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Paediatric Update

Neuroblastoma

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The neuroblastic tumours, derived from primordial neural crest cells which ultimately populate the sympathetic ganglia, adrenal medulla and other sites, (Brodeur GM and Castleberry RP. Neuroblastoma. In Pizzo PA, Poplack DG, eds, *Principles and Practice of Pediatric Oncology*. Philadelphia, J. B. Lippincott Co., 1997, 761–797) are an enigmatic group of neoplasms which have the highest rate of spontaneous regression of all human malignant neoplasms yet one of the poorest outcomes when occurring as disseminated disease in children. Significant advances in understanding and predicting the natural history of neuroblastoma have resulted from translational studies coupling tumour biology and clinical features to form prognostic strata and allowing more accurate routeing of patients to risk-related management. While this strategy has clarified the management for lower risk tumours, little improvement in survival for higher risk disease has been realised. Ironically, this latter patient subset, for which the most innovative therapeutic strategies are needed, is also the one from which the least tumour biology is gleaned owing to inadequate tissue sampling. This update will summarise the evolving biology of neuroblastoma and its relationship to current risk-related therapy and future management strategies. Throughout this report, prognostic grouping by age will be infants (<1 year) versus children (≥1 year) since the change of risk according to age seems most distinct at this cut-off point. © **1997 Published by Elsevier Science Ltd.**

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AETIOLOGY AND EPIDEMIOLOGY

THE INCIDENCE of neuroblastoma, which accounts for 8–10% of all childhood cancers, is 8.0 and 8.7 per million per year, respectively, in caucasian and black children under the age of 15 years [2,3]. The median age at diagnosis is 22 months with more than 95% of cases detected by 10 years of age; the male:female ratio is 1.2:1 [1].

The aetiology of neuroblastoma is unknown. There are a number of unconfirmed studies [4–9] suggesting that select environmental factors (e.g. prenatal exposure to hydantoin, phenobarbital, or alcohol) are associated with a higher risk for neuroblastoma in the offspring. Since neuroblastic tumours arise from neural crest tissue and demonstrate differentiation patterns mimicking normal neuronal differentiation, it has been postulated that their pathogenesis may relate to aberrant regulation of cellular differentiation. Of the known ligands and their cellular receptors which participate in the regulation of neuronal differentiation [10], perhaps the most intriguing data involve nerve growth factor (NGF) and its receptor, TRK-A [11]. In the laboratory, neuroblastic cells which express TRK-A differentiate when NGF is present and die in its absence [12]. Clinically, neuroblastomas with normal TRK-A expression are associated with favourable biological characteristics (normal *MYCN* copy number), clinical features (low stage and age), and high cure rates [12–16].

Since the first description by Beckwith and Perrin [17] that microscopic cell rests of neuroblastic nodules, so called *in situ* neuroblastoma, are found in some infants dying of other causes, it has been reported that virtually all fetuses have such foci [18]. Whilst it is still unclear whether these cell rests are the site of origin of malignant neuroblastic tumours, the concept that neuroblastic neoplasms may spontaneously regress remains an intriguing one which has recently been supported by clinical observations [19] and data from neuroblastoma screening studies in Japan and Quebec [20,21]. This experience is the basis of current studies designed to observe patients with low risk neuroblastic tumours and gross

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residual disease, if tumour biology favours spontaneous neoplastic involution. (See Treatment, below.)

CLINICAL FEATURES, DIAGNOSIS AND STAGING

The frequency of primary tumour sites, as well as the patterns and frequencies of metastatic spread, are a function of age [1]. Children demonstrate a higher incidence of adrenal tumours and a lower incidence of thoracic and cervical tumours than do infants. One per cent of patients will have no detectable primary tumour. Although haematogenous metastases occur most commonly in bone marrow, bone, liver and skin, extension to lung and brain parenchyma is now more commonly recognised, possibly a consequence of an alteration to the natural history of the disease due to more effective current treatment [22–24].

Internationally accepted criteria for confirming the diagnosis of neuroblastoma, for initial patient evaluation and for staging have now been established and revised by the International Neuroblastoma Staging System (INSS) working committee [25–27]. The INSS (Table 1) incorporates the best features of other staging methods [28–34] and standardises controversial areas, e.g. the definitions of localised, unresected and regional disease. Partially resected tumours are subdivided into stages 2A, 2B and 3 to facilitate the analyses necessary to resolve the controversy of the prognostic impact of regional lymph nodes metastases and midline primary tumours in the light of tumour biology [35–38]. Stage 4S [29, 39] has been retained in the INSS representing a unique subset of infants with a distinct pattern of disseminated disease and a high chance of spontaneous regression and cure with or without non-surgical therapy [39–41]. While the INSS criteria are not perfect, their universal application over the last few years has demonstrated that the system is feasible and predictive of outcome when combined with age [42, 43] and furnishes a stable clinical background upon which analyses of biologically-based risk groups can be performed.

PROGNOSTIC FACTORS

Clinical

Considered alone, the two most important clinical prognostic variables are disease stage and patient age at diagnosis [1, 44–49]. The rates of 3-year, event-free survival (EFS) range as follows: for all patients with INSS stages 1, 2 and 4S, 75–90%; for infants with INSS stage 3 and 4 tumours, 80–90% and 60–75%, respectively; and for children with INSS stage 3 and 4, 50% and 15%, respectively. After adjusting for stage and age, primary site has not proven to be a statistically significant predictor of outcome.

Various serum markers (ferritin, neuron-specific enolase, lactate dehydrogenase) [50–55] have been investigated for prognostic power. Common to all these is their lack of specificity for neuroblastic tumours and their probable dependency upon tumour burden. Therefore, it is predictable that early studies suggested a strong relationship of these factors to patient stage and perhaps histopathology subtype, both of which have some relationship to tumour burden. The usefulness of serum markers as independent prognostic factors is under scrutiny in studies which account for genetic features.

Histopathology

The three classic histopathological patterns of neuroblastic tumours (neuroblastoma, ganglioneuroblastoma and ganglioneuroma) reflect a spectrum of maturation, differentiation and clinical outcome. Like staging, histopathological criteria for classifying these tumours and for predicting clinical behaviour have varied. The most widely-used system was developed by Shimada and colleagues [56], and revised by Joshi and colleagues [57]. To develop a set of definitions and criteria which are universally accepted, Shimada, Joshi and other noted paediatric pathologists have devised and tested an international neuroblastoma pathology classification [58]. This classification will be validated by prospective evaluation, in parallel with genetic abnormalities identified in the tumour [27].

Tumoral genetic features

A number of genetic features, especially *MYCN* copy number, ploidy, deletion or loss of heterozygosity of chromosome 1p [59–65] appear to have predictive value, independent of patient age and most INSS stages.

Recognition that double minutes and homogeneously staining regions in neuroblastic tumours [66] represented amplification of the proto-oncogene *MYCN* launched a series of studies which ultimately determined that *MYCN* amplification occurs in approximately 25% of primary, untreated neuroblastomas, is associated predominantly with advanced stages of disease at diagnosis (5–10% of low stage tumours and 30–40% of high stage tumours), and portends rapid tumour progression and poor outlook [59, 60, 65]. Recently, the grave outlook associated with *MYCN* amplification has been challenged in patients with localised tumours [67] or INSS 4S disease [68]. In the study by Cohn and associates [67] the lack of association of *MYCN* amplification with unfavourable Shimada histology and diploid DNA content, and the presence of *MYCN* protein in 4 of the 5 patients they assessed, suggest that this group of patients with localised, *MYCN* amplified tumours is biologically different from patients with regional or disseminated, *MYCN* amplified tumours.

Table 1. *The international staging system for neuroblastoma* [25–27]

Stage 1	Localised tumour confined to the area of origin; complete gross resection, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph node negative for tumour.
Stage 2A	Unilateral with incomplete gross resection; identifiable ipsilateral and contralateral lymph node negative for tumour.
Stage 2B	Unilateral with complete or incomplete gross resection; with ipsilateral lymph node positive for tumour; identifiable contralateral lymph node negative for tumour.
Stage 3	Tumour infiltrating across midline with or without regional lymph node involvement; or unilateral tumour with contralateral lymph node involvement; or midline tumour with bilateral lymph node involvement.
Stage 4	Dissemination of tumour to distant lymph nodes, bone marrow, liver, or other organs except as defined in 4S.
Stage 4S	Localised primary tumour as defined for stage 1 or 2 with dissemination limited to liver, skin or bone marrow.*

*< 10% of nucleated marrow cells are tumour cells.

Deletion or allelic loss of the short arm (p) of chromosome 1 is correlated with poor survival [62, 69, 70]. However, it is not yet clear that this finding represents an independent prognostic factor, since most cases in which 1p deletions are noted also to have *MYCN* amplification [69, 70]. The 1p region is of major interest to molecular investigators since it may contain the so-called 'neuroblastoma gene(s)' [70].

Total DNA content of tumour cells, assessed by flow cytometric analysis, falls into two patterns: (1) increased DNA content (DNA index or DI > 1) designated hyperdiploid; and (2) normal DNA content (DI = 1) termed diploid. When correlated with clinical features, DI provides little prognostic information in children over 2 years of age at diagnosis [63]. However, infants with hyperdiploid tumours are more likely to have lower stages of disease at diagnosis, to respond better to cyclophosphamide and doxorubicin and have a favourable prognosis regardless of stage. In contrast, those with diploid tumours will typically have advanced stages of disease, poor response to this drug combination and a less favourable outcome [63, 64]. The favourable prognostic association of tumour hyperdiploidy in infants is probably the result of whole chromosome gains, which contrasts with children in whom chromosomal structural changes are more likely to occur [64].

The expression of numerous genes are being investigated for prognostic potential or for providing insight into neuroblastoma tumorigenesis; e.g. the neurotrophin receptor gene (*TRK-A*), genes related to the multidrug resistance phenotype (*MDR1* and *MRP*), and genes related to invasion and metastasis (*nm23* and *CD44*) [12, 71–74]. Of these, *TRK-A* and *MRP* (multi-drug resistance protein) are most compelling regarding prognosis, tumorigenesis and possible therapeutic strategies. As noted above (see Aetiology and Epidemiology) high expression of TRK-A (the receptor for NGF) is associated with other favourable prognostic features (normal *MYCN* copy number, low stage, low age, high cure rates) [12–16]. The upregulation of *TRK-A* in TRK-A non-expressing, high risk neuroblastic tumours is a potential therapeutic strategy to be evaluated as new agents or gene therapy evolves. *MRP* is a powerful predictor of survival and EFS, independent of age, *MYCN* copy number and TRK-A expression [72]. Norris and colleagues postulated that *MYCN* may regulate expression of *MRP*, potentially explaining the development of drug resistance and disease progression in *MYCN* amplified tumours. Supporting this hypothesis, the same research group reported recently that decreased *in vitro* MRP expression and increased drug sensitivity in NBL-S cells (a drug resistant cell model) followed down regulation of *MYCN* transfected with *MYCN* antisense constructs [75]. As the interaction of *MRP* and *MYCN* expression is further elucidated, manipulation of these processes may represent another target for future therapy.

In an attempt to explain the heterogeneity of clinical behaviour of neuroblastic tumours, a hypothetical model, based upon clinical and tumoral genetic features, has been proposed (Table 2) [76, 77]. The 3 types appear congruent with the prognostication schemas independently developed in both paediatric oncology cooperative groups in the US for the purpose of planning therapeutic trials. Ongoing evaluation and refinement of this model in the context of evolving therapy is needed to clarify if type 2 will collapse into types 1 and/or 3, leaving only two genetic sub-types of neuroblastoma and to determine if 'type-switching' (good to bad tumour biology or vice versa) really occurs. Currently, most biological findings appear to be stable, but there are rare exceptions where tumours exhibit different biological features at different times.

Table 2. Genetic/clinical subsets of neuroblastoma [76, 111]

Feature	Type 1	Type 2	Type 3
MYCN gene	Normal	Normal	Amplified
Karyotype/ ploidy	Hyperdiploid triploid	Near-diploid Near-tetraploid	Near-diploid Near-tetraploid
1p LOH	Absent	Present	Present
TRK-A expression	High	Variable (low)	Low or absent
Age	< 1 year	≥ 1 year	1–5 year
INSS stage	1, 2, 4S	3, 4	3, 4
3-year survival	~95%	25–50%	~5%

An international study will soon commence to examine all major clinical and biological variables in a large number of patients and determine which single factor or combination of factors best predict outcome. Under the direction of the International Neuroblastoma Risk Groupings (INRG) working committee (formerly the INSS), this effort will provide standardised international risk groupings so studies of small but important subsets of patients can be planned on a worldwide scale [27].

TREATMENT

General

In recent years, the management of neuroblastoma has been both simplified and complicated. With the evolution of prognostic strata, more detailed pre-treatment evaluation of tumour biology is required in every patient and the routeing of patients to the appropriate treatment plan is becoming more tedious. However, clarifying the natural history of low to intermediate risk tumours through these efforts has allowed significant reduction or elimination of post-operative treatment while maintaining high cure rates [78]. Attempts to improve the dismal outcome of high risk patients have led to dose-intensive chemotherapy regimens, including marrow ablative therapy with stem cell re-infusion, requiring more and lengthier hospitalisations.

Over the last 2 decades, the objectives of surgery in neuroblastic tumours have been clarified [43, 79] and include establishing the diagnosis, collecting tissue for biological studies and assessing response to other therapy modalities. While the INSS criteria for diagnosis [25, 26] may obviate tumour biopsy in some patients, the heavy dependency of treatment plans upon tumour biology provides a strong rationale for sampling the primary tumour in most patients.

The role of radiotherapy in the management of these tumours has changed dramatically as prognostic strata and risk-related therapy have emerged. Once considered the treatment of choice when combined with chemotherapy in regional disease (INSS stages 2B/3) in children [80], radiotherapy may no longer be indicated in the light of dose-intensive chemotherapy regimens and when patients with high risk biological features (*MYCN* amplification and unfavourable histopathology) are given high risk regimens [37, 81]. Cross-table irradiation is indicated in neonates with INSS 4S neuroblastoma who have respiratory distress secondary to hepatomegaly [82, 83]. Total body irradiation is

used as an integral part of the preparative regimens of many autologous bone marrow transplant procedures. Other less clearly defined uses of radiotherapy include treatment of intraspinal tumours and control of local and metastatic disease in patients with INSS stage 4 tumours.

Chemotherapy is the predominant treatment modality in neuroblastoma. A complete listing of response rates in single and multi-agent trials has been recently published [1]. Most multi-agent regimens include cyclophosphamide and its congener ifosfamide, doxorubicin, the epipodophyllotoxins (teniposide and etoposide) and the platinum-based agents, cisplatin and carboplatin.

Risk-related therapy

Specific management plans for these tumours are determined by the predicted risk of recurrent disease based upon age at diagnosis, INSS stage and selected biological features. A prognostic stratification model has been devised by the Pediatric Oncology Group (POG) and the Children's Cancer Group (CCG) to provide the basis for intergroup studies of low and intermediate risk patient subsets (Table 3). This paradigm will assuredly change as new biological variables are identified, the individual impact of factors are clarified by the INRG study and better therapy is developed.

Described below are the therapy plans for low and intermediate risk groups in the current POG/CCG studies:

Low risk patients (predicted EFS > 95%). With the excellent cure rates achieved in previous studies, even when there is residual disease after initial surgery (as in INSS stages 2A/2B) [30, 31, 35, 37, 43] these patients are managed with surgery alone. Subsequent surgery and possibly chemotherapy will be indicated in the event of local recurrence; the likelihood of metastatic disease in this group appears low. Because of the high rate of spontaneous regression documented in infants with 4S disease who are asymptomatic [19, 29, 39–41, 84] these tumours are considered low risk. Patients with biologically favourable INSS stage 4S tumours with symptoms, such as respiratory distress due to hepatomegaly or with unfavourable histology or ploidy, will receive chemotherapy and/or local irradiation.

Intermediate risk patients (predicted 3 year EFS > 85%). Though still at low risk for succumbing to disease, these cases probably require some chemotherapy and second-look surgery. The number of courses of chemotherapy will be determined by biological features. Irradiation is not thought to be indicated in INSS stages 2B/3, biologically favourable tumours [37, 85], although these patients will be monitored carefully for local and systemic control during the POG/CCG study. Infants with INSS stage 4 (disseminated) disease who have biologically favourable tumours are considered in this category.

High risk disease remains the group for which very little real improvement in ultimate outcome has been realised over the last 40 years. Given the dismal figures associated with conventional chemotherapy regimens (3 year EFS < 15%), numerous trials of myeloablative chemotherapy with autologous marrow re-infusion (ABMT) have been conducted over the last decade and are summarised in recent reviews [86, 87]. Most are single arm, uncontrolled ABMT studies [88–92] which report this modality to be well tolerated, to result in prolonged disease control compared with conventional therapy and possibly curative in selected subsets of patients, e.g. those with *MYCN* amplified tumours. In unselected patient populations, however, local and metastatic recurrences continue to appear as long as 7 years after ABMT, resulting in survival rates similar to those noted following conventional chemotherapy [93]. The only large scale randomised trials of ABMT versus conventional therapy have been conducted by the European Neuroblastoma Study Group (ENSG) [94, 95] and by CCG. The ENSG study demonstrated superior survival rates at 2 years for ABMT, but this difference was not sustained in subsequent analyses. The CCG trial results are pending.

Initial experience with peripheral blood stem cells (PBSC) as a source of marrow replacement demonstrates a reduction in toxicity and duration of hospital days following marrow ablative procedures [96]. As evaluation of marrow ablative therapy continues, PBSC procedures will take a more prominent role from both therapeutic and cost-containment perspectives.

A radiotherapy-based strategy for managing large regional tumours and disseminated disease is the use of ^{131}I-MIBG alone or in combination with chemotherapy [97–101]. While responses are well documented, the role of this modality in relation to marrow ablative therapy remains unclear.

Table 3. Risk group and protocol assignment schema — POG/CCG

INSS stage	Age (years)	*MYCN* status	Shimada histology	DNA ploidy	Risk group/study
1	0–21	Any	Any	Any	Low
2A/2B	< 1	Any	Any	Any	Low
	≥ 1–21	Non-amplified*	Any	NA	Low
	≥ 1–21	Amplified†	Favourable	NA	Low
	≥ 1–21	Amplified	Unfavourable	NA	High
3	< 1	Non-amplified	Any	Any	Intermediate
	< 1	Amplified	Any	Any	High
	≥ 1–21	Non-amplified	Favourable	NA	Intermediate
	≥ 1–21	Non-amplified	Unfavourable	NA	High
	≥ 1–21	Amplified	Any	NA	High
4	< 1	Non-amplified	Any	Any	Intermediate
	< 1	Amplified	Any	Any	High
	> 1–21	Any	Any	NA	High
4S	< 1	Non-amplified	Favourable	> 1	Low
	< 1	Non-amplified	Any	= 1	Intermediate
	< 1	Non-amplified	Unfavourable	Any	Intermediate
	< 1	Amplified	Any	Any	High

**MYCN* copy number ≤10. †*MYCN* copy number > 10. NA = not applicable.

Mass screening for neuroblastoma to improve long-term outcome assumes that high risk disease evolves from lower risk disease due to a delay in clinical detection. Given that most neuroblastic tumours secrete elevated levels of urinary catecholamines and most infant tumours are associated with a favourable prognosis, such an approach seems rational and potentially cost-effective. Mass screening studies in early infancy have been carried out in Japan, Europe and North America to test this hypothesis [20, 21, 102, 103]. To date, data from these programmes have shown it is unlikely that good risk tumours progress to high risk tumours if left undetected and, at least in the population-based Quebec study, that screening has not reduced the incidence nor mortality associated with high risk neuroblastoma in older children. The final analyses of these studies will be completed in the next few years and the role, if any, for this strategy in the management of neuroblastoma should be settled.

Future therapeutic strategies

In the next decade, as in the past, the overall approach will be to continue to use every clinical case as a source of biological information, applying results of biological studies at the 'bedside' to develop and test innovative therapeutic strategies.

Following the ongoing POG/CCG and co-operative European studies of low and intermediate risk tumours, further refinement of therapy will require international collaborative efforts due to the large number of patients required in such trials. The INSS, INRG and the international histopathology classification will provide a collaborative base for these studies.

Devising more effective therapy of high risk neuroblastoma remains a significant challenge. With the expanding window of time provided by marrow ablative procedures during which there is only microscopic disease, the next series of studies in high risk disease will test the efficacy of unique therapeutic strategies to eradicate this minimum residual disease. Candidate approaches to be evaluated include differentiating agents such as the retinoids [104], targeted therapy with antibodies against the ganglioside component of neuroblastic cell membranes (anti-GD_2) [105, 106], or with radiolabelled meta-iodobenzylguanidine (MIBG) [100, 107], immunotherapy such as IL2 [108], and drugs which result in cell kill through unique mechanisms which do not require the cell to be dividing (deferrioximine, topoisomerase inhibitors) [109, 110]. Eventually, gene therapy will be tested, targeting putative neuroblastoma gene(s) or genes regulating cell differentiation or apoptosis.

The co-operation of basic scientists and clinical scientists, and the prompt referral of these patients to paediatric oncology centres will be critical for achieving the future goals of refining and improving the therapy for neuroblastoma. Clearly, continued assessment of tumour biological features in all patients will provide new insights into tumorigenesis, cell differentiation and cell death pathways and thus, the potential for developing newer therapies for patients with high risk disease.

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Commentary

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FOR MORE than 130 years physicians have been aware of a tumorous disease called 'neuroblastoma', which may prove to be not only a malignant tumour, but also an embryonal remnant. In 1864, Rudolf Virchow was the first person to describe a child with an abdominal tumour with predominant microscopic features of a glioma [1]. The gliomatous aspect of neuroblastoma has been neglected for more than a century, but is now considered the reactive, stromal component of the tumour. This idea came from the observation that Schwann cells did not show the molecular abnormalities found in the neuroblasts and appear to play a key role in the process of maturation from neuroblastoma to ganglioneuroblastoma and to ganglioneuroma [2].

As summarised in R.P. Castleberry's excellent update, the detection of numerous molecular characteristic has considerably increased our ability to discriminate between neuroblastoma with a good or poor prognosis. This was possible by the close association of factors such as MYCN amplification, loss of heterozygosity on chromosome 1p36.2→ter, DNA euploidy, loss of CD44 or trkA expression and others with stage and outcome. MYCN proved to be the most powerful single prognostic factor in most series, reliably predicting poor outcome in nearly all amplified cases. A low risk group with MYCN amplification in stage 2A/2B ≥ 1 to 21 years of age, a composite of criteria from the Childrens' Cancer Study Group and the Pediatric Oncology Group (see Table 3 of the Update) would therefore not be accepted universally. The molecular factors are certainly not independent from each other (e.g. MYCN and LOH 1p and nonexpression of CD44 are correlated). They predict the outcome of a fraction of a defined group only (e.g. MYCN amplification in 30% of all stage 4 neuroblastoma experiencing an 80% death rate) and therefore require the addition of clinical risk factors, such as stage, age, serum LDH (lactate dehydrogenase) level, platelet count and others [3]. Furthermore, their specific roles in oncogenesis and function at the cellular level are hardly understood, but might be a prerequisite in order to understand and manipulate regression, maturation or progression in neuroblastoma cells.

Regression is a common feature of the embryofetal life including the development of the sympathetic system. The adrenal gland, for example, presents at week 12 and is the same size as the kidney, but it regresses during fetal and infant development until it is a small gland. Similarly the Zuckerkandl's ganglion at the origin of the A.mes.sup. appears as a large paired organ at gestational week 8. The cells of embryonal paraganglia resemble and appear indistinguishable from the neuroblasts of neuroblastoma. Thus, spontaneous regression of stage 4S neuroblastoma may be comparable to the regressive process of the Zuckerkandl and other paraganglia.

Since patients with microscopic residual stage 1 disease have a survival rate close to 100% without cytotoxic therapy, these *in situ* residual cells presumably also undergo regression. Kushner and associates recently reported on 2 patients with recurrent or enlarging tumours which regressed spontaneously [4]. In our series, 8 patients with Evans' stage III neuroblastoma who did not receive chemo- or radiotherapy to treat the residual disease, survived for 4–14 years suggesting some level of spontaneously remission. Seven of the 8 patients were infants at diagnosis. Finally, the 2.7 fold increased standardised incidence ratio of neuroblastoma in screening areas compared with regions without screening reflects the detection of cases which would otherwise have gone undetected but would have spontaneously regressed (in the absence of screening). This leads to the hypothesis that neuroblastoma may represent an embryonal remnant and a malignant tumour. The embryonal residuum predominantly presents early in life (stages $4S > 1–3 \gg 4$) *and* has the ability to spontaneously regress. The malignant tumour appears later ($4 \gg 1–3 > 4S$) and shows characteristically progression (Figure 1).