EUROPEAN JOURNAL OF CANCER 45 (2009) 3220–3227

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Neuroblastoma in the newborn. A study of the Italian Neuroblastoma Registry

Anna Rita Gigliotti [a], *Andrea Di Cataldo* [i], *Stefania Sorrentino* [a], *Stefano Parodi* [e], *Antonino Rizzo* [b], *Piero Buffa* [b], *Claudio Granata* [c], *Angela Rita Sementa* [d], *Anna Maria Fagnani* [f], *Massimo Provenzi* [g], *Arcangelo Prete* [h], *Carmelita D'Ippolito* [j], *Anna Clerico* [k], *Aurora Castellano* [l], *Gian Paolo Tonini* [m], *Massimo Conte* [a], *Alberto Garaventa* [a], *Bruno De Bernardi* [a,*]

[a] *Department of Haematology–Oncology, Giannina Gaslini Children's Hospital, Largo Gerolamo Gaslini, 5, 16147-Genova, Italy*
[b] *Department of Surgery, Giannina Gaslini Children's Hospital, Genova, Italy*
[c] *Service of Diagnostic Radiology, Giannina Gaslini Children's Hospital, Genova, Italy*
[d] *Service of Pathology, Giannina Gaslini Children's Hospital, Genova, Italy*
[e] *Service of Epidemiology–Biostatistics, Giannina Gaslini Children's Hospital, Genova, Italy*
[f] *Ospedale Maggiore Foundation, Mangiagalli-Regina Elena Policlinic, Milano, Italy*
[g] *Department of Paediatrics, Civic Hospital, Bergamo, Italy*
[h] *Department of Paediatrics, University of Bologna, Bologna, Italy*
[i] *Department of Paediatrics, University of Catania, Catania, Italy*
[j] *Department of Paediatrics, University of Brescia, Brescia, Italy*
[k] *Department of Paediatrics, University of Roma, Roma, Italy*
[l] *Department of Oncology, Bambino Gesu' Children's Hospital, Roma, Italy*
[m] *Translational Paediatric Oncology, National Institute for Cancer Research, Genova, Italy*

ARTICLE INFO

Article history:
Received 4 August 2009
Accepted 21 August 2009
Available online 18 September 2009

Keywords:
Neuroblastoma
Infant
Newborn
Prenatal diagnosis
Stage 4S disease
MYCN gene

ABSTRACT

Aim: Presenting features, treatment and outcome of 134 newborns with neuroblastoma diagnosed over a 27-year period are described.
Methods: Analyses were performed on the entire cohort and on patients distributed over three periods of diagnosis.
Results: Twenty-seven tumours (20.1%) were detected prenatally. Localised disease prevailed (65.7%) with an increase of stage 1 patients over time from 18.8% to 46.5%. Disseminated disease accounted for 34.3% of tumours with only one stage 4 and 45 stage 4S. Five-year overall survival (OS) of the entire cohort was 88.3%. Five/88 patients with localised disease died, including three who died of complications (OS, 95.3%). The only stage 4 patient survived. Eleven/45 stage 4S patients died, including 7/18 symptomatic and 4/27 asymptomatic (OS, 74.1%).
Conclusion: The outcome of neuroblastoma in newborns is excellent. In localised tumours, surgery-related deaths outnumbered deaths due to disease. Symptomatic stage 4S patients were at greater risk of dying.

* *Corresponding author:* Tel.: +39 010 56 36 464; fax: +39 010 56 36 714.
E-mail address: brunodebernardi@ospedale-gaslini.ge.it (B. De Bernardi).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.08.020

1. Introduction

Neuroblastoma originates from cells of the primitive neural crest and accounts for 8–10% of all paediatric malignancies.[1] It mainly occurs in preschool age[2] and sometimes even in newborns, i.e. the first month of life.[3] Diagnoses of neuroblastoma in newborns may increase due to the widespread use of gestational ultrasonography which can reveal a number of otherwise undetectable abdominal masses, some of which turn out to be neuroblastoma.[3–6] Of note, neuroblastomas diagnosed in newborns have been referred to by several names including foetal,[7] connatal,[8] neonatal,[9–11] congenital,[12] and perinatal,[13,14] thus generating some confusion. Although neuroblastomas detected at such an early age are thought to have the same good prognosis as in older infants, they may possess specific features and are certainly difficult to manage, considering that any therapeutic manoeuvre carried out at this age is potentially riskier than at older ages. The literature concerning neonatal neuroblastoma is scarce and, in the authors' view, does not adequately illustrate its clinical and biologic specificities, if any, nor does it provide reliable therapeutic guidelines.

In an attempt to obtain new, potentially useful information that may be derived from a large series of such patients, we reviewed the data of the Italian Neuroblastoma Registry (INBR) over a 27-year period. Analyses were performed on study patients as a whole and divided into three groups based on date of diagnosis to detect possible changes over time in presenting features, clinical course and outcome.

2. Patients and methods

The records of all children aged 0–18 years registered in the INBR between January 1980 and December 2006 were screened for eligibility for this study. The INBR has been active since 1979 and includes patients with newly diagnosed peripheral neuroblastic tumours (PNT, i.e. neuroblastoma, ganglioneuroblastoma and the benign ganglioneuroma) enrolled by the paediatric oncology institution members of the Italian Association for Paediatric Haematology–Oncology (AIEOP). It is assumed that in the last decade more than 90% of the PNTs diagnosed in Italy were recruited through this network.[15] Informed consent was provided by a parent or guardian for each patient enrolled in the study. Study approval was obtained from the local institutional review boards.

Children with malignant PNTs diagnosed in the first month of life were eligible. Diagnosis was made in most instances on histological grounds. Alternatively, it was based on the detection of tumour cells in the bone marrow associated with elevated urinary catecholamines.

To evaluate disease extension, the criteria of the International Neuroblastoma Staging System (INSS)[16] were used, prospectively from 1989, and retrospectively afterwards. The primary tumour was most often studied by ultrasonography and computed tomography. Bone marrow infiltration was ruled out by at least two aspirates. Skeletal involvement was evaluated by standard roentgenograms and, as of the mid-1980s, by metaiodobenzylguanidine scintigraphy (MIBG). Biochemical studies included the assay of vanillymandelic (VMA) and homovanillic (HVA) acids in the urine, and of lactate dehydrogenase (LDH) in the serum. VMA, HVA and LDH levels were considered to be abnormal if they exceeded twice the upper normal value. Biological studies included *MYCN* gene, chromosome 1p and DNA content, and were performed in the only certified national laboratory, located at the National Cancer Institute, Genova. *MYCN* gene and chromosome 1p deletion were assayed by fluorescence *in situ* hybridisation,[18] while DNA index was assayed by flow cytometry.[19] *MYCN* gene amplification was defined as a more than fourfold increase in the *MYCN* signal number, as compared with the reference probe located on chromosome 2.

2.1. Treatment

Treatment mainly depended on disease extension. In brief, tumour resection was the only therapy that was applied in patients with stage 1 and 2 disease. In the first two study periods, stage 3 patients received several chemotherapeutic courses before attempting tumour resection. In the third period, chemotherapy was given according to the SIOPEN protocol for unresectable disease and consisted of two to four courses of cyclophosphamide plus vincristine (CO) and, in case of poor response, two to four courses of carboplatin plus etoposide (CE), followed by surgery. The only stage 4 patient was treated by the 99.3 SIOPEN protocol described elsewhere.[17] Until 1985, stage 4S patients received one to two chemotherapy courses. Subsequently, these patients could avoid receiving any therapy if they were asymptomatic,[17] while symptomatic patients were mainly treated with courses of CE till symptom regression. Resection of the primary tumour was not encouraged due to the lack of proof regarding any possible benefits in these patients.[18]

2.2. Statistical analyses

Statistical analyses were performed on study patients as a whole and divided into three groups based on date of diagnosis (January 1980 to December 1989, January 1990 to December 1999, and January 2000 to December 2006). Descriptive statistics were reported as absolute frequencies and percentages for qualitative data. Differences in the frequencies of each variable were evaluated by χ^2 test, or Fisher's exact test, when appropriate. Overall survival (OS) was estimated by the Kaplan–Meier method, and the differences between groups were assessed by the log-rank test. All tests were two-sided and P values <0.05 were considered significant. All analyses were performed by Stata package (release 9.2, Stata Corporation, College Station, TX, USA).

3. Results

Between 1980 and 2006, a total of 1849 children with malignant PNTs (425, 709 and 715 in the three enrolment periods, respectively) were enrolled in the INBR (Table 1). Among them, 134 (7.2%) were evaluable for this study, including 32

out of 425 (7.5%) in the first group, 59 out of 709 (8.3%) in the second, and 43 out of 715 (6.0%) in the third group (Table 1). Diagnosis was histological in 127 patients (neuroblastoma in 123, ganglioneuroblastoma in four), while it was based on positive bone marrow plus elevated urinary catecholamines in seven.

The presenting characteristics of the 134 study patients are reported in Table 2. Twenty-seven tumours (20.1%) were

Table 1 – Study patients and their distribution by period of diagnosis.

	Entire study period 1980–2006	First period 1980–1989	Second period 1990–1999	Third period 2000–2006
Total patients	1849	425	709	715
Patients/year	68.5	42.5	70.9	102.1
Total newborns	134	32	59	43
Newborns/year	5.0	3.2	5.9	6.1

Table 2 – Patient and tumour characteristics.

	Total (*n* = 134)		1980–1989 (*n* = 32)		1990–1999 (*n* = 59)		2000–2006 (*n* = 43)		*P*
	No.	%	No.	%	No.	%	No.	%	
Time of detection									.890
Prenatal	27	20.1	6	18.7	13	22.0	8	18.6	
Postnatal	107	79.9	26	81.3	46	78.0	35	81.4	
Gender									.327
Male	73	54.5	20	62.5	28	47.5	25	58.1	
Female	61	45.5	12	37.5	31	52.5	18	41.9	
Primary site									.733
Adrenal	73	54.5	17	53.1	33	55.9	23	53.5	
Abdomen	39	29.1	8	25.0	17	28.8	14	32.6	
Thorax	10	7.5	3	9.4	5	8.5	2	4.7	
Neck	7	5.2	2	6.3	3	5.1	2	4.7	
Pelvis	2	1.5	0	0.0	0	0.0	2	4.7	
Undetected	3	2.2	2	6.3	1	1.7	0	0.0	
Disease extension									<.001
Localised	88	65.7	12	37.5	42	71.2	34	79.1	
Disseminated	46	34.3	20	62.5	17	28.8	9	20.9	
INSS stage									.004
1	48	35.8	6	18.8	22	37.3	20	46.5	
2	15	11.2	2	6.3	10	17.0	3	7.0	
3	25	18.7	4	12.5	10	17.0	11	25.6	
4	1	0.8	0	0.0	0	0.0	1	2.3	
4s	45	33.6	20	62.5	17	28.8	8	18.6	
VMA (107 tested)									
Normal	48	44.9							
Elevated	59	55.1							
HVA (78 tested)									
Normal	34	43.6							
Elevated	44	56.4							
LDH (103 tested)									
Normal	71	68.9							
Elevated	32	31.1							
MYCN (95 tested)									
Not amplified	93	97.9							
Amplified	2	2.1							
1p chromosome (74 tested)									
Normal	70	94.6							
Deleted	4	5.4							
DNA index (68 tested)									
Aneuploid	57	83.8							
Diploid	11	16.2							

detected prenatally, including six out of 32 (18.7%) in the first group, 13 out of 59 (22.0%) in the second group, and eight out of 43 (18.6%) in the third group ($P = 0.890$). These 27 tumours were described by imaging studies as adrenal masses in 13, abdominal masses in eight, cystic adrenal masses in two, mesenteric cyst, nephromegaly, cervical mass, and mediastinal mass plus foetal hydrops, in one case each. Six of these 27 patients had stage 4S disease, including the one with foetal hydrops who died at birth.

The primary tumour was more often located in the adrenal site ($n = 73$), followed by the abdomen ($n = 39$), thorax ($n = 10$), neck ($n = 7$), and pelvis ($n = 2$). No primary tumour was identified in three patients (Table 2). There were slightly more males than females (54.5 *versus* 45.5%). Localised prevailed over disseminated disease (65.7% *versus* 34.3%, $P<0.001$). The incidence of patients with localised disease increased along the study period from 37.5% to 79.1%. Among the 88 localised tumours, the radically resected ones (stage 1) prevailed (35.8%) with a marked increase along the study period from 18.8% to 46.5%, while the tumours that were resected with minimal residue (stage 2) and the unresectable ones (stage 3) accounted for 11.2% and 18.7%, respectively, without clear changes over time (Table 2). The 46 patients with disseminated disease included only one stage 4 patient (bone involvement shown by MIBG), and 45 stage 4S patients. Among the latter, the sites of metastasis included the liver alone ($n = 22$), liver plus bone marrow ($n = 11$), liver plus skin ($n = 5$), bone marrow alone ($n = 4$), skin alone ($n = 1$), and bone marrow plus skin plus liver ($n = 2$).

3.1. *Biochemical and biological analyses*

Elevated levels of urinary VMA and HVA were detected in approximately half of the cases that were tested. LDH levels were elevated in a minority of tested patients (Table 2). *MYCN* gene was assayed in 95 tumours, two of which (2.1%) had gene amplification. Chromosome 1p36 deletion was searched for in 74 tumours and was detected in four of them (5.4%). DNA index was evaluated in 68 tumours and was found to be diploid in 11 (16.2%) (Table 2).

3.2. *Clinical course*

3.2.1. *Stage 1*

None of the 48 patients received adjuvant therapy after radical surgery which included unilateral nephrectomy in two of them. No major surgery-related complications were reported. One patient developed local relapse and was successfully re-operated on. Another patient developed hepatic lesions at 3 months of age that regressed spontaneously within the following 6 months. All 48 patients are alive disease-free at a median follow-up of 79 months (range, 1–223), for a 5-year overall survival (OS) of 100% (Fig. 1A).

3.2.2. *Stage 2*

Four of the 15 patients were symptomatic (dyspnea due to tracheal compression in two, vomiting and hypertension in one case each). Three patients died of surgery-related complications (abdominal haemorrhage, multiple organ failure, and gram-negative sepsis). Two deaths occurred in the second and one in the third period of diagnosis. Extensive pneumomediastinum occurred in another patient who required transient mechanical ventilation. As was the case for stage 1, none of these 15 patients received adjuvant therapy. In conclusion, 12 of 15 patients are presently alive disease-free with a median observation of 68 months (range, 0.1–139), for an OS of 79.4% (95% CI, 48.8–92.9) (Fig. 1A).

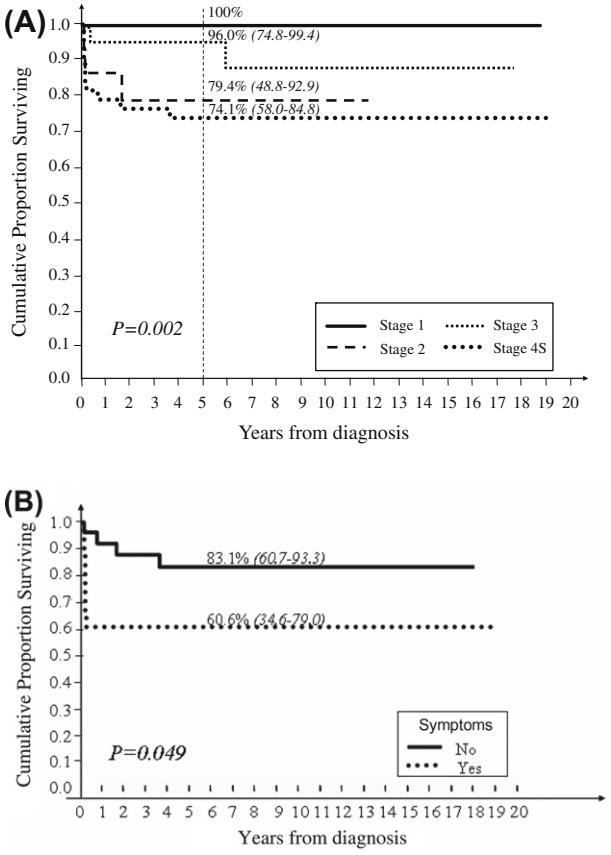


Fig. 1 – Five-year overall survival in relation to stage (panel A) and presence of symptoms at diagnosis (panel B).

3.2.3. *Stage 3*

Eleven out of 25 patients were symptomatic at presentation (motor deficit in six, dyspnea in four, diarrhoea and fever in one). After biopsy, all patients received chemotherapy (median courses = 6; range, 2–9). The combinations that were used were CO in 36 courses, CE in 33, and others in 30. No fatal chemotherapy-related complications occurred. One patient developed local tumour progression while on therapy and died shortly afterwards. Another patient developed pelvic and skeletal recurrence and eventually died at 70 months from diagnosis. Both deaths occurred in the first period of diagnosis. Twenty patients underwent tumour resection that was complete in 11 and incomplete in four, and seven were not operated on because the tumour had disappeared or shrunk to a negligible size. No major surgery-related complications were reported. In conclusion, two of the 25 patients died of disease and 23 are alive disease-free with a median follow-up of 70 months (range, 3–210), for an OS of 96.0% (95% CI, 74.8–99.4) (Fig. 1A).

3.2.4. *Stage 4*

The only stage 4 patient responded well to treatment and is alive and well 70 months from diagnosis (not included in Fig. 1).

3.2.5. *Stage 4S*

Of 45 patients, 24 never developed symptoms. Of them, two received no treatment (both alive) and 22 underwent some treatments consisting of resection of primary tumour ($n = 7$; all alive), one to two chemotherapy courses ($n = 14$; 13 alive and one dead of sepsis), and irradiation of the hepatic area ($n = 1$; alive) (Fig. 2). Eighteen patients developed symptoms within the first month of life, which included dyspnea related to massive liver involvement in 16 patients, and vomiting and diarrhoea in two (Fig. 2). Two patients died the day of birth and 16 underwent treatment consisting of chemotherapy ($n = 8$; six alive, two dead), irradiation of the hepatic area ($n = 4$; one alive, three dead), resection of primary tumour ($n = 2$; both alive), or tumour resection + chemotherapy ($n = 2$; both alive) (Fig. 2).

The remaining three patients died of disease progression at 7, 19 and 42 months, of whom two had evidence of disease progression to stage 4 (bone involvement) (Fig. 2).

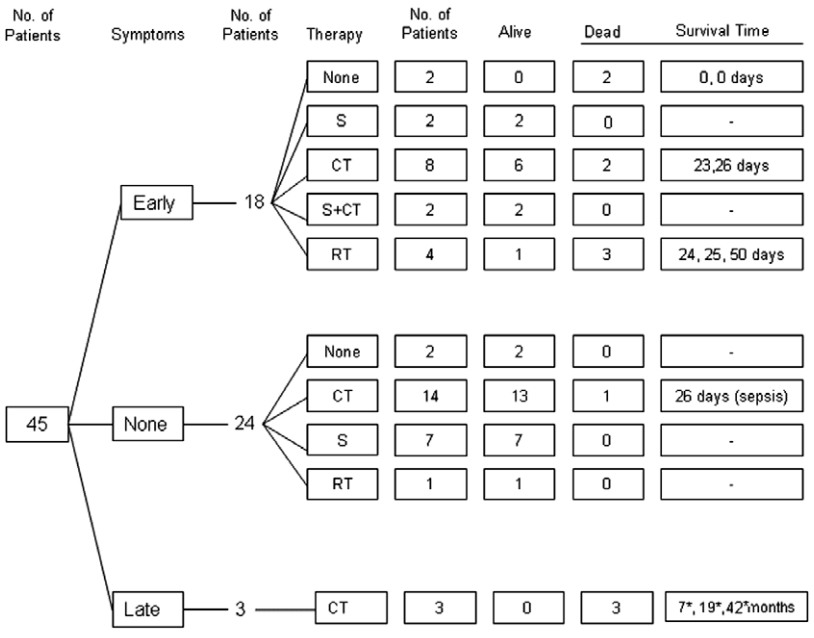
Death occurred in four patients diagnosed in the first enrolment period, six died in the second period, and one died in the third. In conclusion, after a median follow-up of 66 months (range, 0–228), 34 of the 45 stage 4S patients survived, and 11 died, for an OS of 74.1% (95% CI, 58.0–84.8) (Fig. 1A).

3.2.6. *Entire cohort*

The median follow-up for the 134 patients was 72 months (range, 0–228) and it was 135 months (range, 0–228), 76 months (range, 0–151), and 65 months (range, 0.5–107) for the three groups, respectively. The estimated OS was 88.3% (95% CI, 81.4–92.8) and it was 83.1% (95% CI, 64.0–92.6) for the first group, 86.2% (95% CI, 74.3–92.9) for the second group, and 95.4% (95% CI, 82.7–98.8) for the third group. Patients with localised disease fared significantly better ($P=0.001$) compared to patients with disseminated disease (OS, 95.3%; 95% CI, 88.0–98.2 *versus* 74.7%; 95% CI, 58.9–85.2). Stage 1 patients (OS 100%) fared significantly better ($P = 0.002$) compared to patients in stage 2 (OS 79.4%; 95% CI, 48.8–92.9), stage 3 (OS 96.0%; 95% CI, 74.8–99.4), and stage 4S (OS 74.1%; 58.0–84.8) (Fig. 1A). As previously mentioned, the only stage 4 patient survived.

Analyses aimed at assessing the impact of potential prognostic factors on OS were limited to stage 4S patients (Table 3) due to the small number of events that occurred in patients with localised disease. OS was significantly worse ($P = 0.048$) for symptomatic patients (60.6%; 95% CI, 34.6–79.8) compared to the asymptomatic ones (83.1%; 95% CI, 60.7–93.3) (Fig. 1B). OS was better for patients of the third period of diagnosis compared to the previous ones (87.5% *versus* 78.1% and 64.2%), but the difference was not statistically significant. No difference in OS was detected in relation to time of tumour detection, gender, primary tumour site, sites of metastases, urine VMA and HVA, and LDH serum level (Table 3).

Data concerning biological features are presented in Table 4. Of the 95 patients who were studied for *MYCN* gene, two (2.1%) had gene amplification (one in stage 1 and one in stage 4S). Both were treated by surgery alone and survived. Of the 74 patients who were evaluated for chromosome 1, four (5.4%) had a deletion of the short arm (one in stage 1, one in stage 2 and two in stage 4S), of whom one in stage 4S died and three survived. Of the 68 patients who were studied for DNA content, eleven (16.2%) had a diploid content, of whom the seven with localised disease survived, while three of the four 4S stage patients died.



Abbreviations: S, surgery; CT, chemotherapy; RT, radiotherapy.

*, progression to stage 4 (bone)

Fig. 2 – Treatment and outcome of 45 stage 4s patients.

Table 3 – Five-year overall survival of 45 newborns with stage 4S disease.

Characteristic	No. of patients	No. of deaths	OS (95% CI)	P
	45	11	74.1 (58.0–84.8)	
Prenatal detection				.603
Yes	6	2	66.7 (19.5–90.4)	
No	39	9	75.1 (57.4–86.3)	
Period of diagnosis				.495
1980–1989	20	4	78.1 (51.4–91.2)	
1990–1999	17	6	64.2 (36.9–82.1)	
2000–2006	8	1	87.5 (38.7–98.1)	
Symptoms				.049
Yes	18	7	60.6 (34.6–79.8)	
No	27	4	83.1 (60.7–93.3)	
Gender				.608
Male	24	5	78.1 (55.1–90.3)	
Female	21	6	69.8 (44.3–85.4)	
Primary site				.494
Adrenal	29	8	69.7 (48.0–83.8)	
Other	16	3	80.8 (51.4–93.4)	
Metastases				.189
Liver	39	11	70.6 (53.1–82.6)	
Other	6	0	100	
VMA				.168
Normal	7	0	100	
Pathologic	29	8	71.1 (50.2–84.4)	
HVA				.747
Normal	4	1	75.0 (12.8–96.1)	
Pathologic	20	7	64.2 (39.0–81.1)	
LDH				.244
Normal	22	7	65.9 (41.2–82.2)	
Pathologic	10	1	88.9 (43.3–98.4)	

Table 4 – Results of biological studies.

	Tumours		Patients	
	No.	%	Alive	Dead
MYCN gene				
Total	95	100	86	9
Normal	93	97.9	84	9
Abnormal	2	2.1	2	0
Chromosome 1p				
Total	74	100	65	9
Normal	70	94.6	62	8
Abnormal	4	5.4	3	1
DNA index				
Total	68	100	61	7
Aneuploid	57	83.8	53	4
Diploid	11	16.2	8	3

4. Discussion

There are only a few publications regarding newborns with neuroblastoma. Moppett et al.[22] reported 33 such patients, including 15 with localised disease (all alive), four with stage 4 (two deaths), and 14 with stage 4S (one death), resulting in an OS of 91%. Tsuchida et al.[9] reported 21 newborns, of whom 13 had localised and three had stage 4 disease (all alive), and five had stage 4S disease (two deaths), resulting in an OS of 89%. Finally, Michalowski et al.[10] reported 52 newborns with localised disease, three of whom died of treatment-related complications. In the face of a 7.7% toxic death rate, the authors warned that treatment for neonatal neuroblastoma may imply a greater risk than the disease itself.

The series of 134 neonatal neuroblastomas in this report is the largest one published to date. The only presenting feature that differed significantly in the three periods of diagnosis was the percentage of stage 1 patients that increased from 18.8% to 46.5%. This remarkable change may be explained by the increasing use in Italy of abdominal ultrasonography in the neonatal period, mainly aimed at carrying out early detection of urinary tract malformations. An additional factor may be the greater attention paid to the care of newborns, which in the last two decades led to a minimum of two medical examinations in the first month of life, thus leading to the discovery of a number of abdominal masses that might have otherwise gone unnoticed. Of note, there was no difference along the three periods of diagnosis in the percentage of patients discovered by prenatal ultrasonography (18.7%, 20.5%, and 18.6%, respectively). This indicates that, at least in the

Italian context, the use of this technique did not translate into a significant increase of diagnoses.

Unlike what has been reported in previous publications,[9,10,19] we detected only one patient with stage 4 features. Stage 4 could well be under-diagnosed in newborns due to the difficulty in carrying out full metastatic work-up at such a young age. However, only two of our 45 stage 4S patients developed overt disease progression to stage 4 and died because of it.

The OS of our patients was very good (88.3%) and parallels the outcome of the three previous studies.[9,10,19] Newborns with localised disease fared especially well (OS, 95.3%), but it has to be stressed that three of the five deaths recorded among our patients were surgery-related, thus confirming the experience of Michalowski et al.[10] The risk connected with tumour resection for these patients could likely be reduced by taking into consideration the recently identified imaging-defined risk factors that may help to plan safe surgery in these patients.[20] Until now, tumour resection has been considered mandatory for these patients. However, prospective studies aimed at evaluating the ability of some of these tumours to regress spontaneously are in progress.[21]

The outcome of stage 4S (OS, 71.3%) was less satisfactory, but not unexpected, since it is well known that stage 4S infants diagnosed in the first 2 months of life bear a greater risk than older infants.[22,23] Of interest, ten of the 11 deaths occurred in the two earlier periods of diagnosis, as compared to one alone that occurred in the third period. Conceivably, the better supportive measures given to the most recent patients have contributed to saving some lives.

It must be pointed out that although therapeutic guidelines did not recommend giving any treatment to asymptomatic stage 4S patients, the vast majority of them did receive some kind of treatment. This highlights the fact that a number of paediatric oncologists are still not inclined to accept a wait-and-see strategy for such patients.[17]

The patients' clinical course did not correlate with any particular biological features, with the possible exception of diploid DNA content, as also found by others.[24,25] Of note, only two of the 95 patients tested for *MYCN* had amplification of the gene. Both these patients survived without receiving chemotherapy. This is in contrast to the common belief that an amplified *MYCN* gene is associated with a very poor outcome,[23,26–28] although both Tonini et al.[29] and Schneiderman et al.[30] reported a number of such patients who did well despite the genetic abnormality. Additional investigation into the tumour is needed to clarify the intimate biological features of neuroblastoma occurring at this age.

Conflict of interest statement

None declared.

Acknowledgements

We thank the SIOPEN Board for allowing the inclusion of some patients enrolled in SIOPEN studies, Lisa Baracco for secretarial assistance, Valerie Perricone for revising the text, Riccardo Haupt and Guido Pastore for helpful suggestions, Filippo Papio and Barbara Galleni for data management.

Supported in part by the Italian Neuroblastoma Foundation. SP is a recipient of a grant provided by the Italian Neuroblastoma Foundation.

REFERENCES

1. De Bernardi B, Pistoia V, Gambini C, Granata C. Peripheral neuroblastic tumors. In: Sheaves R, Jenkins PJ, Wass JA, editors. *Clinical endocrine oncology*. 2nd ed. Oxford: Blackwell Science; 2008. p. 360–9.
2. De Bernardi B, Di Tullio MT, Cordero di Montezemolo L, et al. Neuroblastoma under on year of age. Clinical aspects and management. In: Lampert F, Cordero di Montezemolo L, Pession A, editors. *Contributions to oncology – cancer in the first year of life*. Basel: Karger; 1990. p. 118–28.
3. Potter EL, Craig JM. Clinical manifestation of neuroblastoma in the fetus and infant. In: Gilbert-Barness E, editor. *Potter's pathology of the fetus and infant*. 2nd ed. Philadelphia: Mosby Elsevier; 1975. p. 1659–67.
4. Acharya S, Jayabose S, Kogan SJ, et al. Prenatally diagnosed neuroblastoma. *Cancer* 1997;**80**(2):304–10.
5. Tomà P, Lucigrai G, Marzoli A, Lituania M. Prenatal diagnosis of metastatic adrenal neuroblastoma with sonography and MR imaging. *Am J Roentgenol* 1994;**162**(5):1183–4.
6. Granata C, Fagnani AM, Gambini C, et al. Features and outcome of neuroblastoma detected before birth. *J Pediatr Surg* 2000;**35**(1):88–91.
7. Jennings RW, LaQuaglia MP, Leong K, Hendren WH, Adzick NS. Fetal neuroblastoma: prenatal diagnosis and natural history. *J Pediatr Surg* 1993;**28**(9):1168–74.
8. Kerbl R, Urban CE, Lackner H, et al. Connatal localized neuroblastoma. *Cancer* 1996;**77**(7):1395–401.
9. Tsuchida Y, Ikeda H, Iehara T, Toyoda Y, Kawa K, Fukuzawa M. Neonatal neuroblastoma: incidence and clinical outcome. *Med Pediatr Oncol* 2003;**40**(6):391–404.
10. Michalowski MB, Rubie H, Michon J, et al. Neonatal localized neuroblastoma: 52 cases treated from 1990 to 1999. *Arch Pédiatr* 2004;**11**(7):782–8.
11. Lukens JN. Neuroblastoma in the neonate. *Semin Perinatol* 1999;**23**(4):263–73.
12. Luis AL, Martinez L, Hernandez F, et al. Congenital neuroblastoma. *Cir Pediatr* 2004;**17**(2):89–92.
13. Sauvat F, Sarnacki S, Brisse H, et al. Outcome of suprarenal localized masses diagnosed during the perinatal period. *Cancer* 2002;**94**(9):2474–80.
14. Nuchtern JG. Perinatal neuroblastoma. *Sem Ped Surg* 2006;**15**(1):10–6.
15. Conte M, Parodi S, De Bernardi B, et al. Neuroblastoma in adolescents: the Italian experience. *Cancer* 2006;**106**(6):1409–17.
16. Brodeur GM, Pritchard J, Berthold F, et al. Revision of the international criteria for neuroblastoma diagnosis, staging and response to treatment. *J Clin Oncol* 1993;**11**(8):1466–77.
17. De Bernardi B, Gerrard M, Boni L, et al. Excellent outcome with reduced treatment for infants with disseminated neuroblastoma without MYCN gene amplification. *J Clin Oncol* 2009;**27**(7):1034–40.
18. Guglielmi M, De Bernardi B, Rizzo A, et al. Resection of primary tumor at diagnosis in stage IV-S neuroblastoma: does it affect the clinical course? *J Clin Oncol* 1996;**14**(5):1537–44.
19. Moppett J, Haddadin I, Foot ABM. Neonatal neuroblastoma. *Arch Dis Child Fetal Neonatol* 1999;**81**(2):134–7.
20. Cecchetto G, Mosseri V, De Bernardi B, et al. Surgical risk factors in primary surgery for localized neuroblastoma: the

LNESG1 study of the European International Society of Paediatric Oncology Neuroblastoma Group. *J Clin Oncol* 2005;**23**(33):8483–9.
21. Hero B, Simon T, Spitz R, et al. Localized infant neuroblastomas often show spontaneous regression: results of the prospective trials NB95-S and NB97. *J Clin Oncol* 2008;**26**(9):1504–10.
22. De Bernardi B, Pianca C, Boni L, et al. Disseminated neuroblastoma (stage IV and IV-S) in the first year of life. Outcome related to age and stage. *Cancer* 1992;**70**(6):1625–33.
23. Katzenstein HM, Bowman LC, Brodeur GM, et al. Prognostic significance of age, MYCN oncogene amplification, tumor cell ploidy, and histology in 110 infants with stage D (S) neuroblastoma: the Pediatric Oncology Group experience – a Pediatric Oncology Group study. *J Clin Oncol* 1998;**16**(6):2007–17.
24. Look AT, Hayes FA, Nitschke R, Mc Williams NB, Green AA. Cellular DNA content as a predictor of response to chemotherapy in infants with unresectable neuroblastoma. *N Engl J Med* 1984;**331**(4):231–5.
25. Ladenstein R, Ambros IM, Pötschger U, et al. Prognostic of DNA di-tetraploidy in neuroblastoma. *Med Pediatr Oncol* 2001;**36**(1):83–92.
26. Minard V, Hartmann O, Peyroulet MC, et al. Adverse outcome of infants with metastatic neuroblastoma, MYCN amplification and/or bone lesions: results of the French Society of Pediatric Oncology. *Br J Cancer* 2000;**83**(8): 973–9.
27. Schmidt ML, Lukens JN, Seeger RC, et al. Biologic factors determine prognosis in infants with stage 4 neuroblastoma: a prospective children's cancer group study. *J Clin Oncol* 2000;**18**(6):1260–8.
28. Cañete A, Gerrard M, Rubie H, et al. Poor survival for infants with MYCN-amplified metastatic neuroblastoma despite intensified treatment: the International Society of Paediatric Oncology European Neuroblastoma Experience. *J Clin Oncol* 2009;**27**(7):1014–9.
29. Tonini GP, Boni L, Pession A, et al. MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4s: the Italian experience with 295 children. *J Clin Oncol* 1997;**15**(1):85–93.
30. Schneiderman J, London W, Brodeur GM, Castleberry RP, Look AT, Cohn SL. Clinical significance of MYCN amplification and ploidy in favourable-stage neuroblastoma: a report from the children's oncology group. *J Clin Oncol* 2008;**26**(6): 913–8.