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Clinical prognostic factors in 1277 patients with neuroblastoma: results of The European Neuroblastoma Study Group 'Survey' 1982–1992

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Abstract

In 1982 the European Neuroblastoma Study Group (ENSG) established a prospective registry for patients with newly diagnosed neuroblastoma ('The ENSG Survey'). Clinical information was collected primarily to: (a) establish an ENSG database; and (b) investigate prognostic factors in neuroblastoma. This paper summarises the results of the survey. By 1992, 1277 patients with a median age of 26 months (range: 0–289 months), gender ratio of 1.19 M:F had been registered from 30 centres. The median follow-up of survivors is 9.7 years (range: 1–14 years). Overall 5-year survival (S) is 45% (95% CI 42–48%), and event-free survival (EFS) is 43% (95% CI 40–45%). For both survival and EFS the key established prognostic factors, stage and age, are highly significant ($P < 0.001$). In particular, patients under 1 year of age at diagnosis, whatever the disease stage, had a more favourable prognosis than older patients; stage 2 (EFS 93% (95% (CI 85–97) versus 76% (95% CI 67–86), $P = 0.02$), stage 3 (EFS 91% (95% CI 82–96) versus 52% (95% CI 44–60), $P < 0.001$) and stage 4 (EFS 59% (95% CI 48–69) versus 16% (95% CI 13–19), $P < 0.001$). Multivariate analysis established that the anatomical location of the primary tumour (i.e. abdominal versus other sites) and primary tumour volume also conferred a statistically significant difference. In stage 4 disease the 20% of patients without demonstrable bone marrow involvement had a more favourable prognosis than those with infiltrated marrow (EFS 36% (95% CI 13–19) versus 16% (95% CI 29–45), $P < 0.001$). Urine catecholamine metabolite levels (raised versus normal), histology (ganglioneuroblastoma versus neuroblastoma) and gender had no significant effect on outcome after stage and age were accounted for. 5-year survival following first relapse is only 5.6% (95% CI 2.8–8.4). This ENSG Survey provides secure data for future comparisons with new prognostic factors and treatment programmes.

Keywords: Neuroblastoma; Ganglioneuroblastoma; Prognosis; Infant

1. Introduction

Neuroblastoma accounts for approximately 6% of malignancies in children and is the most common cancer under the age of 1 year [1]. Our understanding of the molecular pathology of neuroblastoma, for example, the role of *N-MYC* gene amplification [2,3], allelic loss of chromosome 1p [4,5], unbalanced gain of material on chromosome 17q [6,7] and tumour ploidy has improved recently but clinical features such as age and stage are still important guides to prognosis and treatment planning [8–10]. Other studies have revealed the potential prognostic importance of clinical characteristics including the site of the primary tumour, regional lymph node involvement (for age >1 year) [11], catecholamine

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metabolite excretion ratios and lactate dehydrogenase levels [12].

From 1982 to 1992, The European Neuroblastoma Study Group (ENSG) established a registry, known as the 'ENSG Survey', for patients with neuroblastoma. All member centres of the ENSG contributed clinical data on all patients admitted during their participation, most of them for the entire 11-year period. The purpose of the 'survey' was to establish the demographic characteristics of neuroblastoma in part of Western Europe. The primary intent of this paper is to assist in treatment planning by presenting the clinical data from large numbers of patients so that rational decisions can be made.

2. Patients and methods

In January 1982, the ENSG established a register of newly diagnosed patients with neuroblastoma and collected clinical data up to December 1992 in order to investigate clinical prognostic factors. This exercise was known as the 'ENSG Survey'. Each treatment centre was required to register every new patient with histologically confirmed neuroblastoma/ganglioneuroblastoma admitted during that period. The 30 participating centres are listed in Appendix A; the French centres registered patients up to 1988 and other centres up to 1992.

In total, details of 1277 patients were documented. Criteria for diagnosis of neuroblastoma varied during the 'survey'. Overall, 59% of patients were diagnosed on the basis of pathological classification of biopsy samples, and 29% by the results of bone marrow investigations (aspirates and/or trephines) combined with elevated levels of urinary hydroxy mandelic acid (HMMA) and/or homovanillic acid (HVA). The remaining 12% were diagnosed on the basis of elevated urine HMMA/HVA levels and radiological evidence alone (one-third of these patients later had histological confirmation following delayed surgical resection). The median age at diagnosis was 26 months (range: 0–289 months) and 90% of patients were under 6 years old. Of the 129 (10%) who were age 6 years or over 98 (8%) were 6–9 years old, 24 (2%) were between ages 10 and 14 years and 7 (0.5%) were of age 15 years or over. 840 patients (66%) were registered by centres of the United Kingdom Children's Cancer Study Group (UKCCSG), representing over three-quarters of the national incidence during this period. At the time of analysis, the median follow-up for survivors was 9.7 years (range: 1–14 years).

Clinical trials co-ordinated by the ENSG [13–18] from 1982 to 1992 are outlined in Appendix B and usually involved only stage 3 and 4 patients. Treatment principles were similar throughout the 11-year period. Immediate or delayed surgical resection of the primary tumour was almost always carried out and chemotherapy was based around the OPEC regime (vincristine, cisplatin, etoposide and cyclophosphamide) [19] for the first 6 years, and thereafter alternating courses of OPEC and OJEC (vincristine, carboplatin, etoposide and cyclophosphamide). Patients aged >1 year with stage 4 disease usually received 'megatherapy' with melphalan $\pm$ other agents and stem cell rescue and some took part in a randomised study of 13-cis-retinoic acid for 2 years after the end of chemotherapy. A few patients received radiotherapy to residual primary tumour and several were treated with ^{131}I-labelled meta-iodobenzylguandine (mIBG).

There are a number of different staging systems for neuroblastoma [11,20,21] but an international consensus has now been achieved and as far as possible, the International Neuroblastoma Staging System (INSS) was used in this study [22,23]. However, most of the children were diagnosed before the INSS recommendations were available and stage 2 patients were analysed as a single group because there was insufficient information in many cases, concerning lymph node involvement, to classify these tumours as either stage 2A or 2B. Using the revised INSS criteria the stage 4S label was restricted to infants aged under 1 year at diagnosis.

Event-free survival is taken as the time from diagnosis to first relapse or time to death in patients who died with no relapse. Patients who died from treatment or from unrelated causes were not censored in this analysis and surviving patients are censored at the time of last follow-up. Kaplan–Meier estimates with 95% confidence intervals (CI) were used for survival curves [24] and for calculating survival (S) and event-free survival (EFS). Prognostic factors were also analysed using a Cox proportional hazards analysis [25]. In statistical tests a 5% level was taken to indicate significance, with no adjustments made for multiple testing. The main proportional hazard analysis involving stage, gender, site and age groups did not include stage 4S patients as, by definition, all these patients were under 1 year of age. These infants were analysed separately. Tumour volume in cubic cm was estimated using a formula incorporating the three maximum diameters ($a \times b \times c \times 0.52$) measured from pathological specimens when surgical resection was the first treatment, or otherwise from ultrasonographic (US) or computer tomographic (CT) imaging. In those patients for whom tumour volume was available a separate forward stepwise regression was undertaken for the following variables; stage, age group, site, gender, urine catecholamine metabolites and histology. Prognostic factors in stage 4 patients were also analysed using stepwise regression for age group, presence/absence of bone marrow metastases, presence/absence of bone metastases and primary tumour site. χ^2 tests were also carried out to test for associations between variables.

3. Results

3.1. Overall event-free survival (EFS), survival and causes of death

Overall 5-year EFS is 43% (95% CI 40–45%) and 5-year survival is 45% (95% CI 42–48%). Patient characteristics and EFS by patient subgroups are provided in Table 1. EFS by INSS stage is displayed in Fig. 1. 5-year EFS ranges from 95% (95% CI 86–98) for stage 1 disease to 20% (95% CI 18–23) for stage 4 disseminated disease. Of 736 reported deaths, 62 were treatment-related (8.4%). 16 (26%) of these deaths were due to overwhelming infections during chemotherapy, 15 (24%) to complications following high-dose therapy and stem cell rescue and in 8 (13%) children were caused by haemorrhage or multi-organ failure attributed to treatment. In addition 4 (6%) patients died from cardiotoxicity, 5 (8%) following surgical complications, 1 (2%) due to radiotherapy complications, and 13 (21%) from other or unspecified treatment-related causes. Of the remaining deaths, 665 (90.4%) were caused by progressive neuroblastoma and 9 (1.2%) were attributed to other, unrelated causes. In a multivariate analysis of patients with stages 1–4 disease, gender was not a significant variable but age group ($<$ or $>$ 1 year), stage and site (abdominal or non-abdominal) were shown to have significant independent influence on EFS. Regression coefficients and hazard ratios are given in Table 2.

Table 1
Patient characteristics and event-free survival (EFS) by category

Patient category	Cases *n* (%)	5-year EFS % (95% CI)
Gender		
Male	693 (54.3)	39 (36–43)
Female	584 (45.7)	47 (43–51)
Age at diagnosis (months)		
0–11	330 (25.8)	80 (76–84)
12–23	245 (19.2)	40 (34–47)
24–35	232 (18.2)	30 (24–36)
36–47	150 (11.7)	23 (17–30)
48–59	120 (9.4)	21 (14–29)
$\geqslant$60	197 (15.4)	25 (19–31)
Unspecified	3 (0.2)	(1/3)
Site of primary tumour		
Abdominal	925 (72.4)	34 (31–38)
Cervical	47 (3.7)	81 (66–89)
Pelvic	43 (3.4)	72 (56–83)
Thoracic	132 (10.3)	71 (62–78)
Thoraco-abdominal	71 (5.6)	51 (39–66)
Multiple primaries	20 (1.6)	45 (23–66)
Other	7 (0.5)	43 (10–73)
Undetected	15 (1.2)	31 (10–55)
Unspecified	17 (1.3)	41 (19–63)
Urine HMMA/VMA		
Elevated	992 (77.7)	40 (36–43)
Normal	212 (16.6)	59 (51–65)
Unspecified	73 (5.7)	40 (29–51)
Tumour stage		
1	62 (4.9)	95 (86–98)
2	152 (11.9)	86 (79–91)
3	213 (16.7)	65 (58–71)
4	766 (60.0)	20 (18–23)
4S	73 (5.7)	76 (65–85)
Unspecified	11 (1.0)	33 (8–61)
Total	1277 (100.0)	43 (40–45)

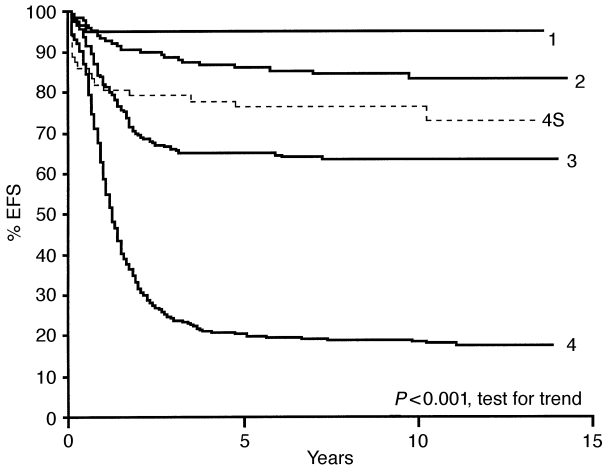

Fig. 1. Event-free survival by INSS stage ($n=1266$). Note: Figure excludes 11 patients for whom stage was unspecified. The numbers at risk at 5 years for stages 1, 2, 3, 4 and 4S were 55, 123, 131, 151 and 52 respectively and at 10 years 23, 60, 65, 74 and 26 respectively.

3.2. Age and stage

Data from this study confirm that, overall, infants aged under 1 year of age have a more favourable outcome than older patients (80% (95% CI 76–85) versus 29% (95% CI 27–32) EFS, $P<0.001$). In part, this difference in prognosis is partly attributable to a higher proportion of low stage patients in infants. Most older patients, by contrast, present with stage 4 disease. Thus, compared with older patients there was a significantly lower proportion of stage 4 disease in infants <1 year of age ($P<0.001$). However, multivariate analysis

Table 2
Results of multivariate analysis of event-free survival (EFS) for international neuroblastoma staging system (INSS) stages 1–4 ($n=1182$)

Regression terms	Coefficient	*P* value	Hazard ratio (95% CI for ratio)
Stage: 2	1.284	0.036	3.61 (1.1–12.0)
Stage: 3	2.072	<0.001	7.94 (2.5–25.2)
Stage: 4	3.094	<0.001	22.07 (7.1–68.9)
Age: >1 year	1.112	<0.001	3.04 (2.3–4.0)
Primary site: abdominal	0.281	0.006	1.32 (1.1–1.6)
Gender: female	−0.069	0.365	0.93 (0.8–1.1)

CI, confidence interval.

Table 3
Five-year event-free survival by international neuroblastoma staging system (INSS) stage and age group

	Age <1 year at diagnosis		Age 1 year or over at diagnosis		
Stage[a]	*n* (%)	% EFS (95% CI)	*n* (%)	% EFS (95% CI)	*P* value[b]
1	29 (8.7)	90 (71–97)	33 (3.5)	100 –	0.19
2	76 (22.9)	93 (85–97)	76 (8.1)	76 (67–86)	0.02
3	70 (21.1)	91 (82–96)	143 (15.3)	52 (44–60)	<0.001
4	84 (25.3)	59 (48–69)	682 (73.0)	16 (13–19)	<0.001
4S	73 (22)	77 (66–85)	–	–	–
Total	332 (100.0)	80 (76–85)	934 (100.0)	29 (27–32)	<0.001

EFS, event-free survival; CI, confidency interval.
[a] For 11 patients details of stage or age were missing.
[b] *P* = significance value for log-rank test.

shows that age remains a significant prognostic factor even after stage is accounted for. Table 3 gives a comparison of 5-year EFS by age group and stage. Infants <1 year of age with stage 3 tumours, for instance, had a more favourable outcome than children ⩾1 year at diagnosis (91% (95% CI 82–96) versus 52% (95% CI 44–60) EFS, $P<0.001$). The same applied to stage 4 patients (59% (95% CI 48–69) versus 16% (95% CI 13–19) EFS, $P<0.001$). EFS for stage 4 by age group is shown in Fig. 2.

3 patients, initially categorised as 'Evans' stage IVs, but who were aged over 1 year (aged 17, 22 and 41 months) at diagnosis were reclassified as INSS stage 4 for the purpose of this analysis. All 3 children died of disease. The median age of infants with true 4S disease ($n=73$) was 2 months (range: 0–10 months), with 12 patients diagnosed within the first week after birth, and 90% at age 6 months or less. The overall 5 year EFS for stage 4S patients is 77% (95% CI 66–85). There was a suggestion of better survival in younger infants aged <3 months at diagnosis but the difference was not statistically significant. Of those diagnosed before the age of 3 months 7/45 (16%) died compared with 4/17 (24%) aged 3–5 months old and 4/9 (44%) infants of 6 months or older.

3.3. Site and stage

Overall, patients with abdominal primaries have a less favourable prognosis than those with cervical, pelvic and thoracic primaries (Table 1). The relationship between site and stage is illustrated in Table 4. In particular, most stage 3 and stage 4 patients presented with abdominal primaries, whilst cervical and thoracic primaries were more common in stage 1 and 2 disease. There were 15 patients with stage 4 disease but no detectable primary tumour. For stage 3 disease the prognosis for children with abdominal primary tumour is significantly worse than for other sites (5-year EFS 58 versus 81%, $P=0.003$), as illustrated in Fig. 3. Similarly, in patients with stage 4 disease those with abdominal primaries had a worse outcome (Fig. 3) (5-year EFS 19% versus 29%, $P=0.02$). No significant influence of site on survival was demonstrable for stages 1, 2 and 4S.

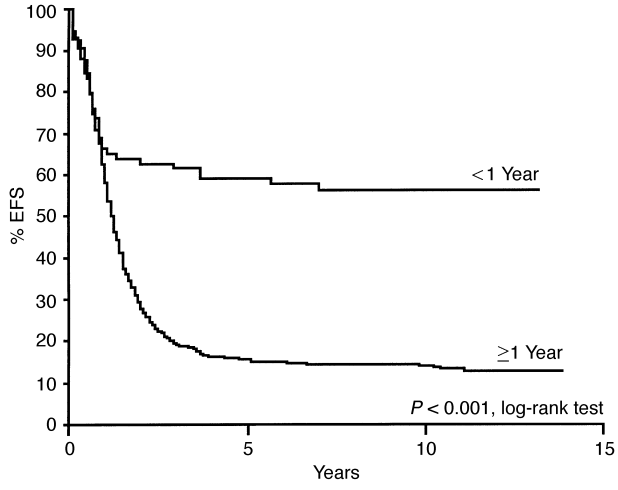

Fig. 2. Event-free survival for stage 4 patients by age-group ($n=766$). Note: the numbers at risk for age <1 and age ⩾1 year at 5 years were 47 and 104 respectively and at 10 years 25 and 49 respectively.

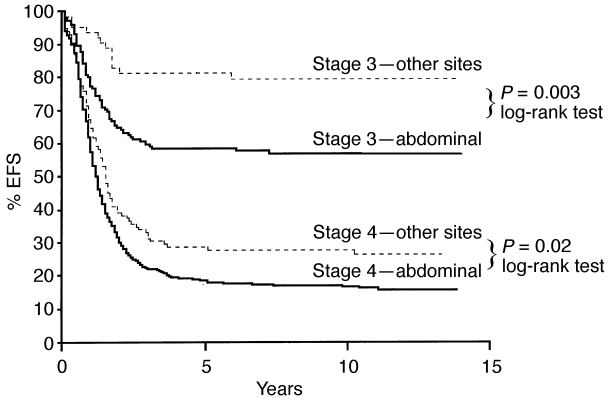

Fig. 3. Event-free survival by primary site for patients with stages 3 and 4 neuroblastoma ($n=967$). Note: figure excludes 12 patients for whom site was unspecified. The numbers at risk at 5 years for stage 4 abdominal primary, stage 4 other sites, stage 3 abdominal and stage 3 other sites were 115, 33, 81 and 50 respectively and at 10 years 51, 21, 40 and 25 respectively.

Table 4
Primary site by international neuroblastoma staging systems (INSS) stage

	INSS stage						
Primary site	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)	4S *n* (%)	Unspecified *n* (%)	Total *n* (%)
Abdominal	28 (45)	56 (37)	148 (69)	638 (83)	49 (67)	6 (55)	925 (72)
Cervical	10 (16)	24 (16)	3 (1)	7 (1)	3 (4)	0	47 (4)
Pelvic	3 (5)	10 (7)	18 (8)	11 (1)	1 (1)	0	43 (3)
Thoracic	21 (34)	47 (31)	26 (12)	34 (4)	3 (4)	1 (9)	132 (10)
Thoraco-abdominal	0	12 (8)	16 (8)	41 (5)	2 (3)	0	71 (6)
Multiple	0	0	0	13 (2)	7 (10)	0	20 (2)
Other	0	2 (1)	1 (1)	3 (0.5)	0	1 (9)	7 (1)
Undetected	0	0	0	8 (1)	7 (10)	0	15 (1)
Unspecified	0	1 (1)	1 (1)	11 (1)	1 (1)	3 (27)	17 (1)
Total	62 (100)	152 (100)	213 (100)	766 (100)	73 (100)	11 (100)	1277 (100)

Data on tumour size were available for 806 (63%) patients and were related to site, stage and age at diagnosis. The median tumour volume was larger in abdominal tumours (median: 187 ml, range: 4–2340 ml) compared with other sites combined (median: 65 ml, range: 1–1798 ml). Tumour size was also related to stage. In infants the median volumes for stages 1, 2 and 3 were 48, 70 and 210 ml for abdominal tumours and 14, 37 and 65 ml for primaries at other sites. In children >1 year of age the equivalent median volumes were 19, 229 and 338 ml for abdominal tumours, and 47, 51 and 142 ml for other primary sites. In a stepwise multivariate analysis ($n=806$) tumour volume had a significant influence on EFS (tumour volume >100 ml Hazard ratio 1.28; 95% CI 1.03–1.59, $P=0.03$) after allowing for stage, age-group and primary site.

3.4. Gender

The overall male to female ratio is 1.19:1. There was an excess of males in stage 4 patients compared with other stages ($P<0.04$) and a slight excess of females in patients with stage 1 and 4S tumours. The 5-year EFS for males was slightly less than that for females (39% (95% CI 36–43) versus 47% (95% CI 43–51), $P<0.01$) but gender is not a significant prognostic factor once stage and age are taken into account. The group of patients with stage 4 disease had a significantly higher proportion of males in the >1 year old age group compared with infants ($P<0.03$). Amongst stage 4 patients, those with bone metastases had an excess of males compared with those in whom none were detected ($P<0.03$).

3.5. Urine catecholamine metabolite excretion

Raised catecholamine metabolite levels were more common in patients with stages 4 and 4S disease than in patients with lower stage disease ($P<0.001$). One-fifth of patients had normal urinary levels of HMMA and/or HVA and, overall, these children had a better prognosis (5-year EFS 59% (95% CI 51–65) versus 40% (95% CI 36–43), $P<0.001$). This difference seems to be accounted for by stage differences between those with raised levels; the two groups. Thus, once stage is taken into account there is no significant difference in EFS between those with normal HMMA/VMA metabolite levels and those with raised levels.

3.6. Histology

There are 120 (9.4%) patients documented with initial histology of 'ganglioneuroblastoma'. Overall, this group has an EFS of 70% (95% CI 62–79) at 5 years. Over half of these patients had stage 1 or stage 2 disease. However, once stage and age were taken into account there was no significant difference in survival between patients with ganglioneuroblastoma and neuroblastoma. The group with ganglioneuroblastoma contained a higher proportion of older patients (median age 33 months for ganglioneuroblastoma compared with 23 months for those with neuroblastoma). Thus, only 17.6% of stage 1 patients aged under 1 year at diagnosis had ganglioneuroblastoma histology, whilst in patients aged 1 year or over the proportion was 76% ($P<0.001$). Similarly, for stage 2 tumours there was a higher proportion of ganglioneuroblastoma histology in older children than in infants.

3.7. Pattern of metastasis in stage 4 disease

Approximately 80% of stage 4 patients had detectable marrow involvement and these children had a worse prognosis than those in whom marrow involvement was not detected (5-year EFS 36% (95% CI 13–19) versus 16% (95% CI 29–45), $P<0.001$). Similarly the 65% of patients with multiple bone metastases had a worse outcome than those with only one or no bone metastases

(5-year EFS 15% (95% CI 24–35) versus 29% (95% CI 12–18), $P<0.03$). In a stepwise multivariate analysis ($n=586$) of stage 4 patients, age group ($P<0.001$), marrow metastases ($P=0.003$) and site ($P=0.05$) were significant prognostic factors regression: hazard ratios 2.9 (95% CI: 2.0–4.2), 1.4 (95% CI: 1.1–1.8) and 1.3 (95% CI: 1.0–1.6), respectively.

3.8. Pattern of relapse and subsequent survival

Tumour recurrence was usually within 2 years of diagnosis and was typically widespread. The most common reported sites at first relapse were marrow in 57% of cases, bone (51%), primary site (45%), abdominal lymph nodes (29%), other lymph nodes (27%), liver (11%) and pleura (5%). Prognosis after relapse is poor. In this series, overall 2-year survival after first relapse was 10.1% (95% CI: 6.7–13.6), and at 5 years 5.6% (95% CI: 2.8–8.4). Of 322 reported first relapses 289 (90%) had been age 1 year or over and stage 3 or 4 at diagnosis and had a significantly worse prognosis compared with other patients following relapse ($P<0.001$), with 8% survival at 2 years from relapse (95% CI: 5–11). Of the remaining patients 12 out of 33 were alive at the time of analysis. Though most relapses occur within two years from diagnosis, late recurrences do occur [26]. The prognosis for patients in this series surviving 5 years or more has been reported elsewhere [27].

4. Discussion

Whilst the ENSG survey is not a true population-based registry, this multicentre and international collaboration has resulted in the accrual of a very large cohort of patients, selected only by referral to a tertiary centre. Since, in the case of the UK, >90% of children with neuroblastoma are known to be referred to one of its 22 paediatric oncology centres the 'survey' is probably demographically representative of the disease as a whole. The survey therefore provides disease-specific information that might not be available from national cancer registries, and yields detailed information about prognostic factors pertinent to clinical trial design.

In this analysis the diagnosis of neuroblastoma was made using criteria recommended by the INSS. However, these criteria changed over the period of the survey and in some cases, the basis for diagnosis would not be sufficient to meet current standards. However, exclusions would introduce an element of bias since most of the patients with no histological confirmation had stage 4 or 4S disease, diagnosed on the basis of significantly elevated (>2 S.D.) catecholamine metabolite levels and a detectable primary tumour. Therefore, we chose to include all patients in whom the criteria for diagnosis accorded with contemporary ENSG definitions. Stage and age are the key prognostic indicators in this series as in others, but primary site and tumour volume are also independently statistically significant.

A report from an Italian group suggested that children under 6 months of age with stage 4S disease had a worse prognosis than older infants [28]. In the ENSG series the results were different, with a suggestion of poorer outcome with increasing age. In contrast, our results were similar to the Italian findings for stage 4 disease; those aged <6 months at diagnosis had a better prognosis than older infants, though the difference was not statistically significant. Several prospective studies including those of the ENSG are investigating the relationship of age to underlying molecular characteristics.

The data reported here regarding tumour volume are novel. However, levels of serum lactate dehydrogenase (LDH), which are related to tumour volume, have also been reported as being a significant prognostic factor in neuroblastoma [29,30].

Our results also suggest that some stage 4 patients with no demonstrable marrow disease have a more favourable prognosis. However, given the technical limitations of marrow sampling in the detection of tumour deposits [31] this finding may well reflect the extent of marrow involvement, as a reflection of metastatic potential rather than a true absence of marrow disease.

There is known to be an excess of males with increasing age and higher stage and less favourable sites [8–10]. However, as previously reported in preliminary form [32], gender is not a significant prognostic factor once stage and age are taken into account. The differences in stage distribution between males and females are, as yet, unexplained. Levels of urinary catecholamine metabolite excretion are directly related to stage [33]. Recent research has focused on the importance of molecular abnormalities such as *N-MYC* amplification, 1p deletion, tumour ploidy, TRK-A expression and 17q translocations. Since 1992 the ENSG has been collecting data on the molecular characteristics of tumours. Current and future research may more clearly define the relationship between these molecular features and clinical characteristics, especially stage, age, gender and tumour volume.

More effective treatments for children with advanced neuroblastoma, especially stage 4 patients who are 1 year old or over, are urgently needed. This group, which accounts for over half of all patients, has a 5-year EFS of only 15% in this and other series. ENSG research aimed at improving outcome in these children includes: (a) comparison of rapid dose-intensive induction chemotherapy versus conventional therapy to see if an increased dose intensity can retard or prevent the development of drug resistance (ENSG 5) [20]; (b) the incorporation of radiolabelled mIGB into induction therapy (ENSG 11); and (c) the role of retinoic acid derivatives in sustaining remission in patients with

residual disease after chemotherapy and surgical resection of the primary tumour (ENSG 4). Other groups are investigating the relative roles of consolidation megatherapy, with stem cell rescue, versus continuing 'induction-type' chemotherapy [34] and the use of monoclonal antibody therapy [35]. In the future, a combination of clinical, histological and molecular characteristics may permit treatment that is 'tailored' to the individual characteristics of each child's tumour.

Appendix A: List of institutions contributing patients between 1982 and 1992

Addenbrooke's Hospital, Cambridge, UK
AZ Kinderen V.U.B., Brussels, Belgium
Barnmedicininska Kliniken, Gothenburg, Sweden
Centre Leon Bernard, Lyon, France
Cliniques Universitaires St-Luc, Brussels, Belgium
Emma Kinder Ziekenhuis HK AMC, Amsterdam, The Netherlands
Great Ormond Street Hospital for Children, London, UK
Institut Curie, Paris, France
Institut Gustave Roussy, Villejuif, France
Ipprokration Hospital, Thessalonica, Greece
Kindergeneeskunde, Leuven, Belgium
Leicester Royal Infirmary, Leicester, UK
Llandough Hospital, Cardiff, UK
Our Lady's Hospital for Sick Children, Dublin, Eire
Royal Aberdeen Children's Hospital, Aberdeen, UK
Royal Liverpool Children's Hospital, Liverpool, UK
Royal Manchester Children's Hospital, Pendlebury, UK
Royal Victoria Infirmary, Newcastle, UK
St Bartholemew's Hospital, London, UK
St James University Hospital, Leeds, UK
The Children's Hospital, Birmingham, UK
Royal Hospital for Sick Children, Edinburgh, UK
Royal Hospital for Sick Children, Glasgow, UK
Queen's Medical Centre, Nottingham, UK
Royal Marsden Hospital, Sutton, UK
Sheffield Children's Hospital, Sheffield, UK
Southampton General Hospital, Southampton, UK
Universita 'Degli Studi di Toma ''La Sapienza'', Rome, Italy
Universitet Oslo, Oslo, Norway
University Hospital of Aarhus, Aarhus, Denmark

Appendix B: ENSG trials 1982–1992

ENSG 1 — Randomised study of high-dose melphalan as consolidation therapy in advanced neuroblastoma 1982–1985 (8202)
ENSG 2 — Study of ifosfamide in patients with relapsed neuroblastoma 1984–1985 (8403)
ENSG 3A — Study of single-agent ifosfamide at diagnosis in patients with neuroblastoma 1985–1986 (8504)
ENSG 3B — Study of high-dose cisplatin and etoposide as initial therapy in stage 4 neuroblastoma 1985–1987 (8505)
ENSG 3C — Study of high-dose cisplatin and etoposide alternating with ifosfamide, vincristine and doxorubicin as initial therapy for stage 4 neuroblastoma 1985–1988 (8505)
ENSG 4 — Randomised double-blind placebo controlled trial of 13-cis-retinoic acid as continuation therapy for patients with advanced neuroblastoma in complete or good partial remission 1988–present (8904)
ENSG 5 — Randomised trial of dose intensity in stage 4 neuroblastoma over the age of 1 year 1990–present (9011)
ENSG 8 — Protocol for infants with neuroblastoma diagnosed under the age of one year 1992–present (9205)

UKCCSG reference numbers are in parentheses. See [15–20].

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