Editorial Commentary

Late health outcomes among survivors of Wilms tumor

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Hard work by many has helped to improve survival rates for pediatric cancer patients over the last several decades. With survivors living well into their adult years, a need has now arisen to put equal efforts into both the education for clinicians and care for patients experiencing long-term complications of pediatric cancer and its treatments. Wilms' tumor (WT) is the most common occurring pediatric renal malignancy and 5th most common occurring childhood tumor with approximately 500 new cases reported annually. Due to the embryological origin of the tumor and its association with a tumor-suppressor gene, WT remains a very treatment-responsive tumor with long-term survival rates around 90% (1). Modern treatment guidelines for WT are generally defined and standardized by two large collaborative organizations, the National Wilms Tumor Study Group (NWTSG)/Children's Oncology Group (COG) and the International Society of Pediatric Oncology (SIOP). Treatments involve chemotherapy combined with tumor/kidney removal and possible radiation therapy, varying by stage and histology of the primary tumor. Treatments have been refined over the years to provide adequate cancer control while attempting to minimize long-term effects of the prescribed therapies on survivors (2). Even in cases of advanced disease, opportunity exists to improve our therapeutic approaches to maximize outcomes and minimize morbidity (3). Additionally, SIOP and COG are now collecting prospective data to allow for clinical and biological tumor data to be collected and analyzed. This will allow clinicians to use both personal risk factors and tumor-specific genetic and histological factors to direct treatment modalities. With this information, more children will be able to have de-escalation of therapy for the more favorable and responsive WT, which subsequently should reduce the long-term secondary effects experienced by survivors (4).

A recent publication by Weil *et al.* in 2023 evaluated the long-term complications, specifically chronic health conditions (CHCs) in patients with unilateral non-syndromic WT. Data was abstracted from the Childhood Cancer Survivor Study (CCSS), a multi-institutional 30-year retrospective cohort study of approximately 25,000 WT patients who were at least 5-year survivors who received care at several children's hospitals throughout the United States and Canada. Mortality data, subsequent cancers, and CHCs were stratified based on the treatments the patient received; primary focus was placed on patients who received primary nephrectomy with vincristine and actinomycin

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D. Individuals receiving this therapy demonstrated a 50% increase in relative risk for moderate and severe CHCs including renal failure, bowel obstruction, ovarian failure, and heart failure. Almost 1/3 of all patients in the cohort experienced at least one significant CHC, which was a 3-fold increase compared to sibling controls. As therapy for WT increased to include radiation therapy or more robust chemotherapies, the relative risk of CHCs skyrockets. As cancer complexity increases, therapeutics increase and long-term health issues such as heart failure can have a 42× increase in relative risk compared to sibling controls (5). Approximately two in five patients with WT will fall into the nephrectomy plus vincristine and actinomycin D treatment category. In this group, while there is a rise in negative outcomes such as additional malignancies and kidney failure, all-cause mortality remains similar to the control population. Heart failure remains similar in this group as well, likely due to lack of exposure to radiation and that doxorubicin is omitted in this group.

The increased relative risk of CHCs and subsequent malignancies in these childhood cancers are staggering when they are observed over this 35-year period. A recent study estimated that 95% of people who survive a childhood cancer will develop a health issue associated with the cancer itself or the treatment that the individual received (6). What should also be noted is the dramatic rise in relative risk of moderate and severe CHCs that occurs as therapeutic interventions increase to include radiation therapy and multiple chemotherapeutic agents. It is important to note that a significant confounder with long-term follow-up studies are the changes in treatment protocols over time which may affect reported results. This may skew the specific data, but likely does not change the significant CHCs now being observed and treated. Progression of health care problems over time are not recognized in this set-up and that is important information The individuals receiving these more advanced treatment modalities are more likely to have more severe disease or present in a more delayed fashion for care. Globally, this is becoming a greater concern due to disparities in health care that exist across an individual country and the world. The reported incidence of WT is highest in low-income countries, and these same countries also demonstrate the lowest overall survival rates (7). North America, Europe, Japan, and India (only recently) have tumor registries and committees that have largely improved cancer care. Children in low- and middle-income countries do not have the benefit of all advances in WT care due to socioeconomic factors, political issues, and more limited access to care (1). This engenders the most vulnerable population to experience more severe disease and require more therapy that leaves these individuals most susceptible to kidney and heart failure, amongst other issues, later in life.

Socioeconomic disparities make a significant impact on the overall outcomes of WT management. In the United States with similar access to modern protocols and therapies, individuals from the most socially deprived areas have lower 10-year overall and cancer-specific survival rates (8). Globally in low-resource settings, the stated survival can be 50% and, in some areas, less than 30% overall survival. In many of these lower-resource countries and areas, lack of access to chemotherapeutics is a major cause. Guidelines for these lower access areas frequently involve radiation therapy if available (9). This likely subsequently pushes those individuals into higher category risk for developing CHCs from their treatment. These global and social disparities further complicate the treatment of WT and its recommended guidelines. These stark differences raise a global educational imperative; emphasis should be placed in training curriculum on the problems childhood cancer survivors face that reaches medical providers caring for all socioeconomic patient populations.

WT is a highly treatable childhood malignancy, but clearly the outcomes are nuanced by a variety of different circumstances. In much of the developed world, survivors are now well into adulthood making studies such Weil *et al.*'s recent publication about long-term morbidity and mortality important research to carry out. Given the high rate of CHCs in the WT survivor population, survivorship guidelines based on treatment modality needs to be developed and distributed (4). Many of the long-term primary care and family medicine providers taking care of these once pediatric patients may be unfamiliar with the screening required for the high preponderance of long-term consequences in this unique population. Additionally patient-centered education on what their long-term issues may be should be more robustly developed and distributed as part of survivorship plans and pathways both in high-income and low-income medical centers world-wide. Primary care providers also need education and pathways

for screening patients for CHCs with a history of pediatric cancer through global public health initiatives. As clinicians taking care of WT, remarkable advancements have been achieved over the past several decades, but based on recent publications, we clearly have work to do to keep our patients healthy well into their adult years.

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