With Every Upside, There Is a Downside: Chest Radiation and Survivors of Childhood Cancers

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Childhood cancer treatment involves numerous therapies, such as chest radiation, that have significant pulmonary toxicity. Treatment may also include lung and/or chest wall resection. Given improvements in cancer therapy, children with acute lymphocytic leukemia and other previously uniformly fatal cancer are increasingly likely to survive to adulthood (1). While ensuring the survival of these children is clearly the central goal in pediatric cancer care, understanding the long-term implications of treatment is also important, both for patient education and for guiding future efforts to improve treatment.

Relatively little is known about risk factors for developing impaired pulmonary function in survivors of childhood cancer. Limited studies published to date report varying rates of abnormal lung function and variable risk factors for impaired function. In one of the largest studies, only questionnaire data were available (2). In that study, self-reported shortness of breath with exercise occurred in 10.5% of cases.

Early studies of childhood cancer survivors, focusing on survivors of hematological malignancies, demonstrated variable but generally high rates of abnormal lung function tests after treatment (12.4–40%) and a particularly high rate of abnormal function after stem cell transplantation (15.7–64%) (3).

Authors of a recent systematic review of pulmonary function in survivors of childhood cancer identified 60 relevant publications, but could not pool the results (4). Despite this caveat, the authors found that several therapeutic exposures,

such as radiotherapy, specific alkylating agents, bleomycin, hematopoietic stem cell transplantation, and thoracic surgery, were associated with later development of pulmonary function impairment. The authors acknowledged important limitations of their review, including their inability to generate a pooled relative risk and the variable post-diagnosis follow-up.

More recent studies have clearly demonstrated long-term adverse effects on lung function. One study reported a restrictive abnormality in almost 18% of patients (5). The most comprehensive study to date evaluated all health outcomes for all 1,713 adult survivors of childhood cancer enrolled in the Saint Jude Lifetime Cohort Study (SJLIFE) (6). The most prevalent adverse health outcome was abnormal spirometry, affecting 65% of survivors overall. By age 50, the cumulative prevalence of pulmonary dysfunction was 81% (6).

None of these more recent studies have evaluated functional impairment by formally measuring exercise tolerance. To understand the long-term burden of childhood cancer therapy, we need to extend observations beyond static tests of lung function. Also needed is a better understanding of risk factors from a larger cohort of survivors of childhood cancer (7).

In this issue of *AnnalsATS*, Green and colleagues (pp. 1575–1585) describe the prevalence of abnormal pulmonary function test results and delineate risk factors for developing abnormal lung function in a cohort of 606 patients derived from the Saint Jude Lifetime Cohort Study

(SJLIFE) (6, 8). To be included in the current study, patients needed to have been treated at the St. Jude's Children's Research Hospital, have survived longer than 10 years from diagnosis, and be 18 years of age or older. To document toxicity, the authors employed the National Cancer Institute Common Terminology Criteria for Adverse Events, thereby making the results relevant to adverse event monitoring of therapeutics. They also used the Global Lung Initiative reference equations for spirometry in addition to reference equations by Hankinson and Miller (9). The potential predictors they tested included 32 specific chemotherapeutic agents, chest surgery, and chest radiation therapy. They recreated radiation dosimetry by using whole lung exposure in 61 cases of chest radiation therapy, creating a mean lung dose and volume of lung receiving 10 Gy, 20 Gy, and 24 Gy.

Abnormal spirometry was common in the study cohort. Altogether, 50.7% had forced expiratory volume in one second (FEV₁) less than 80% predicted; 47.2% had a forced vital capacity (FVC) less than 80% predicted; 31.2% had a total lung capacity (TLC) less than 75% predicted; and 44.6% had a carbon monoxide diffusing capacity (corrected for Hgb) less than 75% predicted. None of the participants had an obstructive lung defects using the Global Lung Initiative criterion of FEV₁/FVC less than the lower limit of normal, but 31.2% had a restrictive lung defect (defined as a TLC < 75%). The authors also found that this lung impairment led to a demonstrable change

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in 6-minute-walk test (6MWT) distance. Importantly, those who did not complete a 6MWT had lower lung function compared with those who did, biasing the results to the null and strengthening their findings of this association.

In a multivariable regression model, lung irradiation and elapsed time since diagnosis were the only variables associated with abnormal FEV₁ and FVC. None of the other commonly cited covariates (chemotherapies, chest surgeries, or current smoking status) were retained in the regression models. This finding is important. Despite many other risk factors known to impact lung function, the one dominant long-term risk to emerge from this study is chest radiation therapy.

One of the key strengths of the study by Green and coauthors is that the investigators employed a well-characterized and inclusive patient cohort. The comprehensive nature of the study cohort, which included a broad spectrum of cancers and cancer treatments, enhances the likelihood that the results are generalizable. The quantification of lung exposure also provided the investigators with a novel approach to assessing exposure. This study design feature contributed to the startling finding that what really matters in this population with respect to later lung function impairment is chest radiation therapy. Inclusion of 6MWT results enhances our understanding of the

functional implications of the abnormalities noted on spirometry.

Another important aspect of the study was the use of Bayesian Model Averaging for assessment of risk factors. Many approaches have been utilized in the literature to assess risk factors by regression modeling, including stepwise regression, assessing confounders based on a 10% change in the point estimate of the confounders of interest (10), or merely adding covariates in the model in blocks. The challenges to regression modeling for risk factors is that one could conceivably conduct hundreds of models and by chance alone find a model that associates a risk factor of interest with outcome. Ideally, one might pick the best model by averaging all the possible models (combinations of predictors) to ensure the right inference—but this is impractical.

Bayesian Model Averaging is a structured approach to selection of the most appropriate model for identification of risk factors by integrating the variables of interest and the model uncertainty, and averaging estimates of dozens of alternative models weighted by their posterior probabilities. This in turn lowers the chance of an incorrect inference (11). Simulation studies of stepwise regression suggest that such approaches to model selection may overestimate the certainty of significance of a risk factor (12). Integrating the uncertainty of a model with Bayesian Model Averaging allows one to generate a

posterior probability that the covariate is really a risk factor (13). The investigators did employ alternative approaches (Least Absolute Shrinkage and Selection Operator [LASSO]), but these approaches yielded less consistent models. The choice of Bayesian Model Averaging led to the parsimonious and consistent models presented in the paper.

There are some important limitations to this study. To their credit, the investigators did compare those who participated in the study with those not participating as well as those with and without spirometry. However, a key finding in this comparison was that the participants had significant differences in cancer diagnosis, treatments, and history of chest surgery. While the authors discounted these differences as small, readers are advised to apply their own judgment regarding these differences.

Childhood cancer outcomes have improved dramatically over time. Understanding the long-term sequelae of various treatment regimens is key to understanding (and to mitigating) adverse effects of treatment in the future. Future studies should focus on achieving the lowest efficacious radiation dose and evaluating potential therapeutic compounds that might protect against radiation lung injury. Pentoxifylline is one example of an agent that might protect against radiation-induced lung injury (14). ■

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