Editorial Commentary

Risks of long-term mortality and chronic health conditions experienced by Wilms tumor survivors

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Wilms tumor (WT), also known as nephroblastoma, is the most common renal tumor in children, accounting for approximately 5% of all childhood cancers (1). The achievements in WT survival have been one of the great success stories of modern medicine. Over the last five decades, collaborative research studies mainly in North America [National Wilms Tumor Study (NWTS) Group/ Renal Tumor Committee of the Children's Oncology Group (COG)] and Europe [International Society of Pediatric Oncology-Renal Tumor Study Group (SIOP-RTSG)] have developed well-established, multimodal treatment protocols for WT. Due to a mortality rate of more than 50% in the 1950s, the main driving force for improvement of overall- and event-free survival in children diagnosed with WT, was the optimization of early treatment plans (2). Later, the identification of adverse prognostic factors of WT such as loss of heterozygosity at chromosomes 1p and 16q has led to the adaption of risk-based utilization of intensified therapies (3). In recent years, the COG and SIOP treatment principles aim to minimize treatment load without reducing survival, limiting patients with WT in need of intensified therapy (4,5). Research supporting this push for de-escalated and optimized treatment regimes originated from several comprehensive cohort studies focusing on long-term outcomes after initial WT therapy (6-9). The Childhood Cancer Survivor Study (CCSS) is one of the largest cooperative studies on late sequelae following WT treatment today. The CCSS is a collaborative, multi-institutional study including pediatric oncology centers across the United States and Canada treating patients according to COG treatment protocols. Since its inception in 1994, the CCSS has been following 38,036 survivors of childhood cancers diagnosed between 1970–1999 in a longitudinal and prospective manner, collecting valuable data on late mortality in relation to the general population and on chronic health conditions as well as self-reported health-related quality of life in comparison to siblings of the CCSS survivors (https://ccss.stjude.org/).

The latest CCSS publication by Weil *et al*. (10), published in the *Journal of Clinical Oncology*, reports on 2,008 long-term survivors (i.e., ≥5 years) after treatment for unilateral, non-syndromic WT, covering more than 35 years of follow-up. Retrospectively, 1,261 (62.8%) could be classified into treatment groups, making it the largest WT study in which late outcomes were evaluated according to the applied treatment regimes. The results show that WT survivors who received treatment limited to nephrectomy, vincristine and actinomycin-D (VA) experienced rates of chronic health conditions and mortality that are largely comparable with the general (non-cancer) population.

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Those 40% of newly diagnosed children with WT, who were treated with unilateral nephrectomy and VA alone (i.e., the current standard of care for stage I and II WT with a favorable histology in North America) had an excellent outcome with a reliable chance of long-term cure. In comparison, those treated with more intense regimens like VA + doxorubicin + abdominal radiotherapy (VAD + ART), VAD + ART + whole lung radiotherapy or ≥4 chemotherapy drugs + any radiotherapy exhibited a statistically significant increase in late health-related mortality and long-term morbidity (e.g., subsequent malignant neoplasms, heart failure, intestinal obstruction and premature ovarian insufficiency). In the overall cohort, there were a total of 142 deaths with a 7.8% of late mortality, most frequently caused by secondary malignant neoplasms, WT relapse and cardiac failure, which is similar to prior results (7-9,11,12).

Weil *et al*. (10) also observed a further important aspect with regard to the long-term consequences of nephrectomy among WT survivors, namely a 2.4% 35-year cumulative incidence of late renal dysfunction (defined as need for dialysis or kidney transplant) across all treatment groups, which is an approximately 10-fold increased rate relative to their siblings. The 30-year threshold appears to be a crucial time point as children born with a solitary kidney are also at increased risk for end-stage renal disease (ESRD) by the age of 30 years. Earlier reports on ESRD in patients with WT estimated a 20-year rate of kidney failure of 0.6–0.7% (13,14). This increase in the incidence of ESRD correlates with findings from other cohort studies that detected a significant decrease in the estimated glomerular filtration rate up to 50 years after the original WT diagnosis (15-18), suggesting that there may be an ongoing risk of kidney failure for WT survivors living beyond reported follow-up times in previous studies. As renal failure, unrelated to flank radiation to the contralateral kidney, has also been described in the 25-year CCSS follow-up study of WT (8), Weil *et al*. argue that the loss of nephrons due to unilateral nephrectomy alone might have been the contributing factor to the development of ESRD in the aging WT population (10). This observation energizes the discussion on nephron-sparing surgery (NSS) in children with unilateral WT as traditional nephrectomy in these cases inevitably leads to the resection of viable and functioning renal tissue along the tumor mass. Clearly, the aim of NSS in WT is to preserve the tumor-free proportion of the kidney, while completely resecting the tumor mass within surgical oncology margins. This technique increases the amount of functional renal units after WT resection and may eventually contribute to a longer lasting renal function. It has been shown that favorable candidates suitable for NSS are WT located to the poles or periphery of the kidney. Confining the tumor mass to these locations by neoadjuvant chemotherapy and thus increasing the resectability chances has been a long-approved concept in bilateral WT (19). Without pretreatment, only a minority of children with WT would be eligible for NSS. Due to the utilization of neoadjuvant therapy, SIOP-based study protocols therefore have an intrinsic advantage over the COG approach, when applying NSS in unilateral WT (20). The application of NSS to unilateral, non-syndromic WT is now incorporated in the Umbrella Study SIOP-RTSG 2016 (5). Future results will show the impact of renal function preservation by NSS in SIOP-treated unilateral WT survivors 20–40 years from now. Hence, the systematic follow-up of these patients into late adulthood will be of significant importance. Currently, there is a paucity of long-term data from SIOP on survivors with WT for a meaningful comparison to the COG population.

Consistent with reports from other WT survivor studies (21-23), Weil *et al.* observed elevated rates of late morbidity (i.e., subsequent malignant neoplasms, heart failure, intestinal obstruction and premature ovarian insufficiency) and mortality among patients that were previously exposed to doxorubicin (≥250 mg/m^2) and/or radiotherapy (>20 Gy) (10). As the risk of premature ovarian insufficiency was associated with the receipt of ART and appeared to be influenced in a dose-dependent manner, there is justification for further discussions focused on fertility preservation (FP) options in female patients with WT. In turn, gonadal dysfunction and infertility may often have been undiagnosed in male WT survivors as they frequently experience normal sexual function later in life. For that reason, there has been a growing exchange in research and regular consultations on FP among members of the COG and SIOP-RTSG. In 2022, the two groups published a joint statement on the relevance of FP in pediatric patients with WT (24). At present, there are no proven methods for FP for prepubertal males (i.e., testicular biopsy for cryopreservation is experimental) and there is only a single option for prepubertal females (i.e., ovarian tissue cryopreservation) (25), posing both technical and ethical challenges. In future, identification of genetic markers of susceptibility to gonadotoxic therapy may help to stratify patient risk of gonadal damage and identify those most likely to benefit from FP methods.

In conclusion, today's long-term survival rates for WT are excellent and approximately 85–90% of patients with a favorable tumor histology can be cured. Nevertheless,

chronic health problems occur in nearly one third of WT survivors, most commonly subsequent malignant neoplasms, intestinal obstruction, kidney/heart failure and premature ovarian insufficiency. Hence, longitudinal follow-up studies such as the one conducted by Weil *et al*. represent one of the cornerstones for development of future WT treatment regimens through identification of relevant therapy- and patient-related late effects (10). In order to limit overall morbidity for WT survivors, one of the major initiatives has been the reduction of doxorubicin and/or radiation dose as well as omission of radiotherapy for certain patient groups. However, many data are still incomplete, missing or pooled because of the low number of WT cases. Clearly, collection and assessment of multi-institutional WT outcome sets can only be achieved by extraordinary efforts of large research consortiums. With the trend towards personalized patient care, the challenges and complexity of long-term data analysis increase. In the world of best practice, risk-based "personalized medicine" will need to include an individualized, life-long follow-up plan (i.e., spanning from early infancy into late adulthood) with surveillance, counseling, screening, prevention and management of potential late complications in WT patients, thereby improving long-term health maintenance. Simultaneously, the search for new anticancer drugs such as novel biologically-targeted agents or immunotherapies needs to be continued. In the future, artificial intelligence algorithms of tumor imaging and three-dimensional (3D) reconstructions of WT may assist the surgeon in defining surgical resection lines, thus improving surgical outcome particularly in cases of NSS. Finally, the longitudinal accumulated data is not only important for health care providers but also provides valuable information frequently asked for by the patients' parents or guardians on the future well-being of their child following treatment of WT. In this context, answers to questions such as "Will my child live a long and healthy life?" or "Will the tumor come back?" will have a more substantial foundation.

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