% CI, 62.1–73.5) in the whole cohort, without significant differences among the 3 eras, while OS was 82.7% (95% CI, 77.4–86.8) in the entire cohort and was better in the third era (89.7%; 95% CI, 82.9–93.9) than in the previous two (76.9 and 77.2%, respectively) ($P = .041$, test for trend) (Fig. 2, plot A and B). Gender did not influence PFS, while OS was better in females (88.5 vs 78.5%; $P = 0.018$). Patients diagnosed in the first month of life (0–29 days) did worse than those diagnosed subsequently (OS, 73.0% vs 85.5%; $P = 0.006$). When survival estimates were stratified by month of diagnosis (Fig. 2) the differences among groups were not significant ($P = 0.067$, test for trend), with patients diagnosed in the 2nd, 3rd and 4th months of life showing similar
| Treatment era          | No. (%) | No. (%) | % (95% CI) | p       | No. (%) | % (95% CI) | p       |
|------------------------|---------|---------|------------|---------|---------|------------|---------|
| 1979–1984              | 26 (9.7)| 8 (30.8)| 69.2 (47.8–83.3) | 0.217#  | 6 (23.1)| 76.9 (55.7–88.9) | 0.041#  |
| 1985–1999              | 116 (43.3)| 43 (37.1)| 62.3 (52.7–70.5) | 26 (22.4)| 77.2 (68.3–83.9) |
| 2000–2013              | 126 (47)| 32 (25.4)| 72.4 (62.4–80.1) | 14 (11.1)| 89.7 (82.9–93.9) |

| Gender                  |         |         |            |         |         |            |         |
|-------------------------|---------|---------|------------|---------|---------|------------|---------|
| Male                    | 156 (58.2)| 52 (33.3)| 65.4 (57.1–72.5) | 0.24    | 34 (21.8)| 78.5 (71.1–84.2) | 0.018   |
| Female                  | 112 (41.8)| 31 (27.7)| 72.1 (62.7–79.5) | 12 (10.7)| 88.5 (80.3–93.4) |

| Age, days               |         |         |            |         |         |            |         |
|-------------------------|---------|---------|------------|---------|---------|------------|---------|
| 0–29                    | 60 (22.4)| 23 (38.3)| 59.8 (45.7–71.4) | 0.058   | 17 (28.3)| 73.0 (59.7–82.5) | 0.006   |
| 30–365                  | 208 (77.6)| 60 (28.8)| 70.7 (64.0–76.4) | 29 (19.9)| 85.3 (79.6–89.7) |

| Symptoms at presentation |         |         |            |         |         |            |         |
|--------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                     | 17 (6.3)| 1 (5.9)| 94.1 (65.0–99.2) | < 0.001# | 0 100  | < 0.001# |
| Yes, minor               | 51 (19.0)| 9 (17.7)| 82.4 (68.8–90.4) | 2 (3.9)| 96.0 (84.9–99.0) |
| Yes, major               | 200 (74.6)| 73 (36.5)| 62.4 (55.1–68.8) | 44 (22.0)| 77.9 (71.3–83.2) |

| Hepatomegaly            |         |         |            |         |         |            |         |
|-------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                    | 82 (30.6)| 15 (18.3)| 81.7 (71.5–88.5) | 0.004   | 4 (4.9)| 94.7 (86.5–98.0) | < 0.001 |
| Yes                     | 186 (69.4)| 68 (36.6)| 62.2 (54.6–68.9) | 42 (22.6)| 77.4 (70.6–82.9) |

| Dyspnea                 |         |         |            |         |         |            |         |
|-------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                    | 216 (80.6)| 57 (26.4)| 73.4 (66.9–78.8) | < 0.001| 24 (11.1)| 88.4 (83.1–92.2) | < 0.001 |
| Yes                     | 52 (19.4)| 26 (50)| 47.1 (32.5–60.3) | 22 (42.3)| 59.5 (44.9–71.4) |

| Organ dysfunctions      |         |         |            |         |         |            |         |
|-------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                    | 234 (87.3)| 72 (30.8)| 68.8 (62.4–74.4) | 0.714   | 36 (15.4)| 84.0 (78.4–88.2) | 0.032   |
| Yes                     | 34 (12.7)| 11 (32.4)| 64.5 (44.3–78.9) | 10 (29.4)| 73.5 (55.3–85.3) |

| Combinations of major symptoms |         |         |            |         |         |            |         |
|--------------------------------|---------|---------|------------|---------|---------|------------|---------|
| No major symptoms              | 68 (25.4)| 10 (14.7)| 85.3 (74.4–91.8) | < 0.001| 2 (2.9)| 97.0 (88.6–99.2) | < 0.001 |
| Hepatomegaly ± Organ dysfunction| 146 (54.5)| 47 (32.2)| 67.4 (59.0–74.4) | 22 (15.1)| 84.4 (77.2–89.5) |
| Dyspnea ± Organ dysfunction    | 12 (4.5)| 5 (41.7)| 58.3 (27.0–80.1) | 2 (16.7)| 83.3 (48.2–95.6) |
| Hepatomegaly ± Dyspnea (±Organ dysfunction) | 40 (14.9)| 21 (52.5)| 43.0 (26.3–58.7) | 20 (50) | 52.4 (36.0–66.4) |
| Organ dysfunction only        | 2 (0.8)| 0 100  | 0 100  |         |         |            |         |

| Abdominal mass              |         |         |            |         |         |            |         |
|-----------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                         | 234 (87.3)| 77 (32.9)| 66.1 (59.5–71.9) | 0.078   | 45 (19.2)| 80.6 (74.7–85.2) | 0.023   |
| Yes                          | 34 (12.7)| 6 (17.6)| 82.4 (64.9–91.7) | 1 (2.9)| 97.1 (80.9–99.6) |

| Cervical mass               |         |         |            |         |         |            |         |
|-----------------------------|---------|---------|------------|---------|---------|------------|---------|
| None                         | 257 (95.9)| 80 (31.1)| 68.0 (61.8–73.4) | 0.797   | 44 (17.1)| 82.8 (77.5–87.0) | 0.896   |
| Yes                          | 11 (4.1)| 3 (27.3)| 72.7 (37.1–90.3) | 2 (18.2)| 77.9 (35.4–94.2) |

| Skin nodules                |         |         |            |         |         |            |         |

**Table 2 PFS and OS by risk factors of 268 stage 4 s neuroblastoma patients**
Table 2 PFS and OS by risk factors of 268 stage 4 s neuroblastoma patients (Continued)

| Entire cohort | Progressions | No. (%) | 10-yr PFS | % (95% CI) | Deaths | No. (%) | 10-year OS | % (95% CI) |
|---------------|--------------|---------|-----------|------------|--------|---------|------------|------------|
| No. (100)     | 268 (100)    | 83 (31) | 68.2 (62.1–73.5) | 46 (17.2) | 82.7 (77.4–86.8) |
| No. (%)       | 83 (31)      | 68.2 (62.1–73.5) | 46 (17.2) | 82.7 (77.4–86.8) |
| No. (%)       | 268 (100)    |          |           |            |        |         |            |            |

Neurologic symptoms

| None | 226 (84.3) | 64 (28.3) | 70.7 (64.1–76.3) | 0.029 | 36 (15.9) | 83.9 (78.2–88.3) |
| Yes | 42 (15.7) | 19 (45.2) | 54.8 (38.7–68.3) | 10 (23.8) | 75.9 (59.7–86.2) |

Primary site

| Adrenal | 175 (65.3) | 59 (33.7) | 65.8 (58.2–72.3) | 0.609 | 33 (18.8) | 80.4 (73.5–85.8) |
| Abdomen | 49 (18.3) | 11 (22.5) | 75.0 (58.7–85.6) | 7 (14.3) | 87.8 (74.8–94.3) |
| Thorax | 22 (8.2) | 7 (31.8) | 68.2 (44.6–83.4) | 1 (4.5) | 95.5 (71.9–99.4) |
| Neck | 9 (3.4) | 3 (33.3) | 66.7 (28.2–87.8) | 2 (22.2) | 71.1 (23.3–92.3) |
| Not detected | 13 (4.9) | 3 (23.1) | 76.9 (44.2–91.9) | 3 (23.1) | 76.9 (44.2–91.9) |

Primary site thorax

| No | 246 (91.8) | 76 (30.9) | 68.9 (62.7–74.4) | 0.944 | 45 (18.3) | 81.5 (75.8–85.9) |
| Yes | 22 (8.2) | 7 (31.8) | 68.2 (44.6–83.4) | 1 (4.5) | 95.5 (71.9–99.4) |

Liver infiltration

| No | 38 (14.2) | 7 (18.4) | 81.6 (65.2–90.8) | 0.084 | 0 | 100 |
| Yes | 230 (85.8) | 76 (33) | 65.9 (59.3–71.8) | 46 (20) | 79.8 (73.7–84.5) |

Positive bone marrow cytology

| No | 157 (58.6) | 49 (31.2) | 68.3 (50.3–75.0) | 0.753 | 28 (17.8) | 81.9 (74.9–87.2) |
| Yes | 111 (41.4) | 34 (30.6) | 66.7 (58.7–73.5) | 18 (16.2) | 83.6 (74.6–89.6) |

Urine VMA (222 tested)

| No | 59 (26.6) | 16 (27.1) | 72.4 (59.0–82.1) | 0.381 | 5 (8.5) | 91.5 (80.8–96.4) |
| Yes | 163 (73.4) | 53 (32.5) | 66.7 (58.7–73.5) | 27 (16.6) | 83.9 (77.2–88.7) |

Urine HVA (112 tested)

| No | 18 (16.1) | 4 (22.2) | 77.8 (51.1–91.0) | 0.253 | 2 (11.1) | 88.9 (62.4–97.1) |
| Yes | 94 (83.9) | 33 (35.1) | 64.0 (53.0–73.0) | 12 (12.8) | 88.3 (79.9–93.3) |

Serum LDH (227 tested)

| No | 131 (57.7) | 33 (25.2) | 74.6 (66.2–81.2) | 0.055 | 14 (10.7) | 89.1 (82.3–93.4) |
| Yes | 96 (42.3) | 35 (36.5) | 60.9 (49.6–70.4) | 20 (20.8) | 78.8 (68.1–86.2) |

Serum Ferritin (193 tested)

| No | 116 (60.1) | 34 (29.3) | 70.5 (61.2–77.9) | 0.859 | 15 (12.9) | 87.0 (79.4–92.0) |
| Yes | 77 (39.9) | 22 (28.6) | 70.0 (58.1–79.1) | 13 (16.9) | 82.8 (72.1–89.6) |

MYCN gene (183 tested)

| No | 168 (91.8) | 53 (31.5) | 67.1 (59.1–73.9) | 0.673 | 21 (12.5) | 86.8 (79.9–91.5) |
| Yes | 15 (8.2) | 6 (40) | 66.0 (31.8–79.7) | 5 (33.3) | 66.7 (37.5–84.6) |

1p chromosome (138 tested)

| No | 110 (79.7) | 31 (28.2) | 71.3 (61.7–78.8) | 0.141 | 10 (9.1) | 89.1 (79.2–94.4) |
| Yes | 28 (20.3) | 13 (46.4) | 50.8 (29.7–68.5) | 10 (35.7) | 67.9 (47.3–81.8) |

DNA index (121 tested)

| Aneuploid | 80 (66.1) | 24 (30) | 70.0 (58.7–78.8) | 0.734 | 3 (8.3) | 96.3 (88.8–98.8) |
| Di-tetraploid | 41 (33.9) | 14 (34.2) | 65.8 (49.1–78.1) | 10 (24.4) | 70.8 (49.2–84.5) |

Histology INPC (75 tested)
intermediate” outcomes, and those diagnosed after the 4th month having a better outcome (Fig. 1, plot B).

The presence of major symptoms on diagnosis significantly affected PFS and OS. The combination of hepatomegaly and dyspnea +/- organ dysfunction was associated with the lowest PFS and OS (43.0 and 52.4%, respectively) (Table 2 and Fig. 3, plot C and D). A significant association with better OS, but not better PFS, was found

### Table 2: PFS and OS by risk factors of 268 stage 4 s neuroblastoma patients (Continued)

| Table 2 | PFS and OS by risk factors of 268 stage 4 s neuroblastoma patients (Continued) |
|---------|--------------------------------------------------------------------------------|
| Entire cohort | Progressions | 10- yrs PFS | p | Deaths | 10-year OS | p |
| No. (%) | No. (%) | % (95% CI) | No. (%) | % (95% CI) |
| Favourable | 69 (92) | 16 (23.2) | 73.9 (59.3–83.9) | 0.78 | 5 (7.3) | 94.2 (85.3–97.8) | 0.147 |
| Unfavourable | 6 (8) | 2 (33.3) | 66.7 (19.5–90.4) | 0.333 | 2 (33.3) | 66.7 (19.5–90.4) |
| Upfront treatment | | | | | | |
| Observation | 69 (25.8) | 31 (44.9) | 55.1 (42.6–65.9) | 0.015 | 13 (18.8) | 81.1 (69.7–88.6) | <0.001 |
| Chemotherapy | 90 (33.6) | 29 (32.2) | 66.8 (55.8–75.6) | 0.461 | 23 (25.6) | 73.2 (62.2–81.5) |
| Resection of primary | 76 (28.4) | 14 (18.4) | 81.1 (70.2–88.3) | 0.032 | 4 (5.3) | 94.3 (85.4–97.9) |
| Chemotherapy + Resection of primary | 19 (7.1) | 4 (21.1) | 76.6 (48.0–90.7) | 0.123 | 2 (10.5) | 94.7 (68.1–99.2) |
| Radiotherapy + Other | 14 (5.2) | 5 (35.7) | 64.3 (34.3–83.3) | 0.123 | 4 (28.6) | 71.4 (40.6–88.2) |

### Table 3: Multivariable analysis in 266* patients with stage 4 s neuroblastoma

| Table 3 | Multivariable analysis in 266* patients with stage 4 s neuroblastoma |
|---------|--------------------------------------------------------------------|
| No. (%) | 266 | PFS | Multivariate | OS | Multivariate |
| Univariate | HR (95% CI) | p | HR (95% CI) | p | HR (95% CI) | p |
| Major symptoms | | | | | | |
| None | 68 (25.4) | 1 | <0.001 | 1 | <0.001 | 1 | <0.001 | 1 | <0.001 |
| Dyspnea ± Organ dysfunction | 12 (4.5) | 3.5 (1.2–10.2) | 3.1 (1.1–9.3) | 5.9 (0.8–41.6) | 4.6 (0.6–33.2) |
| Hepatomegaly ± Organ dysfunction | 146 (54.5) | 2.4 (1.2–4.7) | 2.2 (1.1–4.3) | 5.3 (1.2–22.6) | 4.6 (1.1–19.8) |
| Hepatomegaly + Dyspnea (± Organ dysfunction) | 40 (14.9) | 5.5 (2.6–11.7) | 5.5 (2.6–11.8) | 24.4 (5.7–104.4) | 24.1 (5.6–103.4) |
| Treatment era | | | | | | |
| 1979–1984 | 25 (9.4) | 1 | 0.202# | 1 | 0.355# | 1 | 0.041# | 1 | 0.049# |
| 1985–1999 | 116 (43.6) | 1.3 (0.6–2.7) | 1.4 (0.7–3.0) | 1 | 0.4–2.4 | 1 | 0.5–2.8 |
| 2000–2013 | 125 (47.0) | 0.8 (0.4–1.8) | 0.9 (0.4–2.0) | 0.5 (0.2–1.3) | 0.5 (0.2–1.3) |
| Gender | | | | | | |
| Male | 154 (57.9) | 1 | 0.209 | 1 | 0.707 | 1 | 0.013 | 1 | 0.091 |
| Female | 112 (42.1) | 0.8 (0.5–1.2) | 0.8 (0.5–1.3) | 0.5 (0.2–0.9) | 0.6 (0.3–1.1) |
| Age, days | | | | | | |
| 0–29 | 60 (22.6) | 1 | 0.077 | 1 | 0.637 | 1 | 0.011 | 1 | 0.639 |
| 30–365 | 206 (77.4) | 0.6 (0.4–1.0) | 0.9 (0.5–1.5) | 0.4 (0.2–0.8) | 0.9 (0.4–1.6) |
| Abdominal mass | | | | | | |
| None | 232 (87.2) | 1 | 0.052 | 1 | 0.751 | 1 | 0.006 | 1 | 0.813 |
| Yes | 34 (12.8) | 0.5 (0.2–1.1) | 1.2 (0.4–3.6) | 0.1 (0.0–1.0) | 0.7 (0.1–8.4) |

Abbreviations: PFS progression-free survival, OS overall survival, HR hazard ratio, CI confidence interval.

*; excluding 2 patients presenting with organ dysfunction as only major symptom

#; test for trend
in the case of an abdominal mass in the absence of hepatomegaly (OS, 97.1% vs 80.6%; \( P = 0.023 \)), absence of liver infiltration (OS, 100% vs 79.8%; \( P = 0.004 \)), normal levels of serum LDH (OS, 89.1% vs 78.8%; \( P = 0.031 \)), and absence of abnormalities of biologic features, in particular MYCN gene (OS, 86.8% vs 66.7%; \( P = 0.021 \)). 1p chromosome (OS, 89.1% vs 67.9%; \( P < 0.001 \)) and DNA index (OS, 96.3% vs 70.8%; \( P < 0.001 \)) (Table 2).

Patients who underwent early resection of the primary tumor, either alone or combined with chemotherapy, had a more favorable outcome (PFS, 81.1 and 76.6%; OS, 94.3 and 94.7%, respectively) than those who were initially observed (PFS 55.1%; OS, 81.1%), those who received upfront chemotherapy (PFS, 66.8%; OS, 73.2%), and those who were treated with liver irradiation, alone or with other modalities (PFS, 64.3%; OS, 71.4%) (\( P < 0.001 \)) (Table 2).

Multivariable analysis of the combined effect of the different risk factors was limited to evaluation of the clinical and demographic data significantly associated with outcome in the univariate analysis (Table 3). It was therefore carried out in 266/268 patients, as 2 who had organ dysfunction as the only major symptom had no events, and thus were not suitable for inclusion in the model. The only factor that independently affected the risk of disease progression and/or death was the presence of major symptoms. Compared to subjects without major symptoms, those who had the combination of hepatomegaly and dyspnea \( \pm \) organ dysfunction had a 5.5-fold higher risk of progression (95% CI, 2.6–11.8) and a 24.1-fold higher risk of death (95% CI, 5.6–103.4) (Table 3). Patients with hepatomegaly \( \pm \) organ dysfunction and those with dyspnea \( \pm \) organ dysfunction had 3.1 (95% CI, 1.1–9.3) and 2.2 (95% CI, 1.1–4.3) -fold higher risks of progression and 4.6 (95% CI, 0.6–33.2) and 4.6 (95% CI, 1.1–19.8) -fold higher risk of death, respectively, than those without major symptoms (Table 3).

**Discussion**

Overall, we found few significant differences in the presenting features of patients diagnosed in the successive periods, the main one regarding the number of patients who presented without symptoms; this was chiefly because of the increasing use of ultrasound in pregnancy and early life.

As in one published series [12], but not in others [11, 13], male gender prevailed. Females, however, had a significantly better outcome, although this previously unreported finding was not confirmed on multivariate analysis. Our data confirm the worse outcome of patients diagnosed in the first 2 months. However, the highest number of deaths occurred in the first month of life, while comparable numbers of deaths occurred among those diagnosed in the 2nd, 3rd, and 4th months.

The presence of any major symptom was associated with lower OS (77.4% for hepatomegaly, 59.5% for dyspnea; 73.5% for organ dysfunctions). However, it was the association of hepatomegaly and dyspnea that drastically lowered OS to 52.4%; this was confirmed on multivariate analysis. Patients without major symptoms usually presented in good condition and did well (OS, 96.0%). The absence of symptoms in the 17 patients whose disease was discovered by means of ultrasound was associated with a 100% OS.

The commonest primary tumor site was adrenal, and bilateral involvement was observed in 9 cases. The high frequency of bilateral involvement (5.1% vs 0.2% in the entire RINB population; unpublished) has previously been reported [12–14], and been considered an expression of the multifocal character of stage 4 s disease [28]. Retroperitoneal ganglia were four times less likely to be the primary site. In these instances, the tumor mass, by definition, crossed the midline, and this would have excluded these patients from enrollment as stage 4 s. However, the fact that similar patients were included in other series [10, 11, 13], and that their outcome was comparable to that of our patients with adrenal primary tumors (87.8% vs 80.4%; not significant) justifies their inclusion. On the other hand, the concept of midline-crossing no longer appears in the recent INRG (International Neuroblastoma Risk Group) definition [3].

Abnormal biologic features did influence patient outcome. MYCN gene amplification was found in 8.2% of the 183 patients tested, a lower figure than in infants with stage 4 disease and older patients [14, 18, 22]. Although the 86.8% OS of patients with a normal MYCN gene was significantly better than the 66.7% OS of patients with an amplified gene (\( P = 0.021 \)), 10 of 15 patients with abnormal MYCN survived, including 3 of the 6 who received standard chemotherapy or underwent primary resection as the only therapy. Similar results have previously been reported by other investigators, who have hypothesized that the biology of some MYCN-amplified favorable tumors differs from that of advanced-stage tumors [29, 30]. Patients with amplified MYCN may have gained some advantage from an aggressive therapeutic approach, as only one of the 7 so treated died of disease. This supports the data of a recent SIOPEN study [27]. Both abnormalities of 1p chromosome and a di/tetraploid DNA index were associated with worse OS (67.9% vs 89.1; \( P < .001 \) and 70.8% vs 96.3%; \( P = .001 \)), confirming previous data [11–14].

The influence of therapeutic modalities on outcome was not easily assessable. Patients assigned to a wait-and-see policy were free from major symptoms on presentation. Nevertheless, their survival was no better than that of the overall population (81.1% vs 81.5%); indeed, 45% of them eventually suffered disease progression and 19% died.
Whether administering upfront chemotherapy to these patients would have reduced the number of progressions and deaths remains unclear. With the exception of the first era, it was the presence of major symptoms on presentation and/or the evidence of rapid disease progression that led clinicians to initiate chemotherapy. This was not always life-saving, as these patients eventually had a low survival probability (73.2%).

Overall, the chance of cure for our stage 4 s neuroblastoma patients did improve over time, reaching a survival probability of 89.7%, which is close to the rates reported in recent series [13, 14]. The OS of patients of the first 2 eras was very close (76.9% vs 77.2%). However, it should be noted that no fatal progression was recorded in patients of the first treatment era, suggesting that, in the initial years of the study, some critical patients might have succumbed without reaching oncologic attention. Patients of the third treatment era did better. The following reasons may partially account for this result. First, the majority of asymptomatic patients (all of whom survived) belonged to this group. Second, the prevalence of hepatomegaly was lower and that of abdominal tumors was higher in later patients, both of which are features associated with a favorable outcome. Third, patients with amplified MYCN gene did better when they underwent aggressive therapy, which was administered to later patients only. Finally, enrollment of the third era patients in a large international SIOPEN study may have meant that they underwent a better management strategy.

Patients who underwent early primary tumor resection, either as the only therapy or in association with chemotherapy, did very well (OS, 94.3 and 94.7%, respectively), supporting the hypothesis that primary resection is associated with favorable outcome [31, 32]. However, as patients undergoing early primary tumor resection usually presented in good condition, their outcome did not come as a surprise. Indeed, with the exception of the 2 surgery-related deaths, which occurred in the middle years of the study, operations were usually performed safely. Whether resection of the primary tumor may confer a real survival advantage remains a matter of debate [26]. Patients in whom radiotherapy was part of the treatment did poorly, as it was usually undertaken in severely ill patients (OS, 71.4%).

Conclusions
Raising the cure rate above the currently achievable 90% is a challenge for pediatric oncologists. The main obstacle to full patient cure is constituted by the association of hepatomegaly and dyspnea. In these patients, symptom progression can be overwhelmingly rapid and frustrate “traditional” therapy. Saving these patients could possibly depend on the timely use of surgical techniques that require specific operator experience. The positioning of a silastic patch in the case of life-threatening abdominal expansion is an established procedure [33, 34]. Intra-arterial liver chemoembolization has recently been attempted with success in infants who fail to respond to chemotherapy [35, 36]. Finally, liver transplant has proved life-saving in some patients [37, 38]. A sequential treatment algorithm based on initial tumor behavior and response to therapy has been proposed by Weintraub et al.[39] According to this, chemotherapy should be reserved for patients who present with, or develop, a rapid increase in abdominal girth, especially when this is associated to respiratory distress. Non-responders should be considered for immediate liver chemoembolization. Liver transplantation could be undertaken in the event of failure, but must be carried out in the few institutions with specific expertise.

The establishment of a well-organized network of centers that deal with high-risk neuroblastoma patients is a prerequisite to the implementation of such a strategy. Identifying these centers through the European Reference Networks of the European Commission (ec.europa.eu/health/ern_en) is an important step in this direction. Stage 4 s patients with risk features should be identified early and, in the event of poor response to initial therapy, promptly referred to a dedicated institution.

Appendix
The following Italian institutions participated in this study (with main investigators):
IRCSS Istituto Giannina Gaslini, Genova (Bruno De Bernardi, Riccardo Haupt, Alberto Garaventa, Anna Rita Gigliotti, Stefano Avanzini, Claudio Granata, Angela Rita Sementa, Katia Mazzocco); Bambino Gesù Children’s Hospital, Roma (Aurora Castellano, Alessandro Inserra); Department of Pediatric Hematology-Oncology, University Hospital, Catania (Andrea Di Cataldo); Department of Woman and Children’s Health, University of Padova, Padova (Elisabetta Viscardi, Giovanni Cecchetto); Division of Pediatric Oncology, Istituto Nazionale Tumori, Milano (Marta Podda, Roberto Luksch); Hemato-Oncology Unit, S.Osola Malpighi Policlinic, Bologna (Fraia Melchionda); Department of Pediatrics, University La Sapienza, Roma (Alessandra de Grazia, Anna Clerico); Department of Pediatrics, University of Palermo, Palermo (Paolo D’Angelo, Fortunato Siracusa); Department of Hematology-Oncology, Regina Margherita Children’s Hospital, Torino (Elisa Tirtei, Maurizio Bianchi); Oncology Unit, Burlo Garofalo Children’s Hospital, Trieste (Andrea Giulio Zanazzo, Marco Rabusin); Paediatric Surgery Unit, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano (Anna Maria Fagnani); Santobono-Pausilipon Children’s Hospital, Napoli (Simona Vetrella); Department of Pediatrics, Civic Hospital, Bergamo (Massimo Provenzi); Department of Pediatrics,
University Hospital, Bari (Francesco De Leonardis); Department of Pediatrics, Civic Hospital, Brescia (Carmelita D’Ippolito, Fabian Schumacher); Anna Meyer Children’s Hospital, Firenze (Annalisa Tondo, Angela Tamburini); Department of Pediatric Haematology-Oncology, Agostino Gemelli Hospital, Roma (Stefano Mastrangelo); Pediatric Microcitemic Hospital, Cagliari (Antonella Nonnis, Rosa Maria Mura); Pediatric Oncology-Hematology, University Hospital, Verona (Simone Cesaro); Paediatric Hematology-Onco

Additional file

Additional file 1: Table S1. Outlines of therapy for stage 4 s neuroblastoma patients (DOCX 16 kb)

Abbreviations

AIEOP: Italian Association of Pediatric Hematology-Oncology;
INPC: International Neuroblastoma Pathology Classification;
INRG: International Neuroblastoma Risk Group; INRGSS: International Neuroblastoma Staging System; NSIS: International Neuroblastoma Staging System; RINB: Italian Neuroblastoma Registry; SIOPEN: International Society of Pediatric Oncology Europe Neuroblastoma

Acknowledgments

The authors thank Sonia Scaramuccia for her excellent secretarial assistance and Barbara Galleni for data management, Prof. Stefano Parodi for his thoughtful suggestions concerning statistical analyses, and Prof. Bernard Patrick for revising the English language of the paper. The authors are deeply grateful to the families who allowed the use of their children’s data, and the numerous doctors and nurses who contributed to patient treatment and data review.

Funding

This work was supported by the Associazione OPEN, Napoli, and Fondazione Italiana per la Lotta al Neuroblastoma, Genova, Italy. The co-authors GE, ARG and KM were recipients of grants provided by Fondazione Italiana per la Lotta al Neuroblastoma.

Availability of data and materials

Data are available to the Editor.

Authors’ contributions

BEIB, AG, KM, PW, ARG and RH prepared the study design and wrote the paper. GE and RH provided the statistical data and carried out the final analyses. ADC, EV, MGP, AC, PDA, ET, FM, SV, FDL, CDI, AT and AN provided clinical data on the patients of their respective institutions. KM was responsible for the biological studies. All the authors approved the final manuscript as submitted and take full responsibility for the manuscript itself.

Ethics approval and consent to participate

The RINB structure and protocol was approved by all the ethics committees of each participating center as a retrospective and prospective observational study. To be enrolled in the RINB, an informed consent form had to be signed by patients’ parents or guardians. For this reason, no specific further consent for this retrospective study needed to be sought. The RINB database is located at the secure Italian Inter-University Consortium CINECA headquar

Competing interests

The authors declare that they have no competing interests.

Publisher’s Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

1Department of Hematology-Oncology, IRCCS Istituto Giannina Gaslini, Via Gaslini S 1, 16147 Genova, Italy. 2Department of Pediatric Hematology-Oncology, University Hospital, Padova, Italy. 3Department of Oncology, Istituto Nazionale Tumori, Milan, Italy. 4Department of Pediatric Oncology, Bambino Gesù Children’s Hospital, Rome, Italy. 5Department of Pediatrics, University of Palermo, Palermo, Italy. 6Department of Pediatric Hematology-Oncology, Regina Margherita Hospital, Turin, Italy. 7Hematology-Oncology Unit, Sant’Orsola-Malpighi Polyclinic, Bologna, Italy. 8Department of Hematology-Oncology, Santobono-Pausilipon Children’s Hospital, Naples, Italy. 9Department of Pediatrics, University Hospital, Bari, Italy. 10Department of Pediatrics, Civic Hospital, Brescia, Italy. 11Department of Hematology-Oncology, Anna Meyer Children’s Hospital, Florence, Italy. 12Pediatric Oncology-Hematology, Civic Hospital, Cagliari, Italy. 13Epidemiology and Biostatistics Unit, IRCCS Istituto Giannina Gaslini, Genova, Italy.

Received: 14 November 2018 Accepted: 19 December 2018

References

1. D’Angio GJ, Evans AE, Koop C. Special pattern of widespread neuroblastoma with a favorable prognosis. Lancet. 1971;11:1046–9.
2. Brodeur GM, Pritchard J, Berthold F, De Bernardi B, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. J Clin Oncol. 1993;11:1466–77.
3. Cohn SL, Pearson ADJ, London WB, Monclair T, Ambros PF, Brodeur GM, et al. The international neuroblastoma risk group (INRG) staging system: an INRG task force report. J Clin Oncol. 2008;27:289–97.
4. Brodeur GM. Spontaneous regression of neuroblastoma. Cell Tissue Res. 2018;372:277–86.
5. Evans AE, Chatten J, D’Angio GJ, Gerson JM, Robinson J, Schnauffer L. A review of 17 IV-S neuroblastoma patients at the Children’s hospital of Philadelphia. Cancer. 1980;45:833–9.
6. Stokes SH, Thomas PRM, Perez CA, Vetti TJ. Stage IV-S neuroblastoma: results with definitive therapy. Cancer. 1984;53:289–93.
7. Stephenson SR, Cook BA, Meade AD, Ruymann FB. The prognostic significance of age and pattern of metastases in stage IV-S neuroblastoma. Cancer. 1986;58:872–5.
8. Suarez A, Hartmann O, Vassal G, Giron A, Habrand JL, Valteau D, et al. Treatment of stage IV-S neuroblastoma: a study of 34 cases treated between 1982 and 1987. Med Pediatr Oncol. 1991;19:743–477.
9. De Bernardi B, Pianca C, Boni L, Brisigotti M, Carli M, Bagnulo S, et al. Disseminated neuroblastoma (stage IV and IV-S) in the first year of life. Outcome related to age and stage. Italian cooperative group on neuroblastoma. Cancer. 1992;70:1625–33.
10. Strommer D, Shuster JJ, McWilliams N, Nitschke R, Smith EI, Joshi VJ, et al. Results of pediatric oncology group protocol 8104 for infants with stages D and DS neuroblastoma. J Ped Hematol Oncol. 1995;17:254–9.
11. Katzenstein HM, Bowman LC, Brodeur GM, Thornor PS, Joshi W, Smith EI, et al. Prognostic significance of age, MYCN oncogene amplification, tumor cell ploidy, and histology in 110 infants with stage DS neuroblastoma: the pediatric oncology group experience. J Clin Oncol. 1998;16:2007–17.
12. Nickerson HJ, Matthy CK, Seeger BC, Brodeur GM, Shimada H, Perez C, et al. Favorable biology and outcome of stage IV-S neuroblastoma with supportive care or minimal therapy: a Children's Cancer Group study. J Clin Oncol. 2000;18:477–86.
13. Schleiermacher G, Rubie H, Hartmann O, Bergeron C, Chastagner P, Mechinaud F, et al. Neuroblastoma Study Group of the French Society of Paediatric Oncology: stage 4S neuroblastoma — report of 10 years’ experience of the French Society of Paediatric Oncology (SFOP). Rev. Fr. Cancer. 2003;89:470–6.
14. Taggart DR, London WB, Dubois SG, Monclair TF, Nakagawa A, De Bernardi B, et al. Prognostic value of the stage 4S metastatic pattern and tumor biology in patients with metastatic neuroblastoma diagnosed between birth and 18 months of age. J Clin Oncol. 2011;29:4358–64.
15. Hsu LL, Evans AE, D’Angio GJ. Hepatomegaly in neuroblastoma stage 4S: criteria for treatment of the vulnerable neonate. Med Pediatr Oncol. 1996;27:521–8.
16. Simon T. GPOH guidelines for diagnosis and treatment of patients with neuroblastic tumors. Klin Pädiatr. 2017;229:147–79.
17. Scaruffi P, Parodi S, Mazzocco K, Defferrari R, Fontana V, Bonassi S, et al. Detection of MYCN amplification and chromosome 1p36 loss in neuroblastoma by cDNA microarray comparative genomic hybridization. Mol Diagn. 2004;8:93–100.
18. Torino GP, Verdone G, De Bernardi B, Sansone R, Massimo L, Corniglia-Ferrari P. N-myc oncogene amplification in a patient with IV-s neuroblastoma. Am J Pediatr Hematol Oncol. 1987;9:8–11.
19. Schleiermacher G, Michon J, Ribeiro A, Pierron G, Mosseri V, Rubie H, et al. Segmental chromosomal alterations lead to a higher risk of relapse in infants with MYCN-non-amplified localised unseetable disseminated neuroblastoma (a SIOPEN collaborative study). Br J Cancer. 2012;107:419–22.
20. Spitz R, Hero B, Simon T, Berthold F. Loss in chromosome 11q identifies tumors with increased risk for metastatic relapses in localized and 4S neuroblastoma. Clin Cancer Res. 2006;12:2368–73.
21. Bernardi B, Ragouz G, Kaffmann A, Valant A, Ripoche H, Joulin V, et al. Detection of MYCN amplification and chromosome 1p36 loss in neuroblastoma by cDNA microarray comparative genomic hybridization. Mol Diagn. 2004;8:93–100.
22. Schleiermacher G, Michon J, Ribeiro A, Pierron G, Mosseri V, Rubie H, et al. Segmental chromosomal alterations lead to a higher risk of relapse in infants with MYCN-non-amplified localised unseetable disseminated neuroblastoma (a SIOPEN collaborative study). Br J Cancer. 2012;107:419–22.
23. Haupt R, Garaventa A, Gambini C, Parodi S, Cangemi G, De Bernardi B, et al. Improved survival of children with neuroblastoma between 1979 and 2005: a report of the Italian neuroblastoma registry. J Clin Oncol. 2010;28:2311–8.
24. Shimada H, Ambros IM, Dehner LP, Hata J, Yoshi W, Roald B, et al. The international neuroblastoma pathology classification (the Shimada system). Cancer. 1999;86:364–72.
25. De Bernardi B, Conte M, Mancini A, Donfrancesco A, Alvisi P, Tomà P, et al. Localized resectable neuroblastoma: results of the second study of the Italian cooperative group for neuroblastoma. J Clin Oncol. 1995;38:84–93.
26. Guglielmi M, De Bernardi B, Rizzo A, Federici S, Poglio C, Siracusa F, et al. Rejection of primary tumor at diagnosis in stage IV-S neuroblastoma: does it affect the clinical course? J Clin Oncol. 1996;14:1357–64.
27. Cahete A, Gerrard M, Rubie H, Castel V, Di Cataldo A, Munzer C, et al. Poor survival for infants with MYCN-amplified metastatic neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology Europe Neuroblastoma Experience. J Clin Oncol. 2009;27:1014–9.
28. Van Noesel MM. Neuroblastoma stage 4S: a multifocal stem-cell disease of the developing neural crest. Lancet Oncol. 2012;13:29–30.
29. Tonini GP, Boni L, Pession A, Rogers D, Iolascon A, Basso G, et al. MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4S: the Italian experience with 205 children. J Clin Oncol. 1997;15:85–93.
30. Schneideman J, London WB, Brodeur GM, Castleberry RP, Look AT, Cohn SL. Clinical significance of MYCN amplification and ploidy in favorable-stage neuroblastoma: a report from Children’s Oncology group. J Clin Oncol. 2008;26:936–43.
31. Bethold F, Harms D, Lampert F, Niethammer D, Zieschang G. Risk factors in neuroblastoma of infants. Contrib Oncol. 1990;41:101–17.
32. Martinez DA, King DR, Gin-Pease ME, Hase GM, Wiener ES. Resection of the primary tumor is appropriate for children with stage IV-S neuroblastoma: an analysis of 37 patients. J Pediatr Surg. 1992;27:1016–20.
33. Keene DJ, Minford J, Craigie RJ, Humphrey G, Bruce J. Laparotomy closure in stage 4S neuroblastoma. J Pediatr Surg. 2001;46:1–4.