CORRESPONDENCE

Re: Late Recurrence in Pediatric Cancer: A Report From the Childhood Cancer Survivor Study

In their comprehensive analysis of late recurrences of pediatric cancer in the Childhood Cancer Survivor Study (CCSS), Wasilewski-Masker et al. (1) reported a cumulative incidence of late recurrences of 6.2% at 20 years for patients who had been continuous disease-free survivors at 5 years. We would suggest that the methodology used by the authors is bound to have led to an overestimate of late recurrences. Although most of the reported recurrences will indeed have been local or metastatic manifestations of the original cancer, others will rather have been second primary cancers, which just happened to belong to the same “diagnosis group” as the first malignancy. After all, some of the original pediatric cancers in the CCSS series will have developed on the basis of cancer predisposition syndromes. Affected patients would have continued to be at an increased risk for the de novo development of cancers of the same diagnosis group even after successful therapy for their first malignancy. For patients with Li-Fraumeni syndrome, just to name one well-known example, this would have included the development of secondary soft tissue sarcoma after soft tissue sarcoma, of secondary osteosarcoma after osteosarcoma, or of secondary astrocytoma after astrocytoma (2), all of which would have been classified as late recurrences by the authors.

Even in the absence of genetic predisposition, treatment-related factors will have favored the sequential development of malignancies with similar or identical histologies. For instance, radiotherapy to the brain is commonly used to treat astrocytomas, but—as the CCSS itself has previously elegantly demonstrated—it is also a well-established risk factor for the development of exactly this type of brain tumor (3). Therefore, is it not possible that Wasilewski-Masker et al. (1) found a diagnosis of central nervous system tumor and combination treatment with chemotherapy and radiation to be among the greatest risk factors for late recurrence because they inadvertently counted radiation-induced secondary brain tumors among the late recurrences of first brain tumors?

In some cancers, such as acute lymphoblastic leukemia and Ewing tumors, molecular subtyping may allow second primary malignancies to be distinguished from true recurrences, and it has indeed been able to do so in selected cases (4). Such knowledge would be important to know which problem needs to be addressed: If it is late recurrences, first-line antineoplastic treatment may need to be intensified to prevent their development. Such an approach, however, may even be detrimental if the goal should rather be to reduce the incidence of second primary cancers. In addition, a second primary malignancy, other than the late recurrence arising after multimodal treatment, would be chemotherapy naïve. Knowledge about the true origin of such a neoplasm should influence treatment decisions and, potentially, outcomes.

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References

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