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# Characteristics and outcome of patients with ganglioneuroblastoma, nodular subtype: A report from the INRG project

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ABSTRACT

*Aim:* Describe characteristics and outcome of INRG patients with ganglioneuroblastoma, nodular subtype (GNBn).

*Patients and methods:* Amongst 4071 patients in the INRG database with known INPC histological category, 232 patients with GNBn were identified. Patients were categorised by clinical, pathological and genetic characteristic. For event-free survival (EFS) and overall survival (OS), Kaplan–Meier curves and lifetables were generated, and the outcome of subgroups was compared using log rank test.

*Results:* Patients with GNBn were older (83% >18 months), a higher proportion had unfavourable INPC pathology (83%), and rarely had *MYCN* gene amplified tumours (2%). Otherwise, the distribution of clinical and biological risk factors including stage, ferritin, initial treatment, grade of NB differentiation, MKI, 11q, 1p, and 17q were similar between patients with GNBn and the overall INRG cohort. EFS and OS were 54% ± 5% and 68% ± 5%, respectively. A cohort with superior outcome was identified: OS for GNBn patients younger than 18 months was 95% ± 5% ($n = 39$) and for GNBn patients with stage 1, 2, 3, 4s was 95% ± 3% ($n = 125$). Conversely, a poor outcome sub-group could also be identified: OS for stage 4 was 35% ± 7% ($n = 107$).

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*Conclusions:* Patients with GNBn tumours are rare and have a very heterogeneous outcome. Except for LDH and MKI, the factors prognostic in the overall NB cohort are also prognostic in patients with GNBn. Similar to the overall NB cohort, patients with GNBn older than 18 months of age, with stage 4 disease represent a high-risk sub-group and should be considered for aggressive treatment upfront.



## 1. Introduction

Neuroblastic tumours represent the most common extracranial tumour of childhood, and account for a relevant proportion of cancer deaths in children (SEER data).[1] In the spectrum of differentiation of neuroblastic tumours, ganglioneuroblastoma (GNB), nodular subtype, occupies a unique position. The International Neuroblastoma Pathology Classification (INPC) defines it as a stroma-dominant or stroma-rich tumour (ganglioneuroma or intermixed GNB), surrounding one or more macroscopic nodules of stroma-poor neuroblastoma.[2–4] The prognostic implication of this entity has been controversial. In the original Shimada and INPC classification GNB nodular was invariably considered an unfavourable pathology.[4,5] In contrast, the revised INPC classifies it as favourable or unfavourable based on characteristics (grade of differentiation and mitosis karyorrhexis index – MKI) of the nodules,[2–4] and this approach has been subsequently validated in a separate European series.[6] In the International Neuroblastoma Risk Group (INRG) analysis[7] GNB nodular was associated with a poor prognosis in comparison to other pathologies (neuroblastoma, or GNB intermixed). Finally, the biology underlying nodular GNB is also still elusive. The nodules are thought to be clonal in origin, distinct from the stroma-rich part of the tumour. However, evidence of this relies on few case reports, in which neuroblastic cells in the macroscopic nodules have been shown to harbour *MYCN* oncogene amplification, in contrast with cells of the stroma-rich component of the tumour.[8] The paucity of cases, which represent only about 10% of neuroblastic tumours,[4,9,10] and the complex pathology, may affect the results and interpretation of biological assays, and limit the development of specific biological studies. Furthermore, known clinical and biological prognostic factors have not been validated in this unique subset of patients.

The INRG classification system was developed to establish a consensus approach to pre-treatment risk stratification. It led to the establishment of the largest international database of patients, which is now available for analysis. We describe the INRG series of GNB nodular patients, focusing on prognostic factors (grade of tumour differentiation, MKI, MYCN amplification, 1p, 11q abnormalities) and outcome.

## 2. Patients and methods

### 2.1. Patient cohort

For the INRG project, data from the major cooperative groups, COG (North America and Australia), the German Pediatric Oncology and Hematology Group (GPOH), the Japanese Advanced Neuroblastoma Study Group (JANB), the Japanese Infantile Neuroblastoma Co-operative Study Group (JINCS) and SIOPEN were submitted for analysis. A total of 8800 unique patients met the following eligibility criteria for INRG project: confirmed diagnosis of neuroblastoma, date of diagnosis between January 1, 1990 and December 31, 2002, and non-missing outcome data.

The details of the INRG project are described in Cohn et al.[7] Amongst these 8800 patients, 4071 had reported data for INPC histological category, and 232 patients with a diagnosis of GNB, nodular subtype, were identified. All the GNB, nodular subtype tumours had been retrospectively reviewed to confirm the diagnosis and classify them as favourable or unfavourable histology. These 232 patients form the cohort analysed for this report.

### 2.2. Methods

Patients were categorised into one of two groups for each risk factor or characteristic, and the proportion of patients in each group was calculated. For event-free survival (EFS) and overall survival (OS), Kaplan–Meier curves and lifetables were generated, and log-rank tests were performed to compare the two groups for each factor.[11] Kaplan–Meier curves are presented for risk factors or characteristics where the log-rank test $p < 0.05$. Event-free survival (EFS) time was calculated from the time of enrolment on the front-line or biological study until the time of the first occurrence of relapse, progressive disease, secondary malignancy or death, or until the time of last contact if no event occurred. Overall survival (OS) time was calculated until the time of death or until last contact if the patient was alive. EFS and OS are expressed as the estimate ± the standard error, with standard errors calculated per the methods of Peto.[12]

## 3. Results

Amongst 8800 patients in the INRG database, INPC diagnostic category was known in 4071 patients, 232 (5.7%) of whom had a diagnosis of GNB, nodular subtype. Clinical features are detailed in Tables 1 and 3, and are similar to those of the overall population.[7] One-hundred and nine patients (47%) were diagnosed before 1996. Thirty-nine patients (17%) were younger than 547 days at diagnosis, and 193 (83%) were older. About half of the patients over 18 months of age had stage 4 disease, whilst slightly more than one-third of the patients less than 18 months of age had stage 1 disease (Table 3). The primary tumour was adrenal in 99 cases (43%), abdominal not adrenal in 57 (25%), cervical in 3 (1%), thoracic in 46 (20%), pelvic in 10 (5%) and other in 18 (8%), including one patient with multiple primary tumours. Amongst the 107 patients (46%) with stage 4 disease at presentation, the most frequent site of metastasis

**Table 1 – Clinical characteristics of GNB, nodular INRG patients ($n = 232$).**

| Factor | $n$ (%) | 5-year EFS ± SE (%) | EFS $p$-value | 5-year OS ± SE (%) | OS $p$-value |
|---|---|---|---|---|---|
| Overall cohort | 232 | 53 ± 5 | N/A | 68 ± 5 | N/A |
| Age | | | | | |
| <547 days | 39 (17%) | 86 ± 8 | 0.0002 | 94 ± 5 | 0.0003 |
| ⩾547 days | 193 (83%) | 46 ± 6 | | 61 ± 5 | |
| Year of enrolment/diagnosis | | | | | |
| <1996 | 109 (47%) | 52 ± 6 | 0.8193 | 65 ± 5 | 0.1063 |
| ⩾1996 | 123 (53%) | 58 ± 10 | | 70 ± 10 | |
| Initial treatment | | | | | |
| Observation, surgery, or std chemo. | 129 (65%) | 68 ± 6 | <0.0001 | 83 ± 5 | <0.0001 |
| Intensive multi-modality | 69 (35%) | 28 ± 8 | | 42 ± 9 | |
| INSS stage | | | | | |
| 1, 2, 3, 4s | 125 (54%) | 80 ± 5 | <0.0001 | 95 ± 3 | <0.0001 |
| 4 | 107 (46%) | 23 ± 6 | | 35 ± 7 | |
| Serum ferritin (ng/ml) | | | | | |
| <92 | 40 (53%) | 72 ± 11 | 0.0012 | 88 ± 8 | 0.0004 |
| ⩾92 | 35 (47%) | 31 ± 10 | | 46 ± 11 | |
| LDH (U/L) | | | | | |
| <587 | 57 (73%) | 55 ± 9 | 0.7743 | 74 ± 7 | 0.5381 |
| ⩾587 | 21 (27%) | 58 ± 22 | | 64 ± 22 | |
| Histological classification (INPC) | | | | | |
| Favourable | 38 (17%) | 87 ± 8 | 0.0001 | 91 ± 6 | 0.0006 |
| Unfavourable | 188 (83%) | 45 ± 6 | | 61 ± 5 | |
| Grade of NB differentiation (INPC) | | | | | |
| Differentiating | 25 (17%) | 80 ± 11 | 0.0082 | 87 ± 9 | 0.0100 |
| Poorly differentiated or undifferentiated | 122 (83%) | 45 ± 8 | | 60 ± 8 | |
| MKI (INPC) | | | | | |
| Low, intermediate | 158 (90%) | 55 ± 6 | 0.8815 | 67 ± 6 | 0.6938 |
| High | 18 (10%) | 51 ± 16 | | 62 ± 17 | |

**Table 2 – Genetic characteristics of GNB, nodular INRG patients ($n = 232$).**

| Factor | $n$ (%) | 5-year EFS ± SE (%) | EFS $p$-value | 5-year OS ± SE (%) | OS $p$-value |
|---|---|---|---|---|---|
| MYCN status | | | | | |
| Not amplified | 201 (98%) | 54 ± 6 | 0.0005 | 68 ± 5 | <0.0001 |
| Amplified | 5 (2%) | (5 events) | | 20 ± 18 | |
| Ploidy | | | | | |
| >1 (hyperdiploid) | 32 (44%) | 81 ± 20 | 0.0944 | 100 ± 0 | 0.0384 |
| ⩽1 (diploid, hypodiploid) | 41 (56%) | 64 ± 22 | | 75 ± 22 | |
| 11q | | | | | |
| No aberration or balanced | 48 (73%) | 61 ± 12 | 0.0218 | 76 ± 10 | 0.2704 |
| Deletion, imbalance or unbalanced | 18 (27%) | 33 ± 19 | | 58 ± 19 | |
| 1p | | | | | |
| No loss or no aberration | 81 (86%) | 65 ± 8 | 0.0089 | 72 ± 7 | 0.1283 |
| LOH, deletion, or imbalance | 13 (14%) | 34 ± 16 | | 66 ± 16 | |
| 17q gain | | | | | |
| No gain | 11 (44%) | 55 ± 16 | 0.9380 | 72 ± 22 | 0.1982 |
| Gain | 14 (56%) | 39 ± 21 | | 51 ± 25 | |

was the bone marrow (63 cases, 27% of total cases), followed by bone (49 cases, 21%), distant lymph-nodes (26 cases, 11%), liver (5 cases, 2%), skin (1 case, 1%), lung (2 cases, 1%), CNS (1 case, 1%) and other sites (22 case, 10%). Serum ferritin was elevated in 35 cases (47% of patients for whom the data was available), and LDH was elevated (>587 IU/L) in 21 of 78

**Table 3 – Distribution of GNB, nodular INRG patients ($n$ = 232) by INSS stage and age.**

| Age | INSS stage | | | | | Overall |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4s | 4 | |
| <18 mo | 15 (38%) | 11 (28%) | 6 (15%) | 1 (3%) | 6 (15%) | 39 |
| ⩾18 mo | 29 (15%) | 38 (20%) | 25 (13%) | 0 | 101 (52%) | 193 |
| Total | 44 | 49 | 31 | 1 | 107 | 232 |

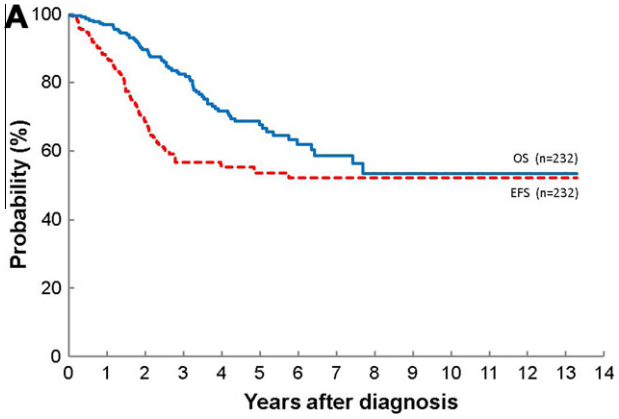


**Fig. 1A – Kaplan–Meier curves of EFS and OS for 232 patients with ganglioneuroblastoma (GNB), nodular subtype.**

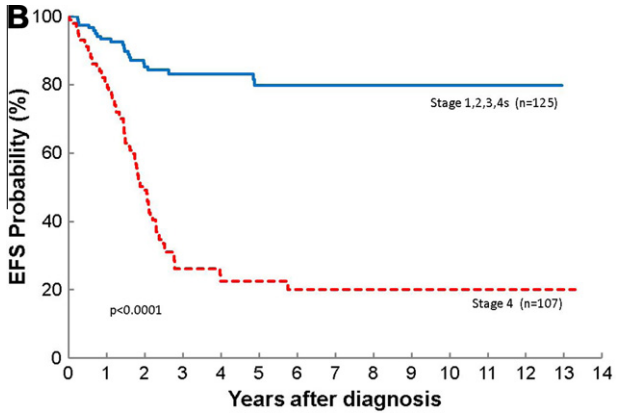


**Fig. 1B – Kaplan–Meier curves of EFS and OS for 232 patients with ganglioneuroblastoma (GNB), nodular subtype, by INSS stage (stage 4 versus non-stage 4).**

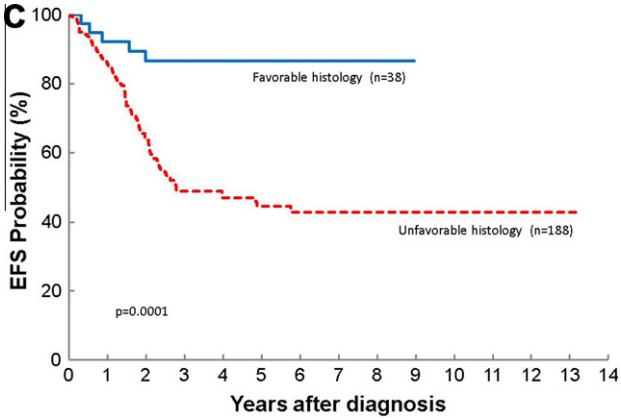


**Fig. 1C – Kaplan–Meier curves of EFS and OS for 232 patients with ganglioneuroblastoma (GNB), nodular subtype, by INPC histology (favourable versus unfavourable).**

patients (27% of patients for whom the data were available). The pathological and biological features of the tumours are summarised in Table 2. Pathology was overall classified as unfavourable in 188 cases (83%) and favourable in 38 (17%). The grade of differentiation was defined as differentiating in 25 patients (17%) and poorly differentiated or undifferentiated in 122 (83%). Mitotic-karyorrhexis index (MKI) was low or intermediate in 158 cases (90%), and high in 18 cases (10%). *MYCN* oncogene was amplified only in 5 of 206 evaluable cases (2%). DNA content was diploid or hypodiploid in 41 of 73 tested cases (56%). 11q abnormalities were found in 18 of 66 tested patients (27%), and 1p abnormalities in 13 of 94 (14%). 17q chromosome was studied only in 25 patients, 14 of whom (56%) had a gain. Of 199 patients for whom information about the treatment was available, 69 (35%) received intensive multimodality treatment at diagnosis. This proportion is similar to the entire INRG cohort, in which 32% of patients received intensive multimodality treatment at diagnosis. The overall EFS and OS were 53% ± 5% and 68% ± 5%, respectively (Table 1 and Fig. 1A). Outcome was not significantly lower for patients with GNB, nodular tumours than those in the overall INRG cohort (5-year EFS and OS of 63% ± 1% and 70% ± 1%, respectively[7]) ($p > 0.05$). Amongst the clinical features, age ⩾547 days at diagnosis, adrenal primary tumour, stage 4 disease, presence of bone marrow or bone metastases, intensive initial treatment and serum ferritin ⩾92 ng/mL were significantly predictive of poor EFS and OS (Fig. 1B shows survival curves of patients with stage 4 tumours versus non-stage 4). Patients with thoracic primary tumour had better EFS and OS. Pathological and genetic characteristics significantly correlating with poor EFS and OS were unfavourable pathology (INPC classification, Fig. 1C), grade of differentiation, *MYCN* oncogene amplification, DNA index ⩽1 (DNA content diploid or hypodiploid). Presence of 11q or 1p chromosomal abnormalities correlated with poor EFS, but not with OS (Table 2). However, MKI and LDH were not prognostic in our cohort.

## 4. Discussion

The INRG project provides the largest available series of neuroblastic tumours, combining cases from five national and international registries.[7] We describe the GNB, nodular subtype population from this series.

Nodular ganglioneuroblastoma represents only a small proportion of neuroblastic tumours, about 10% in published series, only 5.7% in the INRG series here reported. The lower incidence we observed may be related to the strict methodology of diagnosis and pathology review. Only cases in which the diagnosis was performed on tumour tissue, and in which the macroscopic presence of nodules surrounded by Schwannian stroma could be documented at the central review were included in the series.

Nodular ganglioneuroblastoma has historically been associated with a very poor prognosis,[7] though in this INRG series the outcome is moderately poor. The EFS and OS of patients with GNB, nodular tumours is slightly lower than outcome for the overall INRG cohort, but not statistically significantly so. Consistently with this observation, the initial treatment of these patients did not differ from the overall INRG cohort.

These patients present unique clinical and biological features. More than 80% of patients in our series were older than 547 days at diagnosis, but only 46% presented with stage 4 disease. Given the age of our cohort we would have expected a higher proportion of patients with metastasis.[13] Interestingly, only one of the patients with GNB, nodular subtype tumours had stage 4s disease. However, analogous to the overall NB population: (a) the prognosis for GNB nodular patients was heterogeneous and (b) we identified two subgroups of patients who had a very good prognosis: children younger than 547 days, and those with non-stage 4 disease. In contrast, stage 4 GNB nodular patients had much lower survival (5-years EFS of 23%, and OS 35%).

The value of INPC classification[2] was confirmed in this cohort. Patients with favourable pathology represented only a minority (17%), and had a significantly better outcome. Tumour grade was found to be prognostic within GNB, nodular patients as well as in the overall INRG cohort ($n = 3277$) and within a subset of patients older than 18 months ($n = 1270$).[7] MKI was not prognostic within GNB, nodular patients even though it was prognostic in the overall INRG cohort ($n = 3083$) and within the INRG subset of patients younger than 18 months ($n = 1943$).[7] This is consistent with published data, showing that high MKI is prognostically relevant only in young patients.[9]

The current INRG risk stratification is based on biological factors, in addition to age, stage and pathological features (histological category and grade of tumour differentiation): *MYCN* amplification, ploidy and 11q abnormalities. *MYCN* amplification correlates with unfavourable pathology,[14] older age,[15] advanced stage and poor prognosis.[16] However, whilst the prognostic role for *MYCN* amplification in infants with disseminated disease has been established,[17,18] the prognosis for older patients with disseminated disease is poor in both *MYCN* amplified and non-amplified patients.[7] Our series shows an unusual combination of older age, aggressive behaviour, high proportion of unfavourable pathology tumours, but very few *MYCN* amplified tumours (barely 2%). In the majority of cases therefore different and novel biological prognostic factors should be investigated.

The percentage of patients with diploid or hypodiploid tumours in our series is higher than in the whole INRG cohort (56% versus 29%),[7] although this difference is not statistically significant. Since in nodular GNB the tumour nodules are surrounded by Schwannian stroma, whose cells do not carry the same genetic features of the tumour,[19–21,31] it is possible that the genetic analyses have in some cases been performed on stromal cells, thus overestimating the prevalence of diploid tumours. To minimise this risk, guidelines on tumour sampling and processing for biological and genetic testing have been published.[22] The role of the local pathologist, who is responsible for identifying and centralising tissue from all nodules, is paramount to allow reliable genetic and biological testing. Alternatively, the age of the patients in our series (relatively old) may explain the higher prevalence of diploid or hypodiploid tumours.[15,23] Diploid DNA content is more common in older patients, and it is associated with *MYCN* amplification and worse outcome.[24,25] Whilst hyperdiploid, non-*MYCN* amplified tumours have been shown to have a favourable outcome in children 12–18 months of age,[23] the prognostic value of ploidy in older children and those with *MYCN* amplification have not been definitively established.[26]

Although genetic data were only available for a limited number of patients, the results are largely similar to those in the overall INRG cohort. The prevalence of 1p abnormalities is slightly lower (14% versus 23%),[7] and lower than in previous studies.[27] 1p deletion is associated with age at diagnosis above 12 months (40% versus 23%),[28] stage 4 disease, unfavourable pathology (17 versus 48%), *MYCN* amplification (74 versus 13%).[29] Furthermore, 1p36 LOH was not predictive of poor survival in the cohort of patients with COG intermediate or high risk disease.[29] In our series, the low prevalence of 1p LOH may be related to technical issues (as for all the biological studies in nodular GNB), or may suggest (together with the very low prevalence of *MYCN* amplification) that the biology of nodular tumours differs from that of non-nodular tumours. Similar limitations apply to 11q abnormalities, which were found in 18 of 66 tested patients (27%). 11q abnormalities are associated with older age,[30] being as high as 50% in children older than 18 months, advanced stage, unfavourable histology, *MYCN* amplification and hyperdiploid DNA content.[29] Based on published data, we expected a higher prevalence of 11q abnormalities in our series. In addition, 11q LOH has been shown to correlate with poorer progression-free and event-free survival in patients with localised disease[30] and low/intermediate risk.[29] A larger series of patients with genomic data will need to be evaluated to determine if specific loci (eg 1p, 11q) or overall genomic pattern (e.g. segmental versus numerical changes)[31] is predictive of survival in this rare nodular subgroup.

In summary, patients with GNB nodular tumours represent a small subgroup, characterised by a significant heterogeneity in the outcome, analogous to the overall NB population. Clinical, genetic and biological prognostic factors are the same as in the overall INRG NB cohort, with the exception of MKI and LDH, which are not prognostic in nodular

GNB. Similar to patients who do not have GNB nodular tumours, patients with GNB nodular tumours who are older than 18 months of age, with stage 4 disease represent a sub-group with poor outcome and should be considered for aggressive treatment upfront.

## Conflict of interest statement

None declared.

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