INTERNATIONAL NEUROBLASTOMA RISK GROUP
TASK FORCE
PROJECT PROPOSAL

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Proposal Title	**Ganglioneuroma (GN) and Intermixed ganglioneuroblastoma (iGNB): characteristics at diagnosis, natural history and outcome.**
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1. Specific Aims
    a. To describe the natural history of GN and iGNB, with specific focus on outcomes.
    b. To confirm prior findings that GN and iGNB have favourable biology and pathology.
    c. To describe the treatment used in patients with GN and iGNB, by treatment type (observation only, surgery and observation, or chemotherapy) identify changes in treatment over time.
    d. To describe the outcome and the pattern of relapse in patients with GN and iGNB, overall and within patients who experience metastatic relapse.
2. Hypothesis
    a. GN and iGNB are benign tumours. We do not expect metastatic relapses among these cases.
    b. The treatment of GN and iGNB has evolved over time. We hypothesize that more patients undergo simple surveillance in more recent years, compared to the past.
    c. Progression of residual tumour is not associated with mortality, and survival is overall excellent

3. Patient Cohort (Eligibility Criteria)
    a. Age 0-24 year at diagnosis
    b. Diagnosis of GN or iGNB.
    c. Diagnosis between 1999 and 2016

4. Background

    The International Neuroblastoma Pathology Classification (INPC) distinguishes four subtypes of peripheral neuroblastic tumours: neuroblastoma, nodular ganglioneuroblastoma, intermixed ganglioneuroblastoma and ganglioneuroma. Historically iGNB have been treated as neuroblastomas, but there is increasing evidence that they represent benign entities. The latest reports (from COG[1], German group[2] and single Institution study from Alexander et al[3]) combined GN and iGNB and highlighted the favourable prognosis of both. The historical concept that ganglioneuroma can only be diagnosed on full surgical specimen, to avoid missing a nodule with aggressive behavior, is also being challenged by the latest reports. In Alexander et al, 4 GN were reclassified as iGNB, but no tumour was reclassified as neuroblastoma or nodular GNB[3].

    Clinicians seem unsure of the best management, and this translates into inconsistent practice. In the paper from Alexander et al, only 21 or 67 patients had mIBG scan as part of the staging (despite being a single institution series)[3]. In the German series from Decarolis, 146 of 217 patients had mIBG at diagnosis[2]. Although there is evidence showing that GN are less often mIBG avid than iGNB, the radiation exposure may not be justified in patients with a benign condition. One could also argue that very rarely iGNB metastatise, and mIBG may not be the best investigation, as these tumours often show little or no avidity for mIBG. A PET might be more appropriate, if full staging is deemed

necessary. The surgical approach has also evolved, and Alexander et al showed how most of the patients diagnosed after 2004 have been observed. Safe surgery and avoidance of morbidity seem to be the key factors underpinning management decisions. However, there are also reports of significant clinical symptoms (including symptomatic spinal cord compression) from GN or iGNB, thus challenging a conservative approach[4]. Of note, while in the North American series no patient received chemotherapy, in the German series 11 patients underwent chemotherapy, though with no response. Finally, there is no standardized follow up schedule.
There is overall a need to establish an evidence based, standardized approach to staging and treating patients with GN and iGNB.

5. Significance
   Confirming in the INRG database population the data emerging from single Institution or single group publications, will allow to standardize and rationalize the approach to these patients, including staging procedures (with reduced exposure to radiation), surgical approach and surveillance protocol. Given that the INRG database contains only a limited dataset, in particular with respect to imaging data, we expect that the results of this project will stimulate further research within the context of individual cooperative groups, focused on imaging (staging tests, imaging defined risk factors), surgical outcomes and long term morbidity of GN/iGNB.

6. Proposal description
   All patients diagnosed from 1990 to 2016 with a pathological diagnosis of GN or iGNB will be included in the analysis. We will describe the characteristics of patients with GN and iGNB at presentation, including presence and site of metastases, tumour markers, pathology and biology (when available). We will then describe the initial treatment approach (observation, surgery or chemotherapy) and we will explore the presence of changes of practice over time. Finally we will describe the outcome of these patients, relapse rate and site, second malignancy and survival.

7. Statistical methods
   Analyses will be descriptive, using frequency tabulations of patient characteristics and Kaplan-Meier curves of EFS and OS. We will calculate the proportion of patients who have a favorable prognostic features and descriptively compare these results to prior findings. To describe changes in treatment practices over time, we will group patient by treatment era (1990-1996, 1997-2009, 2010-2016) and calculate the proportion of patients by type of treatment in each era, displaying this results in a bar chart. For patients who relapse/progress, we will tabulate the site of relapse. Patients with metastatic relapse will be described in detail.

8. Data Requested
   a. Age
   b. Year of diagnosis
   c. Initial patient treatment
   d. INSS stage
   e. MYCN
   f. Ploidy
   g. DNA index
   h. 11q aberrations
   i. 1p aberrations

j. 17q aberrations
k. Alk genomic status
l. Ferritin
m. LDH
n. Primary site of the tumour
o. Metastatic sites.
p. Revised INPC prognostic group
q. Diagnostic category
r. Life status (alive, dead)
s. Date of last contact (if alive)
t. Date of event (if event)
u. Type of event
v. Date of death (if dead)
w. Cause of death
x. Sex
y. Site of relapse
z. Second malignancy (yes,no)
aa. Date of second malignancy

References.

1. Okamatsu et al. Pediatr Blood Cancer. 2009 October; 53(4):563-569
2. Decarolis et al. BMC Cancer (2016) 16:542
3. Alexander et al. Pediatr Blood Cancer. 2018;65:e26964.
4. De Bernardi et al. J Clin Oncol 2008 April 1; 26(10) :1710-1716