

INTERNATIONAL NEUROBLASTOMA RISK GROUP  
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PROJECT PROPOSAL

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Proposal Title	Pattern and predictors of sites of relapse in neuroblastoma
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**Specific Aims:**

The pattern and predictors of sites of relapse in neuroblastoma have not been systematically characterized. We propose the following aims:

1. To describe the pattern of relapse in patients with neuroblastoma.
2. To compare tumor biologic features in neuroblastoma, including *MYCN* status, histology and segmental chromosomal aberrations, between patients with local vs. distant vs. combined local and distant failure.
3. To compare clinical features in neuroblastoma, including stage and age at initial diagnosis, distribution of metastases at diagnosis, and initial treatment, between patients with local vs. distant vs. combined local and distant failure.
4. To compare clinical outcomes, including second relapse free survival and overall survival, in neuroblastoma according to pattern of relapse.

**Hypothesis:**

We hypothesize that there are clinical, biological, and prognostic differences based upon the patterns of relapse in neuroblastoma.

**Patient Cohort (Eligibility Criteria):**

Since site of relapse is our primary outcome variable, we will restrict our analysis to patients in the INRG database with known sites of relapse. From the online INRG Discovery Cohort search, we estimate that this will include 1,833 patients. Patients will be coded as having local vs. distant vs. combined local and distant failure.

Patients with ganglioneuroma or esthesioneuroblastoma will not be included. Patients with neuroblastoma or ganglioneuroblastoma will be included. There will be no other inclusion or exclusion criteria.

**Background:**

Neuroblastoma is the most common extracranial solid tumor in children, with approximately 650 cases per year in the United States. Over half of children with neuroblastoma present with metastatic disease at diagnosis. The combination of myeloablative therapy, immunotherapy, and differentiation therapy with 13-cis-retinoic acid has led to an improvement in survival for high-risk neuroblastoma. However, >50% of children will

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still undergo relapse systemically. As relapse remains the major obstacle to cure for patients with high-risk neuroblastoma, it is imperative to assess the patterns of relapse and the clinical and biologic predictors of specific patterns of failure.

Previous studies have investigated the sites of relapse after myeloablative chemo-radiotherapy and purged autologous bone marrow transplantation (ABMT) in comparison with sites of disease at diagnosis and before ABMT in high-risk neuroblastoma patients.<sup>1</sup> Forty-one patients treated on study CCG-321P3 with relapsed disease were included in these analyses. The overall probability of relapse 36 months after ABMT was 49%. Tumor recurred in primary (n = 22), bone (n = 20), bone marrow (n = 18), lung (n = 3), and other sites (n = 9). Eight patients relapsed in the primary site alone, 14 in primary and distant sites, and 19 in distant sites only.

Two studies have examined the role of radiation in the sites of relapse in high-risk neuroblastoma. In a retrospective study from institutional databases that included patients at first metastatic relapse, 159 MIBG-avid metastatic sites were identified among 43 patients at first relapse.<sup>2</sup> Eighty-two percent (131/159) of these sites overlapped anatomically with the set of 525 sites present at diagnosis. This distribution was similar for bone sites, but patterns of relapse were more varied for the smaller subset of soft tissue metastases. Among all metastatic sites at diagnosis in the subsequently relapsed patient cohort, only 3 of 19 irradiated sites (15.8%) recurred as compared with 128 of 506 (25.3%) unirradiated sites. These observations support irradiating metastases that persist after induction chemotherapy in high-risk patients. Furthermore, they raise the hypothesis that metastatic sites appearing to clear with induction chemotherapy may also benefit from radiotherapeutic treatment modalities.

The effect of systemic irradiation by use of total body irradiation (TBI) on anatomic patterns of relapse in neuroblastoma were investigated by Li and colleagues.<sup>3</sup> Of the 227 sites of first relapse, 154 sites (68%) were involved at diagnosis. When we compared relapse patterns in patients treated with and without TBI, 12 of 23 patients (52%) treated with TBI had relapse in  $\geq 1$  previously MIBG-avid site of disease whereas 40 of 51 patients (78%) treated without TBI had relapse in  $\geq 1$  previously MIBG-avid site of disease ( $p=0.03$ ). These findings support further investigation into the role of radiopharmaceutical therapies in curative multimodality therapy.

Recurrences of low stage neuroblastoma are infrequent events and the types of its progression have rarely been reported.<sup>4</sup> Berthold et al. investigated the patterns of progression in a large series of patients with long follow-up. Of the 77 relapsing patients in consecutive cooperative trials, 41 (53%) had local and 36 (47%) systemic recurrences. The relapses occurred in 9 of 76 stage I patients (6 local/3 systemic), in 4 of 82 stage II (1 local/3 systemic), and 64 of 223 stage III neuroblastoma (34 local/30 systemic) patients. The main sites of distant metastasis were bone marrow (41%), lymph nodes (39%) and bone (37%). The median transition time from localized to metastatic neuroblastoma was 13 months and the outcome as poor (overall survival 9 +/- 5%) as that of the primary metastatic disease (14 +/- 3%).

Although the patterns of relapse have been investigated, these studies have generally been small. A more comprehensive analysis of the patterns of relapse may have the potential to improve the treatment and outcome for neuroblastoma.

**Significance:**

Understanding differences based upon sites of relapse have the potential to improve the clinical care of children with neuroblastoma. For example, if specific predictors of local failure can be identified, augmented

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local measures could be proposed for evaluation in selected populations. More fundamentally, understanding these differences may inform our understanding of the failure of therapy at these sites.

**Proposal Description:**

We will perform a detailed analysis of biologic, clinical, and prognostic differences according to the pattern of first relapse. Data requested and statistical plan are as follows.

**Data Requested:**

For patients in the analytic cohort, we will analyze the pattern of first relapse (local vs. distant vs. combined local and distant failure) as the main dependent variable and the following independent, or predictor, variables:

Clinical Features

- Age at diagnosis (to be analyzed as continuous variable and dichotomized above and below 18 months of age)
- INSS stage at diagnosis (to be analyzed as categorical variable and also dichotomized as stage 4 vs. all others)
- Among patients with metastatic disease, presence of bone metastasis
- Among patients with metastatic disease, presence of bone marrow metastasis
- Among patients with metastatic disease, presence of liver metastasis
- Among patients with metastatic disease, presence of lung metastasis
- Primary tumor size (maximum diameter; to be analyzed as continuous variable and possibly dichotomized above and below the group mean)
- LDH at diagnosis (dichotomized at 587 U/L, per INRG standard)
- Ferritin at diagnosis (dichotomized at 92 ng/mL, per INRG standard)
- Urine catecholamines at diagnosis (positive vs. negative)
- MIBG avidity at diagnosis, if available
- Extent of surgical resection at the primary tumor site (complete vs. incomplete)
- Initial treatment, categorized as:
  - Surgery alone
  - Conventional-dose chemotherapy (2-8 cycles) plus surgery
  - Intensive multi-modality therapy: specific type unknown
  - Intensive multi-modality therapy: no stem cell or bone marrow transplant
  - Intensive multi-modality therapy: plus stem cell or bone marrow transplant
  - Intensive multi-modality therapy: plus stem cell or bone marrow transplant and anti-GD2

Biologic Features

- *MYCN* status (amplified vs. non-amplified)
- DNA index/ploidy (diploid vs. hyperdiploid)
- LOH at 1p (present vs. absent)
- Gain of 17q (present vs. absent)
- 11q aberration (present vs. absent)
- Pooled segmental chromosomal aberration (LOH at 1p, gain 17q, and/or 11q aberration vs. none of these changes)
- INPC pathology classification (favorable vs. unfavorable)
- MKI (dichotomized as high vs. low-intermediate)

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- Grade of differentiation (dichotomized as differentiating vs. undifferentiated or poorly differentiated)
- Neuroblastoma vs. ganglioneuroblastoma

Clinical Outcomes

- Time from first relapse to second relapse (or last follow-up if no relapse)
- Time to from first relapse to death (or last follow-up if no death)

**Detailed Statistical Plan:**

Aim 1

This is a descriptive aim in which the proportion of first relapses that are local vs. distant vs. combined local and distant will be reported.

Aims 2 and 3

To address Aims 2 and 3, we will perform a series of univariate analyses evaluating potential differences in any of the above independent variables according to the outcome variable, pattern of relapse. For these analyses, continuous independent variables will be analyzed with ANOVA and categorical independent variables will be analyzed with chi square tests.

In this exploratory analysis, no correction will be made for multiple testing.

Aim 4

To address Aim 4, we will use Kaplan-Meier methods to estimate the 5-year relapse-free survival and overall survival rates according sites of relapse (local vs. distant vs. local and distant). We will utilize log-rank tests to compare outcomes between groups defined by pattern of relapse.

**References:**

1. Matthay KK, Atkinson JB, Stram DO, Selch M, Reynolds CP, Seeger RC. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. *J Clin Oncol* 1993;11:2226-33.
2. Polishchuk AL, Li R, Hill-Kayser C, et al. Likelihood of bone recurrence in prior sites of metastasis in patients with high-risk neuroblastoma. *Int J Radiat Oncol Biol Phys* 2014;89:839-45.
3. Li R, Polishchuk A, DuBois S, et al. Patterns of Relapse in High-Risk Neuroblastoma Patients Treated With and Without Total Body Irradiation. *Int J Radiat Oncol Biol Phys* 2017;97:270-7.
4. Berthold F, Hero B, Breu H, et al. The recurrence patterns of stages I, II and III neuroblastoma: experience with 77 relapsing patients. *Ann Oncol* 1996;7:183-7.