Letter to the Editor

Improvements in Children's Oncology Group neuroblastoma risk stratification through a change in age cut-off and use of INRGSS

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We thank the authors for their supportive comments on our manuscript about the revision to the Children's Oncology Group (COG) neuroblastoma risk stratification based on a change in age cut-off from 12 to 18 months (1,2). The authors have provided a well-described and helpful overview of the application of biomarkers to risk stratify patients, as well as describing treatment and late effects. They have nicely summarized the comparative evidence of our successful reduction of therapy due to the described COG risk stratification changes.

In addition to the change in age cut-off, COG risk stratification is anticipated to improve by using the INRGSS (International Neuroblastoma Risk Group Staging System) (3) instead of INSS (International Neuroblastoma Staging System) (4,5). INSS was utilized in 2006 when the change in age cut-off was made, but has since been replaced by the INRGSS in the COG neuroblastoma risk classifier version 2. INRGSS is a pre-surgical staging system which quantifies the disease extent at diagnosis, compared to INSS, which is post-surgical and dependent on surgical discretion.

The authors describe the use of the International Neuroblastoma Pathology Classification (INPC) as a biomarker in COG risk stratification. Age is one of the factors used to classify tumors as INPC favorable or unfavorable. In the context of risk stratification, using both age and INPC leads to a duplication of the prognostic contribution of age, i.e., confounding. Further improvements in risk stratification should utilize the underlying components of INPC [histologic category, mitosis-karyorrhexis index (MKI), and grade of differentiation] as separate risk factors, to eliminate this problematic confounding (6).

We thank the authors for describing the LEAHRN (Late Effects After High-Risk Neuroblastoma) study, the first comprehensive study specifically focused on late effects in survivors of high-risk neuroblastoma (7). These survivors were diagnosed on/after January 1, 2000, with a minimum of 5 years follow-up after diagnosis. The authors state that survivors were treated between 2000–2006; however, many LEAHRN patients were treated after 2006 with more contemporary therapy.

The authors state that "*While this re-classification saved children to be exposed to unnecessary treatments, their outcome should remain unaltered*". Certainly, it was our hope that their outcome remains 'unaltered', but we should clarify our intent. We hypothesized that despite receiving less intensive therapy, these groups would maintain the same outstanding survival outcomes as they had when they received high-risk

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therapy, albeit with fewer late effects. Fortunately, we were able to present evidence supporting that hypothesis.

We agree with the authors that it is a limitation of our study that only 20 of the 105 patients received treatment through enrollment on clinical trials, and actual treatment received is unknown for most. However, there is anecdotal evidence that most patients in North America who are not enrolled on a COG clinical trial are treated "as per" the clinical trial, receiving the standard-of-care intermediate-risk or high-risk treatment according to the COG risk stratification (8).

We agree with the authors that international data harmonization and novel molecular biomarkers will be critically important to further optimize risk stratification and outcomes (9). We only identified 105 patients enrolled over 30 years in our cohort of interest, highlighting the importance of international collaborations and shared data to better characterize and classify rare subgroups. Furthermore, until such time as predictive biomarkers and drugs for targeted therapy are available for neuroblastoma, research on improved prognostic stratification should continue, as one means to continue to improve outcome, minimize toxicity and improve quality of life.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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