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Outcome of children with neuroblastoma after progression or relapse. A retrospective study of the Italian neuroblastoma registry ☆

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ABSTRACT

The Italian Neuroblastoma Registry was investigated to describe 781 children with neuroblastoma experiencing tumour recurrence (424 progressions and 357 relapses). Ten-year overall survival (OS) was 6.8% (95% confidence interval (CI) 4.3–10.0) after progression and 14.4% (95% CI 10.5–18.9) after relapse. For both circumstances, OS was better for age at diagnosis <18 months, less advanced International Neuroblastoma Staging System (INSS) stage, normal lactate dehydrogenase (LDH) serum level, normal *MYCN* gene status ($P < 0.001$) and a non-abdominal primary site ($P = 0.034$ for progression, and $P = 0.004$ for relapses). A local type of recurrence had a significantly better outcome only in case of relapse ($P < 0.001$). Probability of survival increased by era of diagnosis.

Survival of children with recurrent neuroblastoma is very poor. A small cohort of patients, mainly represented by children with stages 1 and 2 who underwent local recurrence or developed late relapse may still benefit from further conventional treatment. For the remaining larger proportion of patients, experimental therapies should be proposed.

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1. Introduction

Neuroblastoma, the most common extracranial solid tumour of childhood, continues to have an unsatisfactory long-term prognosis. In fact, while approximately half of the patients have a localised tumour with high chance of cure, the remaining half present with disseminated disease and have a dismal outcome, except for infants.[1]

Cure of children diagnosed with neuroblastoma mainly depends on achieving complete tumour remission.[2] Factors leading to tumour recurrence (progression or relapse) include inadequate therapy, inability to detect minimal residual disease and the actual incurability of some tumours by current therapeutic modalities. In case of recurrence, treatment is commonly decided on the basis of the type of recurrence, previously administered therapies, as well as on cost/benefit ratio. The literature provides scarce data on the features of recurrence, its treatment and evolution and eventual outcome. Although numerous phase I and phase II studies have evaluated salvage therapies in small cohorts of patients,[3–6] only one study analysed a large number of recurrences, although limited to patients with localised disease.[7] More information on the features and on the clinical course of neuroblastoma patients failing front-line therapy would help clinicians to better tailor treatment strategies.

In this retrospective study we reviewed data from the Italian Neuroblastoma Registry (INBR) regarding children who experienced disease recurrence after being treated with the protocols of the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP).

2. Materials and methods

Inclusion criteria for this study were; diagnosis of neuroblastoma during childhood (0–14 years) between 1979 and 2004, registration in the INBR, treatment according to AIEOP[8–11] protocols and tumour recurrence. The INBR has been active since 1979 and includes patients with neuroblastoma diagnosed at the AIEOP centres. It has been estimated that more than 90% of the neuroblastomas expected each year in Italy are recruited through this network.[12] The INBR collects information on clinical (age, sex, site of the primary, stage) and biological (urinary vanillylmandelic acid – VMA, lactate dehydrogenase – LDH, ferritin and *MYCN* gene status) characteristics at diagnosis, and on front-line treatment protocols. Stage at diagnosis and tumour response is defined according to the International Neuroblastoma Staging System (INSS).[13] Data concerning patients diagnosed before 1992 (when INSS was adopted) were retrospectively revised. Information on tumour response and follow-up is sought through the treatment centres during protocol administration and then updated at least yearly. In case of recurrence, further data are collected on date of the event, type (local, disseminated or combined) and site.

For this study, four time periods were identified based on the following milestone dates: (i) 1979, activation of the INBR, (ii) 1985, use of MIBG scintigraphy; (iii) 1992, adoption of the INSS and systematic assay of *MYCN* gene; and (iv) 1999, central pathology review. Finally, four age at diagnosis categories were defined: 0–17 months, 18 months to 4 years, 5–9 years; $\geqslant$10 years.

Tumour progression was defined as the appearance or the increase by >25% of any tumour lesion(s) in patients who had not previously achieved either complete response (CR) or very good partial response (VGPR).[13] Relapse was defined as the appearance of any new lesion(s) or of previous lesion(s). Both were defined as local if they only occurred at the primary site, or disseminated if occurred outside the primary tumour site. Timing of relapse was defined as early or late using a cutoff of 18 months after achieving CR or VGPR.

During the years covered by this study, front-line treatments changed according to national or international protocols. In general, stage 1 patients were treated by surgery alone. Stage 2 patients enrolled in the first period received post-operative chemotherapy followed in some cases by tumour bed irradiation. In the subsequent two periods, chemotherapy was given only to patients who were older than 1 year with either positive regional lymph nodes or intra-operative tumour rupture. In the last period, chemotherapy was restricted to patients with *MYCN* gene amplification.[8] Stage 3 patients received a variable number of chemotherapy courses before and after tumour resection, while radiotherapy was used occasionally.[9] Treatment of stage 4 patients consisted of standard dose chemotherapy and resection of the primary until 1984. Subsequently, a more intensive chemotherapy, often including a myeloablative course followed by autologous haematopoietic stem cell rescue was given.[10] Stage 4S patients were initially treated with 1–2 chemotherapy courses. Since 1985, recommendations have been given to avoid any therapy, except in case of life- or organ-threatening symptoms.[11]

As salvage treatments varied remarkably throughout the study period, a detailed description of their effects is outside the scope of this analysis. In general, patients who developed a recurrence after having previously undergone surgery as the only therapy were treated by the protocol being used for the stage as defined at the time of the event. Patients who had previously received standard- or high-dose chemotherapy were usually treated with more aggressive regimens which sometimes included megatherapy or radiometabolic therapy.[14–17]

Follow-up was censored at 31st December 2006. Cause of death was defined as (i) cancer-related if death occurred while the patient had active disease, (ii) toxicity-related if death was due to toxic events following therapy while the patient had stable or non-evident disease, (iii) second malignancy-related if death was due to a secondary malignant tumour (SMN); (iv) other causes-related if it was due to other non-cancer-related events.

Since all patients enrolled in the AIEOP NB protocols and registered in the INBR were enrolled in research protocols, they or their guardians signed a consent form allowing the use of their clinical and non-genetic data for clinical research purposes. The procedures we followed were in accordance with ethical standards and with the Helsinki Declaration. According to Italian guidelines, no other specific informed consent was required for purposes of this study.

2.1. Statistical analysis

Descriptive statistics were reported as absolute frequencies and percentages for qualitative data, while median and interquartile range (IQR) were used due to the not normal distribution of most variables. Due to their small sample size, the thoracic, pelvic and other sites were pooled and classified as 'non-abdominal' primaries. Laboratory test results were categorised as normal or abnormal on the basis of the following threshold values: ⩾1000 IU/l for LDH; a ⩾2.5 standard deviation (SD) of normal values by age for VMA urinary excretion. Differences in the frequencies of each variable were evaluated by the χ^2 test or by Fisher's exact test, when appropriate.

Overall survival (OS) after recurrence was evaluated by the Kaplan–Meier method, and differences between groups were assessed by the log-rank test. The combined effect of the various prognostic factors was also assessed by the Cox regression model. However, the results of this analysis should be considered cautiously because of the small sample size of subjects for whom all valid data were available, and the violation of the proportional hazard assumption.[18]

All statistical tests were two-sided and a P value < 0.05 was considered significant. All analyses were performed using the statistical package 'Stata' (release 9.2, Stata Corporation, College Station, TX, USA).

3. Results

Of 1924 children registered in the INBR between 1979 and 2004, a total of 781 (40.6%) developed tumour recurrence.

Table 1 – Descriptive statistics of the original INBR cohort and of the 781 study patients with tumour progression or relapse

Patients' characteristics	At risk (n = 1924)	All (n = 781)	Progressions (n = 424)		Relapses (n = 357)		P
	n (%)[a]	n (%)	n	%	n	%	
Age							0.349
<18 months	907 (47.1)	191 (21.1)	111	26.2	80	22.4	
18 months to 4 years	760 (39.5)	432 (56.8)	222	52.4	210	58.8	
5–9 years	214 (11.1)	132 (61.7)	76	16.9	56	15.7	
⩾10 years	43 (2.2)	26 (60.5)	15	3.5	11	3.1	
Gender							0.148
Male	1065 (55.4)	453 (42.5)	236	55.7	217	60.8	
Female	859 (44.6)	328 (38.2)	188	44.3	140	39.2	
Period of diagnosis							< 0.001
1979–1984	342 (17.8)	207 (60.5)	140	33.0	67	18.8	
1985–1991	455 (23.7)	192 (42.2)	99	23.4	93	26.1	
1992–1998	556 (28.9)	220 (39.6)	104	24.5	116	32.5	
1999–2004	571 (29.7)	162 (28.4)	81	19.1	81	22.7	
Primary site							0.143
Abdomen	1,517 (78.9)	683 (45.0)	378	89.2	305	85.4	
Non-abdominal	407* (21.1)	98 (24.1)	46	10.8	52	14.6	
INSS stage							0.075**
1	330 (17.2)	23 (7.0)	0	0.0	23	6.4	
2	274 (14.2)	46 (16.8)	5	1.2	41	11.5	
3	362 (18.8)	105 (29.0)	61	14.4	44	12.3	
4	778 (40.4)	551 (70.8)	317	74.8	234	65.6	
4s	180 (9.4)	56 (31.1)	41	9.7	15	4.2	
VMA							0.046***
Normal	519 (31.2)	176 (33.9)	84	22.2	92	28.8	
Abnormal	1145 (68.8)	523 (45.7)	295	77.8	228	71.3	
Missing	260 (13.5)	82 (31.5)	45	10.6	37	10.4	
LDH							0.549***
<1000 IU/l	1011 (64.0)	273 (27.0)	139	41.9	134	44.2	
⩾1000 IU/l	569 (36.0)	362 (63.6)	193	58.1	169	55.8	
Missing	344 (17.9)	146 (42.4)	92	21.7	54	15.1	
MYCN status							0.421***
Not amplified	824 (86.3)	213 (25.9)	90	67.7	123	71.9	
Amplified	131 (13.7)	91 (69.5)	43	32.3	48	28.1	
Missing	969 (50.4)	477 (49.2)	291	68.6	186	52.1	

INBR = Italian Neuroblastoma Registry; INSS = International Neuroblastoma Staging System.

a Percentages calculated within column.

* Non-abdominal: thorax = 313; pelvis = 64; other = 30.

** P value calculated after excluding resectable stage.

*** P value calculated on valid data only.

There were 424 children with NB progression (54.3%) and 357 with tumour relapse (45.7%), and were eligible for this study. Table 1 reports the descriptive statistics of the original INBR cohort and of the 781 study patients.

Biological data were not available for all the patients. In particular, *MYCN* gene was not assayed in 969 (50.3%) patients mostly diagnosed before 1992. Recurrences occurred less frequently in children younger than 18 months at diagnosis compared to the subsequent age groups. They also occurred more frequently in males, in patients diagnosed in the earlier period, in those with abdominal primary, with stage 4 disease, with abnormal VMA excretion, high LDH serum levels and with amplified *MYCN* gene copy number (Table 1). The main characteristics of children who progressed or relapsed were similar, except for the period of diagnosis – with more progressions occurring between 1979 and 1984 – and VMA excretion, with fewer abnormal values observed in children who progressed (Table 1).

Tumour progressions were documented at a median of 6.5 months (IQR: 3.2–11.5) from diagnosis, while relapses occurred at a median of 16.2 months (IQR: 9.7–23.4) from diagnosis and 10.7 months (IQR: 5.1–17.7) from date of best response. Most progressions and relapses were disseminated (79.5% and 77.6%, respectively). Children with localised disease more often had local progression (100% in stage 2 patients, 68.9% in stage 3 patients), while those with disseminated disease had disseminated progression (89.3% in stage 4 and 85.4% in stage 4s). A similar pattern was observed for relapses, except for stage 1 patients, among whom most events ($n = 15$; 65.2%) were disseminated, including 7 occurring at metastatic sites only. Among infants, only three patients with localised disease had a dissemination to the stage 4s pattern (skin and liver) and all are still alive and in complete remission.

Of the 357 relapses, 271 (75.9%) occurred early at a median interval of 7.8 months (IQR: 4.2–11.7), while 86 (24.1%) occurred late after a median of 28.4 months (IQR: 21.1–41.3).

All the study patients received salvage treatment based upon their previous treatment history (see Section 2). Only two stage 1 children who experienced local relapse were further treated with only surgery which turned to be radical. Both are still alive, one in complete remission and the other with stable disease after a second relapse. At follow-up, 663 (84.9%) patients had died. There were 384 deaths among children with tumour progression (90.6%) and 279 among those who relapsed (78.2%). Deaths were tumour-related in most of the cases (655 out of 663; 99.0%), while 7 (2 progressions, 5 relapses) were toxicity-related and one was due to a SMN (a malignant peripheral nerve sheet tumour) that occurred in a stage 3 patient 8 years from diagnosis and 4 months from progression. None died from other non-cancer-related causes. The 10-year OS was 6.8% (95% confidence interval (CI) 4.3–10.0) for children with tumour progression and 14.4% (95% CI 10.5–18.9) for those who relapsed (Fig. 1) ($P < 0.001$). The median OS time was 3.5 months after progression and 10.4 months after relapse.

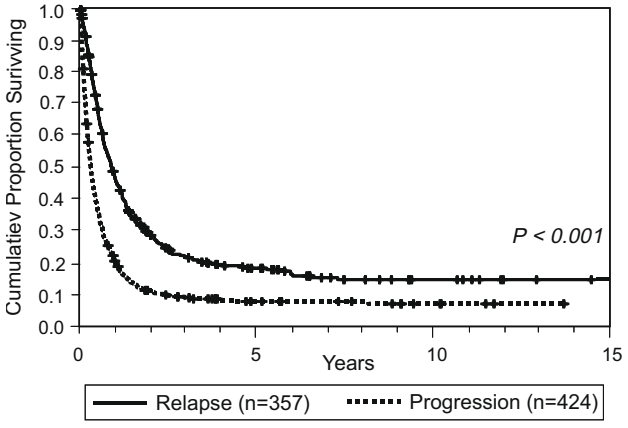

Fig. 1 – Survival after relapse or progression of 781 children with neuroblastoma.

3.1. *Correlation between presenting features and survival*

An analysis of the effect of various prognostic factors on OS is reported in Table 2. Younger age and a less advanced stage at diagnosis, recent era of diagnosis, extra-abdominal primary site, low LDH levels and non-amplified *MYCN* were significantly associated with better 10-year OS after either progression or relapse.

In more detail, children <18 months of age (Fig. 2A and B, Table 2) had always a significantly better probability of survival (22.0% after progression and 42.3% after relapse) as compared to older children, among whom only few survived after 5 years from the event ($P < 0.001$ in both cases). The clinical course of older children ($\geqslant$10 years) appeared to be more indolent, even though always fatal (Fig. 2A and B).

Stage at diagnosis was also significantly associated with survival after progression and relapse ($P < 0.001$ in both cases; Fig. 2C and D; Table 2). In fact, all five stage 2 patients who had tumour progression were rescued, while the OS for stage 4s patients was 39.0%, and only 6.6% and 1.5% for those with stage 3 or stage 4 neuroblastoma, respectively. Similarly, after tumour relapse a high 10-year OS rate (71.6%) was observed for stage 1 children, compared to 38.7%, 12.5% and 2.0%, respectively, for those with stages 2, 3 and 4.

As for the analysis of the period of diagnosis, survival was evaluated at 5 years in order to have comparable data for more recently diagnosed patients (Fig. 2 plots E and F; Table 2). A significantly better OS after both progression and relapse was observed among children diagnosed in the most recent period, and results did not differ significantly even if the analysis was extended to 10 years.

The other risk factors that were consistently and significantly associated to poor prognosis after either progression or relapse were abdominal primary site, high LDH levels and amplified *MYCN* status (Table 2). As for VMA, normal values at diagnosis were found to be significantly associated to poor survival only after progression. If type of event was considered, a disseminated type of the event was significantly associated to poorer survival only in case of relapse while no effect was demonstrated after progression (Table 2).

In multivariate analyses only age, stage at diagnosis and *MYCN* status had an independent effect on the probability of survival after progression (Supplementary Table 1). While site and timing of relapse, stage at diagnosis and *MYCN* status were found to be risk factors for the probability of OS after re-

lapse (Supplementary Table 2). However, these data should be evaluated with caution due to the small sample size (N = 115) and the violation of the proportional hazard assumption.

With regards to timing of relapse, as shown in Fig. 3, early relapses showed a more unfavourable, short term outcome with a rapid decrease in OS in the first months after the event. This was even more evident if only stage 4 children were included in the analysis (Supplementary Fig. 1). At about 6 years after relapse the curves cross each other at about the 16% level of the estimated probability of OS.

4. Discussion

Our study reports the long-term outcome of the largest ever cohort of children with neuroblastoma registered in prospective protocols to undergo disease progression or relapse. Overall, the prognosis for these patients was poor with median survival time less than 1 year, and less than 10% of children surviving more than 10 years after recurrence.

Recurrences occurred more often in association with the following presenting features: age >17 months, disseminated disease, abdominal primary site, elevated LDH and *MYCN* gene amplification. Of note, the frequency of events decreased over the study period, most likely due to the use of more aggressive induction protocols and the refinement of the supportive measures, leading more patients to achieve complete CR.

Almost 80% of recurrences were disseminated due to the fact that stage 4 patients, who made up the majority of the study population, almost exclusively developed metastatic recurrence. The type of events observed in localised diseases had a more complex pattern. While no progressions occurred in stage 1 patients, and relapses were mostly disseminated, in stage 2 and stage 3 patients the progressions were mainly lo-

Table 2 – Ten-year overall survival of 781 neuroblastoma patients after disease progression or relapse, by demographic, clinical and biological characteristics at diagnosis.

Patients characteristics	Progression			Relapse		
	OS %	95% CI	*P*	OS %	95% CI	*P*
Gender			0.978			0.140
Male	5.4	2.8–9.3		12.2	7.6–17.8	
Female	9.5	5.5–14.8		17.6	11.1–25.3	
Age			<0.001			<0.001
<18 months	22.0	14.5–30.4		42.3	30.7–53.5	
18 months to 4 years	1.8	0.46–4.8		7.5	3.9–12.5	
5–9 years	1.9	0.17–8.7		2.5	0.21–11.2	
⩾10 years	0.0	–		0.0	–	
Period of diagnosis*			<0.001			0.023
1979–1984	0.0	–		12.1	5.7–21.2	
1985–1991	8.1	3.8–14.5		15.2	8.8–23.3	
1992–1998	7.8	3.5–14.2		19.6	12.9–27.4	
1999–2004	23.3	14.1–33.8		29.9	18.4–42.2	
INSS stage			<0.001			<0.001
1	–	–		71.6	47.4–86.1	
2	100	–		38.7	22.9–54.2	
3	6.6	1.9–15.3		12.5	4.3–25.4	
4	1.5	0.42–4.1		2.0	0.28–7.4	
4s	39.0	24.3–53.4		33.3	12.2–56.4	
Primary site			0.034			0.004
Other sites	17.6	7.2–31.9		29.0	16.5–42.7	
Abdomen	5.5	3.2–8.9		12.2	8.3–16.9	
VMA			0.002			0.401
Normal	4.8	1.6–10.8		20.4	12.4–29.9	
Pathologic	6.6	3.7–10.7		11.9	7.6–17.3	
LDH			<0.001			<0.001
<1000 IU/l	8.9	3.7–17.1		21.3	14.1–29.6	
>1000 IU/l	5.4	2.7–9.5		6.2	2.5–12.3	
MYCN status			<0.001			<0.001
Not amplified	22.1	13.2–32.6		23.1	14.1–33.3	
Amplified	0.0	–		6.6	1.4–18.0	
Type of recurrence			0.273			<0.001
Local	13.5	7.1–22.0		28.4	17.5–40.4	
Disseminated/combined	5.4	3.1–8.6		10.4	6.7–15.0	

INSS = International Neuroblastoma Staging System.

* Follow-up time truncated at 5 years from progression or relapse.

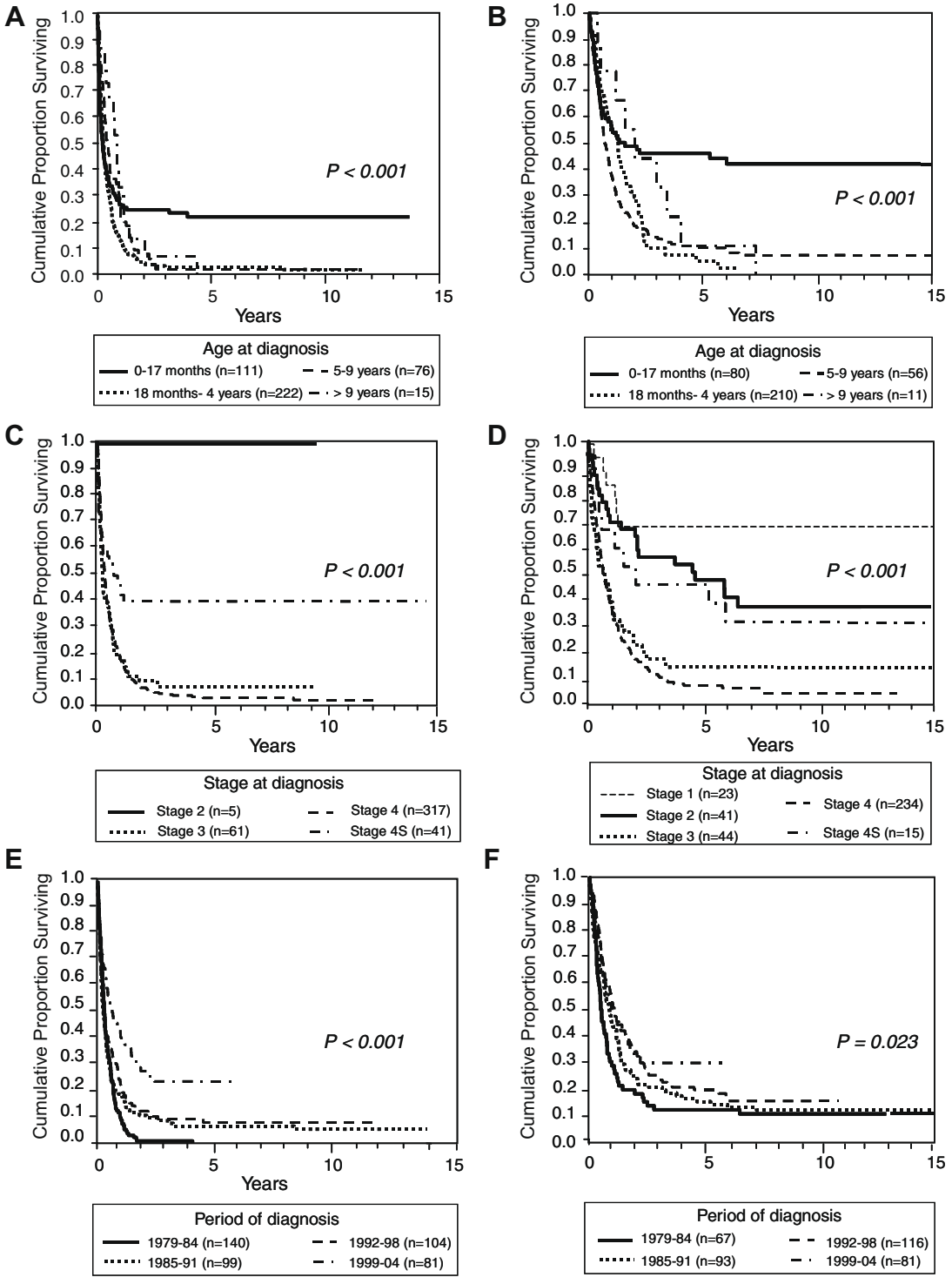

Fig. 2 – Survival after progression or relapse of 781 children with Neuroblastoma by age at diagnosis (Panel A: progression, Panel B: relapse), stage (Panel C: progression, Panel D: relapse) and period of diagnosis (Panel E: progression, Panel F: relapse).

cal and relapses were equally distributed between local and disseminated. The fact that the majority of relapses in stage 1 children were disseminated, with the bone marrow commonly being involved came as a surprise, although a similar finding was previously reported by Berthold and colleagues who attributed it to staging errors.[7] A similar observation was reported by the SIOPEN Group, where 11 out of the 16 recurrences that occurred in stage 1 were disseminated.[19] Of note, 10 out of 16 events were observed in infants and were interpreted as possible instances of unrecognised stage 4s disease.[19] This may also be the case in our series, since 11 out of 15 stage 1 children with disseminated tumour relapse were <12 months old at diagnosis, and were all rescued with salvage therapies.

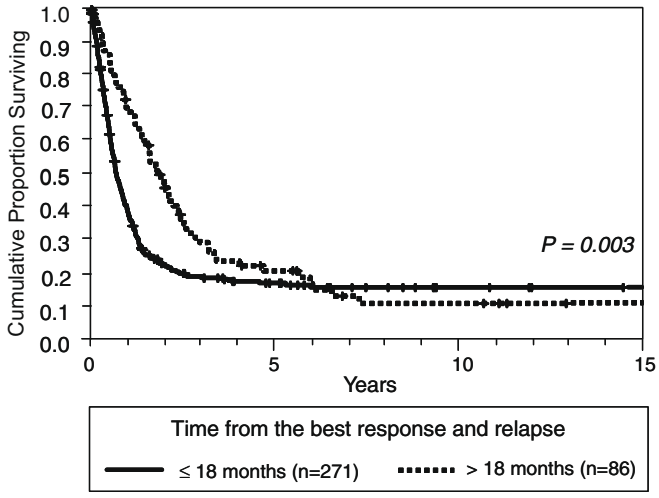

Fig. 3 – Survival after relapse of 357 children with Neuroblastoma by time from the best response and relapse onset.

The unfavourable role on OS played by age >17 months, as well as by early period of diagnosis, advanced disease stage, abdominal primary site, elevated LDH serum levels and amplified *MYCN* gene was confirmed both in patients suffering progression and in those undergoing relapse. Similarly, we confirmed previous observations of a more indolent but always eventually fatal outcome in adolescents (i.e. >9 years old) with neuroblastoma.[20]

Nonetheless, some differences were observed. One difference involved normal levels of urinary VMA, which had an unfavourable effect in case of tumour progression, but not of relapse. The association between normal VMA values and poor survival was already reported by others[21,22] and related to the frequent coexistence with *MYCN* gene amplification. Tumour cells with both features are in fact at an early stage of differentiation and therefore unable to produce catecholamines. In our cohort, using only patients with valid data for both VMA and *MYCN* values ($N = 275$) the association between normal VMA and amplified *MYCN* status was confirmed and was particularly evident in stage 4 children where *MYCN* amplification was observed in 56.5% ($N = 26$) of children with normal VMA values, versus 21.6% ($N = 32$) of those with pathologic VMA; $P < 0.001$.

The other difference we found between tumour progression and relapse was that the type of event significantly affected survival in case of relapse. Better OS was observed for local relapses, while it was not seen in case of progression. This was somehow not unexpected since the inability of the tumour to respond to front-line therapy may be a marker of an unfavourable somatic,[23] or constitutional pattern,[24] which could prevent salvage treatments from being effective. These data suggest that in case of progression, experimental treatments should be taken into consideration regardless of the site of the event, while conventional approaches might be more indicated for local relapse.

Similar remarks may be made when timing of relapse is considered as possible risk factor. As shown in Fig. 3, early relapses had a more rapid, unfavourable course with about 80% of deaths occurring within 2 years, while for late relapses this figure was reached only after about 5 years. The observation that duration of first remission is a powerful predictor of outcome was previously reported in a small group of neuroblastoma patients[25] and with other childhood tumours.[26,27]

In conclusion, our data confirm that treatment of neuroblastoma has a very high failure rate and this remains true even today, although some decrease in both progression and relapse rates has occurred over time. Clearly, new therapeutic front-line strategies are needed to significantly increase survival. In the unfortunate case of recurrence, the data reported in our study may be used when discussing treatment options with the patients' families. We have, in fact, identified a small cohort of patients, mainly in stages 1 and 2, some of whom have undergone local recurrence and others who have developed late relapse, for whom conventional treatment could still be proposed. With regards to the remaining larger proportion of patients, including all the ones with tumour progression, and stage 4 children with relapse, experimental therapies should be proposed. The results derived from these phase I and phase II studies should then be rapidly translated into a new front-line approach. In the process of obtaining informed consent for treatment from patients or their representatives, the issue of the patient's quality of life should also be carefully discussed and evaluated, and strategies for appropriate care when cure appears unlikely should strongly be taken into consideration.

Conflict of interest statement

None declared.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.06.010.

REFERENCES

1. De Bernardi B, Pistoia V, Gambini C, Granata C. Peripheral neuroblastic tumors. In: Hay ID, Wass JAH, editors. *Clinical endocrine oncology*. 2nd ed. Oxford, United Kingdom: Blackwell Science; 2008. p. 360–9.
2. Schmidt M, Simon T, Hero B, et al. The prognostic impact of functional imaging with (123)I-mIBG in patients with stage 4 neuroblastoma >1 year of age on a high-risk treatment protocol: results of the German Neuroblastoma Trial NB97. *Eur J Cancer* 2008;**44**:1552–8.
3. Alvarado CS, Kretschmar C, Joshi VV, et al. Chemotherapy for patients with recurrent or refractory neuroblastoma: a POG Phase II study. *J Pediatr Hematol Oncol* 1997;**19**:62–7.
4. Rubie H, Chisholm J, Defachelles AS, et al. Phase II study of temozolomide in relapsed or refractory high-risk neuroblastoma: a joint Société Française des Cancers de l'Enfant and United Kingdom Children Cancer Study Group–New Agents Group Study. *J Clin Oncol* 2006;**24**:5259–64.
5. Bagatell R, Gore L, Egorin MJ, et al. Phase I pharmacokinetic and pharmacodynamic study of 17-N-allylamino-17-demethoxygeldanamycin in pediatric patients with recurrent or refractory solid tumors: a pediatric oncology experimental therapeutics investigators consortium study. *Clin Cancer Res* 2007;**13**:1783–8.
6. Ladenstein R, Lasset C, Hartmann O, et al. Impact of megatherapy on survival after relapse from stage 4 neuroblastoma in patients over 1 year of age at diagnosis: a report from the European Group for Bone Marrow Transplantation. *J Clin Oncol* 1993;**11**:2330–41.
7. Berthold F, Hero B, Breu H, et al. The recurrence patterns of stages I, II and III neuroblastoma: experience with 77 relapsing patients. *Ann Oncol* 1996;**7**:183–7.
8. De Bernardi B, Conte M, Mancini A, et al. Localized resectable neuroblastoma: results of the second study of the Italian Cooperative Group for Neuroblastoma. *J Clin Oncol* 1995;**13**:884–93.
9. Garaventa A, Boni L, Lo Piccolo MS, et al. Italian Cooperative Group for Neuroblastoma: localized unresectable neuroblastoma: results of treatment based on clinical prognostic factors. *Ann Oncol* 2002;**13**:956–64.
10. De Bernardi B, Nicolas B, Boni L, et al. Italian Co-Operative Group for Neuroblastoma: disseminated neuroblastoma in children older than one year at diagnosis: comparable results with three consecutive high-dose protocols adopted by the Italian Co-Operative Group for Neuroblastoma. *J Clin Oncol* 2003;**21**:1592–601.
11. 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**:1537–44.
12. Baussano I, Maule MM, Dama E, et al. Expected number of childhood cancers in Italy from 2001 to 2015. *Haematologica* 2007;**92**:1258–61.
13. Brodeur GM, Seeger MC, Barrett A, et al. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol* 1998;**11**:1874–81.
14. De Bernardi B, Pastore G, Garaventa A, et al. Phase II trial of amsacrine in children with advanced metastatic neuroblastoma. *Cancer Treat Rep* 1984;**68**:1051–2.
15. Garaventa A, Luksch R, Biasotti S, et al. A phase II study of topotecan with vincristine and doxorubicin in children with recurrent/refractory neuroblastoma. *Cancer* 2003;**98**:2488–94.
16. Dini G, Lanino E, Rogers D, et al. Resistant and relapsing neuroblastoma: improved response rate with a new multiagent regimen (OC-HDP) including high-dose cisplatinum. *Med Pediatr Oncol* 1987;**15**:18–23.
17. Garaventa A, Guerra P, Arrighini A, et al. Treatment of advanced neuroblastoma with I-131 meta-iodobenzylguanidine. *Cancer* 1991;**67**:922–8.
18. Cox DR. Regression models and life-tables (with discussion). *J R Statist Soc B* 1972;**34**:187–220.
19. De Bernardi B, Mosseri V, Rubie H, et al. Treatment of localised resectable neuroblastoma. Results of the LNESG1 study by the SIOP Europe Neuroblastoma Group. *Brit J Cancer* 2008;**99**:1027–33.
20. Conte M, Parodi S, De Bernardi B, et al. Neuroblastoma in adolescents: the Italian experience. *Cancer* 2006;**106**:1409–17.
21. Strenger V, Kerbl R, Dornbusch HJ, et al. Diagnostic and prognostic impact of urinary catecholamines in neuroblastoma patients. *Paediatr Blood Cancer* 2007;**48**:504–9.
22. Parodi S, Papio F, Haupt R, et al. The prognostic role of urinary catecholamine in infants with disseminated neuroblastoma may be mediated by *MYCN* amplification. *Paediatr Blood Cancer* 2007;**48**:594–9.
23. Norris MD, Smith J, Tanabe K, et al. Expression of multidrug transporter MRP4/ABCC4 is a marker of poor prognosis in neuroblastoma and confers resistance to irinotecan in vitro. *Mol Cancer Ther* 2005;**4**:547–53.
24. Ashton LJ, Murray JE, Haber M, et al. Polymorphisms in genes encoding drug metabolizing enzymes and their influence on the outcome of children with neuroblastoma. *Pharmacogenet Genomics* 2007;**17**:709–17.
25. Santana VM, Furman WL, McGregor LM, et al. Disease control intervals in high-risk neuroblastoma. *Cancer* 2008;**112**:2796–801.
26. Malempati S, Gaynon PS, Sather H, et al. Outcome after relapse among children with standard-risk acute lymphoblastic leukemia: Children's Oncology Group study CCG-1952. *J Clin Oncol* 2007;**25**:5800–7.
27. Mazzoleni S, Bisogno G, Garaventa A, et al. Outcomes and prognostic factors after recurrence in children and adolescents with nonmetastatic rhabdomyosarcoma. *Cancer* 2005;**104**:183–90.