INTERNATIONAL NEUROBLASTOMA RISK GROUP
TASK FORCE
PROJECT PROPOSAL

Thank you for your interest in INRG data.

Please send your completed proposal and any questions to scohn@peds.bsd.uchicago.edu

Proposal Title	Gender as a prognostic indicator in neuroblastoma
Principal Investigators	Emily Greengard and Wendy London
Institution	University of Minnesota
E-mail Address	emilyg@umn.edu

NOTE:
- Please limit your request to 5 pages
- If you would like to perform the analysis locally, in lieu of using an INRG statistician, please include the CV of your biostatistician and provide a detailed statistical plan.

Please format your project proposal as follows:

Specific Aims

1) To determine if gender is prognostic of outcome in neuroblastoma
2) To determine the association of gender with other neuroblastoma prognostic factors, and to determine the prognostic strength of gender relative to other factors
3) To explore identification of genetic markers associated with gender that would lead to a better understanding of the differences in biologic processes between males and females that could lead to more aggressive neuroblastoma in one sex than the other.

Hypothesis

1) Males with neuroblastoma have lower EFS and OS than females with neuroblastoma.

Patient Cohort (Eligibility Criteria)

Patients from the INRG database who are diagnosed between 2002-2013 who have known data for gender (cut-off of 2013 is applied to allow sufficient follow-up).

Background

Given the heterogeneity of neuroblastoma, tailored treatment approaches based on the presence or absence of specific clinical and biologic features have been used for decades. Data from the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute have shown the incidence of neuroblastoma to be slightly higher in males than females, with the male-to-female ratio being 1.3 to 1.[1] The International Risk Group (INRG) classification systems uses seven prognostic factor to define pretreatment risk groups, of which gender is not included. These prognostic factors are INRG stage, patient age, histologic category, grade of tumor differentiation, MYCN amplification, segmental chromosomal aberrations and ploidy.[2] To our knowledge, whether gender is prognostic of outcome has not been thoroughly explored.

Significance

If the hypothesis is supported, this could inform genetic studies exploring pathway alterations that vary according to gender and result in a more aggressive phenotype. The results of our study could spark future studies to better understand how the biologic processes of NB growth and dissemination differ between males and females.

Proposal description

1) Kaplan-Meier curves of EFS and OS will be generated, overall and by gender. Curves will be compared by gender using a log-rank test.
2) Crosstabulations will be generated of gender with the following known risk factors: age, stage, MYCN status, ploidy, MKI, grade, diagnostic category, 11q status, 1p status, primary site, location of metastases, and treatment intensity. Tests of association will be performed using a chi-squared test. We will perform multivariable Cox proportional hazards modelling to determine if gender is independently prognostic after adjusting for other significantly prognostic risk factors.
3) We will utilize existing transcriptome data for the patients from our cohort who have results in TARGET. From a list of genes known to be prognostic of poor outcome in neuroblastoma, we will test for associations genetic aberrations with gender in a purely exploratory fashion.

Data Requested
All data items in the iINRGdb for patients diagnosed between 2002-2013, including:
Gender
time to event
Event censoring flag
Time to death
Death censoring flag
Risk Factors: age, INSS stage, MYCN status, ploidy, MKI, grade, diagnostic category, 11 q status, 1p status, primary site, locations of metastases
Treatment intensity

In addition, for patients in the TARGET database, we request ability to link to the TARGET data.

1.   Davis, S., M.A. Rogers, and T.W. Pendergrass, *The incidence and epidemiologic characteristics of neuroblastoma in the United States.* Am J Epidemiol, 1987. **126**(6): p. 1063-74.
2.   Cohn, S.L., et al., *The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report.* J Clin Oncol, 2009. **27**(2): p. 289-97.