Inconvenience of Convenience Cohorts—Letter

Daniel Williamson1, Edoardo Missiaglia2, Julia Chisholm3, and Janet Shipley4

The authors describe systematic sampling bias from so-called "convenience cohorts" in a review of studies addressing the prognostic significance of the PAX–FOXO1 fusion genes in rhabdomyosarcoma (1). They cite evidence that in at least two studies, samples for which fusion gene status was not determined had a different overall survival than those for which fusion status was determined. They postulate that this is a wider issue with the results presented in other studies. We do not dispute that potential sampling bias is an issue. This is a hazard in many retrospective studies and not peculiar to those in rhabdomyosarcoma. However, we believe that the overall picture of uncertainty painted tends to overlook the significant commonalities between the studies.

The majority of independent studies show PAX–FOXO1 fusion gene status correlates significantly with outcome. The presence of PAX–FOXO1 is highly correlated with alveolar subtype of rhabdomyosarcoma that has significantly poorer prognosis. Fusion-positive rhabdomyosarcomas have distinct gene expression profiles and genomic copy number changes (2, 3) and PAX3–FOXO1–positive tumors are associated with a more aggressive clinical phenotype that is consistent with cell line and mouse models in multiple studies. Notably, of the 3 studies cited in the review that do not show a prognostically significant fusion gene, 2 have demonstrable population biases (1, 4), whereas the third included a heterogeneous set of patients in which a difference in overall survival was not seen even among rhabdomyosarcoma histologic subtypes (1).

We have recently published a further analysis of 287 patients demonstrating that the presence of PAX3–FOXO1 is a biomarker that can be used to significantly improve the predictive power of current risk stratification schemes (5). Consistent with the influence of PAX3–FOXO1 on gene expression patterns, we also demonstrated that the predictive power of any prognostic expression signature is largely a consequence of the presence or absence of PAX3–FOXO1 (2, 3, 5).

We would also like to reaffirm that, contrary to the authors’ comments, fusion gene status was determined in all samples used in our studies, including those with embryonal histology (2, 5). We agree that PAX–FOXO1 status should be used for clinical stratification only following properly controlled prospective studies and indeed we have repeatedly stated this. However, given the length of time since the discovery of the fusion gene and the weight of evidence now available, we venture that it is now appropriate to plan prospective studies incorporating molecular classification that have potential to benefit children with rhabdomyosarcoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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