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Original Paper

Prospective Evaluation of the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Response Criteria (INRC) in a Multicentre Setting

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The aim of this study was to classify prospectively a series of neuroblastoma tumours according to the International Neuroblastoma Staging System (INSS) and the International Neuroblastoma Response Criteria (INRC) and to evaluate the difficulties and pitfalls involved in a multicentre setting. Each hospital provided their data for central review. The surgical procedures and their complications were reported. Kaplan–Meier estimates of survival and event-free survival were calculated according to stage and response to therapy. From June 1992 to December 1996, 194 patients were included in the study, with a mean age of 2 years. Initial studies were performed according to INSS recommendations without major problems. INSS stage was correctly applied to all patients except for 9 (95%). Post-operative complications were observed in 15 patients (8.3%). Response to therapy (INRC) was studied in 63 stage 4 patients, 11 of whom were not classified correctly (17%). Differences in survival according to stage (INSS) and group of response to therapy (INRC) were statistically significant ($P < 0.001$). In conclusion the INSS was easy to use and separated different prognostic groups. Surgical complications and mortality did not increase in this series because of using the INSS. The feasibility of INRC was evaluated in a small series of stage 4 patients and the designation of response was problematic in a relatively high proportion of cases. The prognostic value of the different responses was highly significant, but less informative than had been hoped for.

Key words: neuroblastoma, INSS, neural crest tumours
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INTRODUCTION

A VARIETY of staging systems or their modifications has been developed to classify the extent of disease in neuroblastoma patients at the time of diagnosis [1–4]. The differences have made it difficult to compare the results of clinical trials and biological studies performed by different groups and in different countries. In 1988 international criteria for the diagnosis of neuroblastoma, a common neuroblastoma staging system and definitions of response to treatment were established [5]. In 1992 a working group reviewed the experience with the International Neuroblastoma Staging System (Table 1) (INSS) and the International Neuroblastoma Response Criteria (Table 2) (INRC) and discussed modifications and clarifications of the language and objective of the originally proposed criteria [6].

The Neuroblastoma Group of the Spanish Society of Paediatric Oncology started a study in 1992 applying the recommendations of the INSS and INRC. This group investigated the feasibility and accuracy of the INSS in a multicentric

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study and examined the possibility of an increase in surgical complications, as a result of encouraging collaborators to obtain tumour tissue for biological studies and to evaluate stage and resectability on more surgical grounds than in previous studies, where the Evans classification had been used.

PATIENTS AND METHODS

Primary tumours were examined using ultrasound and computed tomography (CT) scans. Magnetic resonance imaging (MRI) was used when there was a suspicion of medullary invasion. A 123-I-metaiodobenzylguanidine ([^{123}I] MIBG) scan, two bone marrow (BM) aspirates and two BM biopsies were performed to study metastases. Biological studies included vanillyl mandelic and homovanillic acid in 24 h urine, lactate dehydrogenase (LDH), neuron-specific enolase and ferritin.

Collaborators were encouraged to obtain tumour tissue from the primary tumour at diagnosis for biological studies at a central laboratory. There, Shimada classification, N-myc amplification, ploidy, P-glycoprotein, proliferating cell nuclear antigen (PCNA) and tyrosine kinase receptor for neurotrophic factor (trkA) were performed. Monoclonal antibodies were not used to study BM invasion.

A copy of the surgical and pathology report of each patient was mandatory for inclusion in the study. Stage of disease was classified according to the INSS in each hospital. The response to chemotherapy and surgery was evaluated in each institution according to INRC. Besides the corresponding study forms, a copy of the second surgical and pathology report was requested.

Stage and response to therapy were centrally reviewed. In case of discordance the study board, comprising four paediatric oncologists, one surgeon, one pathologist and one radiotherapist, studied the case and made the final decision. Surgical complications were also noted.

Statistics

Survival was considered to be the time from diagnosis to death or last visit to the hospital. Event-free survival was calculated from the date of diagnosis to the date of relapse, death or last contact. The probability of survival and event-free survival was calculated from the time of diagnosis according to the Kaplan–Meier product-limit method with standard errors of Peto and colleagues [7]. Statistical significance between curves was studied following Breslow's and Mantle-Haenszel tests. All studies were performed using the SPSS statistical package.

RESULTS

From June 1992 to December 1996, 198 consecutive patients diagnosed as having neuroblastoma were registered

Table 1. *International Neuroblastoma Staging System (INSS)*

Stage	Definition
1	Localised tumour with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumour microscopically (nodes attached to and removed with the primary tumour may be positive)
2A	Localised tumour with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumour microscopically
2B	Localised tumour with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumour. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumour infiltrating across the midline, with or without regional lymph node involvement; or localised unilateral tumour with contralateral regional lymph node involvement; or midline tumour with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumour with dissemination to distant lymph nodes, bone, bone marrow, liver, skin and/or other organs (except as defined for stage 4S)
4S	Localised primary tumour (as defined for stage 1, 2A or 2B), with dissemination limited to skin, liver and/or bone marrow (limited to infants < 1 year of age)

Table 2. *Recommended explorations to evaluate the extent of disease in neuroblastoma patients (INSS)*

Tumour site	Recommended tests
Primary tumour	CT and/or MRI scan with 3D measurements; MIBG scan, if available
Metastatic sites	
Bone marrow	Bilateral posterior iliac crest marrow aspirates and trephine (core) bone marrow biopsies required to exclude marrow involvement. A single positive site documents marrow involvement. Core biopsies must contain at least 1 cm of marrow (excluding cartilage) to be considered adequate
Bone	MIBG scan; ^{99}Tc scan required if MIBG scan negative or unavailable; plain radiographs of positive lesions are recommended
Lymph nodes	Clinical examination (palpable nodes), confirmed histologically. CT scan for non-palpable nodes (3D measurements)
Abdomen/liver	CT and/or MRI scan with 3D measurements
Chest	AP and lateral chest radiographs. CT/MRI necessary if chest radiograph positive or if abdominal mass/nodes extend into chest

INSS, International Neuroblastoma Staging System; CT, computed tomography; MRI, magnetic resonance imaging; 3D, three-dimensional; MIBG, metaiodobenzylguanidine; ^{99}Tc, 99-technetium; AP, anterior–posterior.

Table 3. Diagnostic procedures

	Initial studies ($n = 194$)	Second evaluation (INRC) ($n = 63$)
BM aspirates	184 (95)	58* (92)
BM biopsies	161 (83)	58* (92)
[^{123}I]MIBG	176 (91)	55* (87)
Tc-diphosphonate	93 (48)	3 (5)
Tumour biopsy	186 (96)	47† (75)
Tumour available for biological studies	160 (82)	26 (41)

Data are shown as *n* (%). A second evaluation was performed in 63 stage 4 children after induction chemotherapy. *Five patients were not submitted to the second evaluation because of progressive disease. †Delayed surgery. INRC, International Neuroblastoma Response Criteria; BM, bone marrow; MIGB, metaiodobenzylguanidine; Tc, technetium.

in the protocol N-II-92. Four were excluded owing to incomplete information and the other 194 were eligible for the study. Their mean age was 2.03 years and there was a male/female ratio of 1.3. 90 patients (46%) were under 1 year of age.

The location of the primary tumour was predominantly abdominal in 157 cases, mediastinal in 45, pelvic in 15 and cervical in 8 cases. 32 children had tumours located in 2 or more contiguous anatomical sites: 2 were considered multicentric (bilateral adrenal) and in 4 the primary tumour was not found.

Table 4. Stage of disease classified according to INSS

Stage (INSS)	Number of cases	%
1	46	24
2A	8	4
2B	10	5
3	46	24
4	64	33
4S	20	10

In 9 patients, stage was changed after central review. The numbers correspond to the final classification after review. INSS, International Neuroblastoma Staging System.

Table 5. Method used to obtain tumour tissue at diagnosis and complications observed

	Number of cases	Complications
Resection of the tumour	95	S. Bernard-Horner (2) Bleeding (2) Nephrectomy (2) Tumour rupture (1) Renal artery thrombosis (1) Intestinal obstruction (1) Sepsis (1)
Biopsy	81	Oesophageal perforation (1)
Tumour	72	Bleeding (2)
Metastasis	9	Tumour rupture (1)
Laminectomy	4	Intra-operative death (1)
X-ray-guided biopsy	6	—
Bone marrow	8	—

Resection of the tumour includes any part of it. X-ray-guided biopsy includes 3 tru-cut and 3 fine needle aspiration biopsy (FNAB). Bone marrow includes both biopsy and aspirate. Numbers in parentheses indicate the number of cases suffering from each complication.

[^{123}I]MIBG scan was used in 176 patients (91%), and the tumour and/or metastases were positive in 147 children (84%). Of the 29 negative cases, 3 patients had negative scans performed postoperatively (Table 3). A technetium scan was performed in 93 children and was positive in 29 (31%). It was used because of a negative MIBG scan in 17 children and because MIBG was not available in another 19. Some hospitals routinely used both techniques, even though this was not required for this study.

BM was studied in all patients, but only 156 had two evaluable biopsies and two aspirates (Table 3). 14 of the cases not biopsied had massive infiltration by tumour cells in one or two aspirates. Overall, BM was considered infiltrated in 58 patients, 52 stage 4 and 6 stage 4S. The proportion of BM biopsies was lower in infants under 6 months of age, with only 39/63 (62%) having at least one evaluable BM biopsy.

The stage of tumours after central review is represented in Table 4. It was changed in 9 cases (5%). Of 16 cases considered stage 2B, 6 were changed after review to stage 2A (4 cases), stage 1 and stage 4S (one each). Also, 3 patients staged initially as stage 3 were changed to stages 1, 2B and 4. The mistakes in staging occurred most frequently for pelvic tumours with 3/15 (20%) erroneously staged (versus 3% for adrenal and retroperitoneal and 2% for chest).

In 186 cases, tissue from the primary tumour or metastases was obtained at diagnosis (Table 5). In 95 cases tumours were resected completely or partially, whilst 81 were only biopsied. In 8 patients diagnosis was only made by BM aspiration and evaluation of urinary catecholamine metabolites. Surgical-related complications were observed in 15 patients (Table 5), in 10 cases after resection of the tumour

Table 6. Response to initial treatment according to INRC

Response	Number of cases
CR	17
VGPR	16
PR	20
MxR	1
NoR	4
PD	5
Total	63

In 63 stage 4 neuroblastoma fully evaluable patients, International Neuroblastoma Response Criteria (INRC) were assessed after induction chemotherapy (95 days) plus surgery. CR, complete response; VGPR, very good partial response; PR, partial response; MxR, mixed response; NoR, no response; PD, progressive disease.

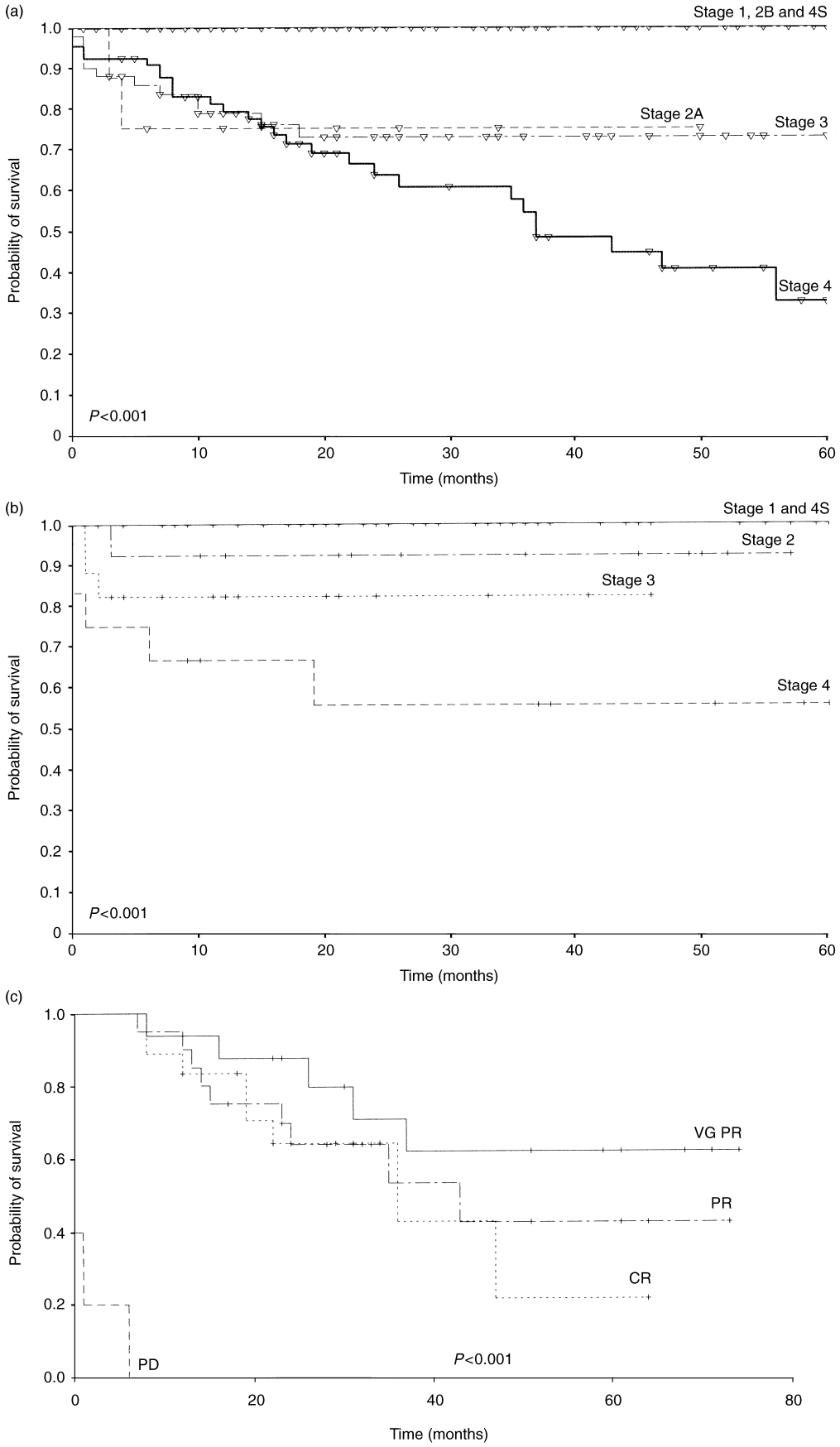

Figure 1. Probability of survival: (a) according to International Neuroblastoma Staging System (INSS) stage for all patients; (b) in relation to INSS stage for infants only; and (c) in stage 4 patients according to response to initial therapy, by International Neuroblastoma Response Criteria (INCR): CR, complete response; VGPR, very good partial response; PR, partial response; PD, progressive disease.

and in 5 after biopsy. Histological examination reported 165 cases as neuroblastoma, 27 cases as ganglioneuroblastoma and 2 compatible with neuroblastoma. Tumour tissue was sent to the reference laboratory in 160 cases (83%), but was considered insufficient or inadequate in 22 samples.

Response to induction chemotherapy plus surgery was evaluable in 63 stage 4 patients. In 11 cases (17%) the central review committee considered that the evaluation of response by the individual institution was incorrect. 4 cases considered to be very good partial responses (VGPR) by their hospital had to be changed to partial response (PR); 3 considered complete responses (CR) were PR (2) or VGPR (1); and 2 considered no response (NoR) had a mixed response (MxR) (Table 6).

Overall actuarial survival at 5 years was 0.68 and event-free survival 0.66. Survival was 100% for stage 1, 2B and 4S, 75% for stage 2A, 73% for stage 3 and 33% for stage 4 (Figure 1a). The difference in survival between stages was highly significant ($P < 0.001$). A similar trend was seen in infants (Figure 1b).

In stage 4 patients, survival varied according to response (INRC), 20% with a survival rate for CR, 67% for VGPR, 44% for PR and 0% for PD (Figure 1c). Differences were statistically significant ($P < 0.001$). The only patient with MxR died at 56 months and 3 of the 4 with NoR died from progression.

DISCUSSION

The Neuroblastoma Group of the Spanish Society of Pediatric Oncology comprises 28 hospitals with different levels of experience in the management of neuroblastoma. In previous studies, the Evans system was used to classify stage of disease [8–10]. Therefore, when this study was started the concerns were related to the feasibility of the INSS classification in a multicentric study and to the possibility of an increase in surgical complications due to the use of a 'more surgical' classification. The INSS classification was easily applied, with only 4 patients out of 198 excluded because of incomplete information and only 9 erroneously staged. The proportion of cases erroneously staged was similar for different tumour locations (around 2–3%), with the exception of pelvic tumours, where the rate was 20%. There was a tendency for pelvic tumours to be considered stage 3 even in cases that were easily resected and therefore stage 1 or 2.

In our previous studies using Evans classification, surgical complications were recorded but not exhaustively analysed [11, 12]; therefore, a comparison of complications between the two staging systems is problematic. Nevertheless, the number of surgical problems encountered when using the INSS recommendations was small (15/180 procedures) and compares favourably with results from other published series [13–18].

The collaboration of hospitals was good and biopsies of 83% of tumours were sent to the reference laboratory; even excluding inadequate samples, informative tissue was obtained for more than 70% of cases.

Survival was similar in stages 1, 2B and 4S and was statistically superior to stages 3 and 4. Stage 2 patients received chemotherapy, so it is not known whether the equivalent survival to stage 1 was due to effective treatment in stage 2 or whether both stages have the same outcome and could be treated only with surgery, as recently hypothesised in a European study [19].

The Pediatric Oncology Group applied the INSS retrospectively to an extensive neuroblastoma series [20]. They found that it was less discriminative for infants, as far as prediction of survival was concerned. In the present series, survival in infants was the same for stage 1 and 4S cases and the difference from other stages was statistically significant ($P < 0.0001$).

All stage 4 patients received the same induction chemotherapy followed by surgery and were evaluated at this point according to the INRC. Response to chemotherapy and surgery (in most cases delayed after an initial biopsy) was evaluable in 63 of the 64 stage 4 patients. The proportion of errors was important (17%) when applying the INRC and affected all response groups.

One of the objectives of the response groups is to identify different subgroups of patients in terms of outcome. The number of cases in some response groups (MxR, NoR) was very small in this series and precluded separate analysis. The best survival was for patients attaining VGPR and the worst for PD patients, but surprisingly patients with CR had a worse outcome than those with PR.

The long-term results of treatment in stage 4 patients continue to be poor in all studies. It is probably for this reason that the value of INRC or any other response staging system cannot be fully appreciated.

In conclusion, the INSS is easy to apply in a multicentre setting. The combination of a common staging system with other biological prognostic factors will allow patients to be stratified in prognostic groups and treated according to their risk. Although the overall results in neuroblastoma have not improved as much as in other tumours, the future appears to be promising.

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APPENDIX: INSTITUTIONS AND MAIN INVESTIGATORS

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