Editorial

Neurocognitive function and CNS integrity in adult survivors of childhood Hodgkin Lymphoma - a commentary on report from Krull and colleagues

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Historically, radiotherapy alone and radiotherapy combined with chemotherapy have led to the cure of many pediatric Hodgkin lymphoma patients. Modern series have demonstrated a 5 year overall survival of greater than 90% for early stage patients. Over the many decades it took to achieve these remarkable results, it became evident that long-term survivors are at increased risk for long-term toxicities such as cardiopulmonary and perhaps neurocognitive toxicities as Krull *et al*. have suggested (1). However, based on the data presented, it is unclear if the difference is caused solely by the use of outdated mantle field radiation doses of ≥30 Gy *vs*. <30 Gy.

It is well established that cardio-vascular toxicities have emerged as the most prominent and serious late complication in children treated for Hodgkin lymphoma. Radiotherapy is a culprit in causing cardiomyopathy, coronary vascular disease, valvular abnormalities, pericardial effusions and scarring (2-6). However, it is not the only culprit. Chemotherapy agents like doxorubicin, commonly used in the treatment of lymphomas, are also directly linked with myocardial damage and subsequent cardiomyopathy (7-10). The cardiovascular toxicities are further accentuated when mediastinal irradiation is combined with anthracycline-based therapy (11). In addition, Bleomycin can cause significantly pulmonary toxicities.

Researchers from St. Jude's Children's Research hospital present new and striking evidence on neurocognitive effects of Childhood Hodgkin Lymphoma (HL) therapy. The neurocognitive effects are thought to be a secondary effect of cardiopulmonary dysfunction (1). There are several short comings of the study presented: (I) a small randomly selected cohort of 62 patients may not be representative of the larger population, (II) confounding caused by the use of doxorubicin and bleomycin causing cardiopulmonary toxicity cannot be well quantified in such a small study, (III) doxorubicin can also have direct effects on neurogenesis (12), impair memory retention (13), and impair memory function (14) when measured in rat models, (IV) radiation received to the different structures of the heart (aortic valve, mitral valve, left ventricle, left anterior descending artery) and the lung are not presented, (V) important differences in the Framingham factors such as smoking, diabetes, age, sex, HDL, total cholesterol, smoking, and diabetes between the group receiving <30 Gy and that receiving ≥30 Gy are not presented, (VI) and mantle fields are now considered outdated by many radiation oncologists.

More importantly, the authors fail to directly show increased rates of neurocognitive impairments in patients receiving ≥30 Gy mantle field *vs*. <30 Gy. What the authors tried to do is provide indirect evidence using imaging correlates and testing along multiple neurcognitive domains which may or may not be applicable for long term cancer survivor patients. Also, the authors fail to demonstrate direct evidence of a difference in diastolic dysfunction as defined by reduction in ejection fraction of <55% between the group receiving ≥30 Gy *vs*. <30 Gy. What the authors noted in their observation is that those patients that had reduced diastolic function had worse performance on working memory, task completion, and fatigue and yet, there were no difference in diastolic pressure, systolic pressure, hypertension, or ejection fraction between the two groups. Thus, it is unclear how the authors were able to conclude that radiation dose was the main culprit.

Studies such as Krull *et al*. raise as many questions as

they answer, and could cause fear and undue anxiety in patients undergoing potentially curable treatments. Due to the controversies involved, expert panels and task forces [Childhood Cancer Survivor Study (CCSS), late-effects task force of Children's Oncology Group (COG), UK Children's Cancer Study Group (UKCCSG) Late Effects Group (LEG), etc.] were created to review and update data on cancer-therapy toxicities in children and/or help design evidence-based long-term toxicity screening guidelines for survivors of childhood malignancies. Larger prospective studies lead by these task forces are needed to better address the issue raised by Krull *et al.*

Hopefully the authors and other groups will continue to pursue these questions in the future in a larger population cohort to help us investigate the known and potentially new factors contributing to the cerebrovascular pathology in HL survivors. Until, then we would advise caution in drawing firm conclusions that radiotherapy is the sole cause of this significant late effect.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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