Chapter

Long-Term Toxicities among Wilms Tumor Survivors

Samir Patel, Andrea Lo, Luke E. Pater, Mary Frances McAleer, Arnold Paulino and John A. Kalapurakal

Abstract

Successive trials conducted by the National Wilms Tumor Study have resulted in very high cure rates for children with Wilms tumor (WT). These trials have also significantly reduced the indications for doxorubicin and higher doses of RT in WT. Late toxicities after multimodality treatment especially RT, continues to be a major problem among WT survivors. Higher doses of RT is the most important factor responsible for the many late effects including congestive heart failure, secondary malignant neoplasms, hypogonadism, infertility and pregnancy complications, pulmonary disease, musculoskeletal effects, renal failure and diabetes mellitus. The potential for novel RT techniques like IMRT and proton therapy to reduce the incidence of these toxicities is discussed. The surveillance recommendations for WT survivors are mainly derived from the COG long-term follow-up guidelines. The future directions in late effects research include novel research to improve current knowledge of association between RT doses to target organs and late effects, discovery of novel biomarkers, and identification of predictive genetic biomarkers. Despite all these advances, there are significant challenges facing the global health care community that need to be overcome before the benefits of these innovations in late effects research can be translated to individual cancer survivors.

Keywords: Wilms tumor, radiation therapy, survivors, late toxicities, surveillance, prevention

1. Introduction

Successive trials conducted by the National Wilms Tumor Study (NWTS) have led to major improvements in the overall survival of children afflicted with Wilms tumor (WT). These trials have also been successful in reducing the indications for and dosages of radiation therapy (RT) and doxorubicin in the majority of children with WT. However, late toxicity of treatment continues to be a concern with radiation therapy (RT) as a major contributor [1]. Organs in the abdomen such as the liver, pancreas, spleen and bowel may be included in the flank RT field. For whole abdominal RT (WART), in addition to these organs, the remaining kidney, uterus and the ovaries are included in the RT field, and the testicles and breast tissue receiving scatter radiation. The heart, lungs, thyroid gland and breast tissue are at risk for late effects when whole lung irradiation (WLI) is utilized.

The bone, muscles and soft tissues are also at risk for growth disturbances when the abdomen and/or chest are irradiated. Finally, there is a potential risk of secondary malignant neoplasms in all of these organs exposed to any dose of RT.

Long-term follow up of the NWTS cohort showed that the standardized mortality ratio (SMR) was 24.3 for the first 5 years, 12.6 for the next 5 years, and remained greater than 3.0 thereafter. Secondary malignant neoplasms and congestive heart failure (CHF) were the commonest causes of long-term mortality [2]. Likewise, in the Childhood Cancer Survival Study (CCSS), the overall survival rate at 25 years after diagnosis of WT was 93.9%. The overall SMR was 4.9, and SMR for survivors who received abdominal and chest RT without doxorubicin was 6.1, and with doxorubicin the SMR was 12.3. Also, the cumulative incidence of chronic health conditions at 25 years after diagnosis was 65.4% and that of severe conditions (grades 3 to 5) was 24.2%. WT survivors had twice the rate of grades 1 to 4 chronic health conditions (Hazard Ratio [HR] 2.0) and 4.7 times higher rates of severe chronic health conditions (grades 3 or 4) (HR 4.7) than the sibling comparison group [3].

Children with WT are typically young, as the median age at initial presentation is between 3 to 4 years; hence, any reduction in RT dose and volume may have an impact on lowering treatment complications. RT dose reduction from 40 to 10 Gy in Stage III FH and the omission of WLI in Stage IV FH WT patients with isolated pulmonary metastases, favorable biology and complete response to chemotherapy are some of the strategies that have been used in the NWTS and Children's Oncology Group (COG) to minimize RT late effects [4, 5]. The use of more modern techniques of RT delivery such as intensity modulated radiation therapy (IMRT) and proton therapy can likewise potentially reduce RT complications. This chapter will examine the acute and late RT toxicities observed in Wilms tumor patients as well as some of the strategies that have been employed to minimize long-term complications.

2. Cardiac toxicity

Cardiotoxicity, specifically congestive heart failure (CHF) is a leading cause of morbidity and mortality in long-term survivors of Wilms tumor [2, 3]. Anthracyclines have preferential myocytic toxicity that results in a reduction of myocardial mass, myofibril dysfunction, decrease in contractility, and cardiomyopathy [6]. The most important risk factor is cumulative anthracycline dose, although all dose levels have been associated with myocyte injury [7]. Asymptomatic echocardiographic abnormalities such as increased end-systolic wall stress or decreased contractility can be found in survivors [8, 9]. Further, cardiac damage from therapy is progressive with an increasing lifelong risk of developing cardiac dysfunction that may necessitate cardiac transplant in some survivors [10, 11]. The severity of late cardiac effects will depend on factors including the age and sex of the child at time of treatment, cumulative anthracycline dose, cardiac radiation exposure, and presence of independent risk factors for cardiovascular disease not related to therapy.

Cardiac irradiation may result in scarring and stiffening of heart tissues resulting in arrhythmias, cardiomyopathy, valvular stenosis or insufficiency, coronary artery disease, and pericarditis or pericardial fibrosis [12]. Risk factors for cardiac morbidity include patient age at time of RT, RT dose and fractionation, irradiated cardiac volume, exposure to chemotherapeutic agents, and presence of cardiovascular risk factors.

The 20-year cumulative frequency of CHF among patients on NWTS-1 to NWTS-4 studies was 4.4% in patients initially treated with doxorubicin and 17.4%

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in patients treated with doxorubicin for first or subsequent relapse [13]. The relative risk (RR) of CHF was increased with female sex (relative risk RR 4.5) and cumulative doxorubicin dose (RR 3.2/100 mg/m2), and left abdominal RT (RR 1.8/10 Gy). In an analysis of patients enrolled on the NWTS-3 and NWTS-4 studies, the 20-year risk of CHF after primary treatment with doxorubicin was 1.2% [14]. In a report from the CCSS, after 25 years of follow up, the HRs were 23.6 for CHF, 50.7 for renal failure, and 8.2 for hypertension (HTN), compared to the sibling group. Exposure to doxorubicin, in the absence of cardiac RT, did not show a clear association with an increased risk of CHF (≤ 250 mg/m2, HR 4.8). Cardiac RT was associated with an elevated risk of developing CHF. In the absence of doxorubicin, cardiac RT was associated with a HR of 6.6 for CHF. The HR for CHF was increased among those who received both cardiac RT and doxorubicin (≤ 250 mg/m2, HR 13.0, > 250 mg/m2, HR 18.3) [3].

The first study to corelate mean cardiac dose with late cardiac morbidity was a study of 4122 five-year French and British childhood survivors (mean follow-up, 27 years). The risk of cardiac death was higher in patients who received a mean cardiac RT dose of >5 Gy (5–14.9 Gy RR 12.5; >15 Gy RR, 25.1) and cumulative anthracycline dose of >360 mg/m2 (RR 4.4). There was a linear relationship between the mean cardiac RT dose and the risk of cardiac death (adjusted RR at 1 Gy, 60%) [15]. In another report of 229 childhood cancer survivors at the Institute Gustave Roussy 15 years or more after doxorubicin therapy, patients who received a mean cardiac RT dose between 5 and 20 Gy had a RR of CHF of 2.52 and those who received ≥20 Gy had a RR 5.65. The 25-year risk of cardiac failure was estimated at 34% in the 34 patients who received ≥250 mg/m2 of doxorubicin and mean cardiac RT dose of ≥5 Gy [16]. A report from the CCSS showed a dose-response relationship between mean cardiac RT dose and any cardiac disease, coronary artery disease and heart failure at mean doses ≥10 Gy. Exposure of low- to moderate-dose RT (5 to 19 Gy) to a large volume of the heart (≥ 50%) had a 1.6-fold increased risk of cardiac disease and exposure of any volume of the heart to RT doses of ≥20 Gy conferred an increased risk of cardiac disease [17].

3. Mitigation strategies and surveillance guidelines

The use of two parallel-opposed anterior-posterior (AP) and posterior-anterior (PA) fields has been the conventional approach for RT of WT for many decades. Modern RT techniques such as cardiac sparing whole lung intensity-modulated radiation therapy (IMRT) techniques haves been shown statistically significant reduction of cardiac and myocardial RT doses compared to standard AP-PA WLI techniques in a prospective clinical trial [12]. Another report showed that the mean cardiac dose was significantly higher when the lung and abdomen RT fields were treated sequentially compared to when they were treated concurrently [18]. All current and future COG protocols will permit the use of cardiac sparing whole lung IMRT with central quality assurance review, concurrent treatment of lung and abdomen RT fields and IMRT/proton therapy for the treatment of flank and whole abdomen.

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 1**.

	Anthracycline Dose	Radiation Dose	Recommendation
Medical history	All survivors		Evaluate for: shortness of breath, dyspnea on exertion, orthopnea, palpitations, chest pain
	Survivors aged <25 years		Abdominal symptoms (nausea, vomiting)
Physical Examination and Counseling	All survivors		Yearly blood pressure and cardiac examination Maintain appropriate weight, blood pressure and heart-healthy diet. Regular exercise should be encouraged for patients who have normal LV systolic function. High-risk survivors should consult with a cardiologist to define limits and precautions for physical activity For female patients who are pregnant or planning to become pregnant, additional cardiology evaluation is indicated in patients who received: ≥250 mg/m2 anthracyclines— ≥ 35 Gy chest radiation, or— Anthracycline (any dose) combined with chest radiation (≥15 Gy)
Echocardiogram	None	< 15 Gy	Not required
	None	≥ 15 Gy and < 35 Gy	Every 5 years
	None	≥ 35 Gy	Every 2 years
	< 250 mg/m2	< 15 Gy	Every 5 years
	< 250 mg/m2	≥ 15 Gy	Every 2 years
	≥ 250 mg/m2		Every 2 years
Electrocardiogram	All survivors		Baseline and as needed thereafter

Table 1.
The Children's oncology group long-term follow-up guidelines recommendations (summary) for surveillance of childhood cancer survivors exposed to anthracycline therapy (http://survivorshipguidelines.org).

4. Secondary malignant neoplasms

With the increase in survivorship in children with WT, there has been an accompanying increase in secondary malignant neoplasms (SMN). Among long-term WT survivors in the CCSS cohort, the cumulative incidence of SMN was 3.0% at 25 years. The most common SMNs were soft tissue sarcomas which occurred in six survivors. Five WT survivors had confirmed breast cancer. RT exposure of the breast in these patients ranged from 13 to 17.5 Gy. There were four bone tumors: two osteogenic sarcomas; one Ewing sarcoma; and one other bone tumor. The other SMNs were four adenocarcinomas, three melanoma, three thyroid cancers, two lymphoid leukemias, one medulloblastoma, and seven other cancers including one secondary renal cell carcinoma. SMNs were the most common cause of death in long-term WT survivors [3]. A SEER database review noted an incidence of SMN in patients treated for WT at 0.6% at 10 years, increasing to 1.6% at 20 years and 3.8% at 30 years [19]. A combined cohort study of patients from the NWTS, CCSS British and Nordic national registries provided data on 13,351 subjects diagnosed under the age of 15 in 1960 or later followed for a median of 11.6 years. After 169,641 person-years (PY) of observation

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through 2005, 174 solid tumors (exclusive of basal cell carcinomas) and 28 leukemias were ascertained in 195 subjects. Age-specific incidence of secondary solid tumors increased from approximately 1 case per 1000 PY at age 15 to 5 cases per 1000 PY at age 40. The cumulative incidence of solid tumors at age 40 was 6.7%. Leukemia risk, by contrast, was highest during the first 5 years following WT diagnosis. The Standardized incidence ratios (SIRs) for solid tumors and leukemias were 5.1 and 5.0, respectively. Among solid tumors, the most common were cancers of the digestive organs, most commonly hepatocellular carcinoma with 8 cases. There were 23 cases of breast cancer, 15 thyroid cancers and 11 osteosarcomas. There was a demonstrated difference in the observed incidence over time. At 10 years from diagnosis, the incidence was 1 SMN per 1000 survivors per year which increased to 5–6 solid tumors per 1000 survivors per year by 35 years after diagnosis. Also noted was a 49% increase in standardized incidence ratio (SIR) for SMN for patients diagnosed and treated after the age of 5 years. The occurrence of a solid SMN dramatically affected survival prospects [20]. The Mayo Clinic reported on 8295 patients treated from 1970 to 2020 for pediatric cancers. Eleven patients were identified to have developed subsequent renal neoplasms. Six of these eleven were patients previously treated for WT with clear cell sarcoma being the most common secondary renal cancer [21].

The use of RT and doxorubicin has been clearly associated with higher risk of SMNs. In the British Childhood Cancer Survivor Study, the majority of solid tumors (35 of 39, 89.7%) of the thorax, abdomen or pelvis developed within irradiated fields [22]. In the NWTS series, RT increased the risk of a SMN (SIR, 1.43/10 Gy) and doxorubicin potentiated the RT effect. Among 234 patients who received doxorubicin and > 35 Gy of abdominal RT, the SIR was 36. The changes in RT doses in NWTS protocols from 40 Gy in the 1960s to 10 Gy in the 1990s was also associated with a decrease in time-specific incidence rates of SMNs [23].

Due to the utilization of WLI in the management of WT with lung metastases, the incidence of breast cancer in WT survivors is significantly increased compared to the general population. A report from the NWTS reported the incidence and risk factors for breast cancer among 2492 female patients treated from 1969 to 1995. There were 29 cases of invasive breast cancer and 6 cases of ductal carcinoma in-situ, representing a SIR of 9.1 for invasive disease and cumulative risk at age 40 (CR40) of 4.5%. Among women who had chest RT, the SIR was 27.6 and CR40 was 14.8%. The majority of patients received 12Gy. WART was associated with a SIR of 7.2 and flank only RT had a SIR of 5.8. The CR40 was 3.1% for female patients who received abdominal RT. Patients not undergoing RT had a SIR of 2.2., The SIR for DCIS in patients undergoing chest or abdominal RT was 9.2, comparable to that for invasive disease [24]. Subsequent analysis of this data set included an assessment of male breast cancer and no excess risk was identified [25]. Among 20,276 CCSS survivors of which 6498 women were eligible for analysis, 95 women had 111 confirmed cases of breast cancer. The majority (65 patients) were treated for Hodgkin lymphoma. Only 3 patients were treated for WT with 2 of the 3 cases receiving chest RT [26].

5. Mitigation strategies and surveillance guidelines

A number of strategies including avoidance of RT and the use of lower doses of RT in modern COG and SIOP protocols may reduce the risk of SMNs. SIOP 93-01 allowed for omission of WLI in patients achieving radiographic CR of lung metastases following 6 weeks of chemotherapy or undergoing resection of all residual lung disease. Only 14%

	Factors that may increase risk	Recommendation
Breast Cancer	Patient factors: Family history of breast cancer. Personal history of BRCA1, BRCA2, ATM or p53 mutation or in absence of personal genetic testing, known BRCA mutation in first degree relative Treatment factors: Higher RT dose, especially ≥10 Gy, longer time since radiation (>5 years).	Yearly, beginning at puberty until age 25, then every 6 months. Teach breast self-exam and counsel to perform monthly beginning at puberty. Mammogram yearly, beginning 8 years after radiation or at age 25, whichever occurs last. Breast MRI yearly, as an adjunct to mammography beginning 8 years after radiation or at age 25, whichever occurs last
Colorectal Cancer screening (Stool multitarget DNA test)		Beginning 5 years after radiation or at age 30 years (whichever occurs last). Every 3 years. Positive result should be followed up with timely colonoscopy.
Thyroid cancer	Patient factors: Younger age at treatment Treatment factors: >5 years after RT, highest risk is between 10 and 30 Gy, thyroid gland directly in RT field, Total Body Irradiation, alkylating agents	Thyroid exam Yearly Ultrasound for evaluation of palpable nodule(s). FNA as clinically indicated. Endocrine and/or surgical consultation for further management.

Table 2.
The Children's oncology group long-term follow-up guidelines (summary) recommendations for surveillance of childhood cancer survivors for secondary malignancy.

of patients required lung RT as upfront therapy with this approach with good survival outcomes [27]. Similarly in COG AREN0533 trial, good survival rates were observed after omission of WLI in children whose tumors were without LOH at 1p and 16q and had complete response of lung nodules following chemotherapy at 6 weeks [28].

The International Guideline Harmonization Group updated their breast cancer surveillance recommendations in 2020. They noted that current data showed correlation between more moderate doses of RT (10–19Gy) and the risk of breast cancer. Additionally, there was a relationship between the use of anthracyclines and risk of breast cancer. Taking into account the risks of increased surveillance and relative benefit, the primary changes to previous recommendations were for surveillance for female patients with exposures of 10Gy or more to the chest, upper abdominal RT exposing the breast tissue at a young age and the use of anthracyclines [29].

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 2**.

6. Hypogonadism, infertility and pregnancy complications

WT is predominantly diagnosed in prepubertal children, with the incidence peaking at 12 months in males and 12–36 months in females, and is among the few malignancies that occurs more frequently in females than males [30]. With current therapeutic regimens that include the of large chest and flank/ WART fields, it is important to consider the impact of these treatments on gonadal function and

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reproduction in WT survivors. The potential RT exposure of the gonads can range from internal scattered doses only (e.g., flank RT) to full RT dose (e.g., whole abdomen [WART] in females).

6.1 Impact of RT on fertility in males with WT

Early reports of small numbers of male survivors of WT identified primary gonadal failure following 15–30 Gy flank or WART at 0.5–4 years of age [31] as well as reduced gonadal volume and sperm production after 2.7–9.8 Gy testicular dose after WART [32]. Of note, these findings were attributed to RT as chemotherapy did not show any such effects. An analysis of over 6000 male childhood cancer survivors, of which 429 had WT, revealed RT >7.5 Gy to the testes significantly reduced the ability to father children compared to survivors with no radiation exposure [33].

6.2 Impact of RT on fertility and gestation in females with WT

As noted for male patients, studies have also shown female patients to have primary gonadal failure following 15–30 Gy flank or WART at 0.5–4 years of age [31]. Another study showed atrophied ipsilateral ovary in half of those treated with 4–41 Gy to the flank and atrophied bilateral ovaries in all patients treated with 21–30 Gy WART prior to puberty [34]. In addition to potential impact on gonadal function, late effects of RT to the abdominopelvic region in young children may impair normal growth and development of the irradiated pelvic bones, vasculature and organs including the uterus that are essential for successful gestation. Early studies of pregnancy outcomes in irradiated female WT survivors have shown increased incidence of perinatal death, low birthweight, and birth defects compared with offspring of unirradiated female survivors, sibling controls or wives of male WT survivors, regardless of chemotherapy exposure [35, 36]. In an analysis of 309 female WT survivors treated on NWTS 1–4, flank RT >25 Gy was associated with significantly increased risk of preterm labor, fetal malposition and lower mean gestational age with odds ratio of 2.36, 6.26 and 4.07, respectively compared to unirradiated female survivors [37]. This effect was not observed for female survivors receiving chemotherapy only or for gestations fathered by male survivors. In a subset of 126 of these female WT survivors who received more than flank RT, only seven were able to conceive at least once. Five of these women received upper abdominal RT, with nine of 10 gestations resulting in live births; the remaining two women received WART, with the one receiving 10.5 Gy able to have a single viable birth and the other receiving 21 Gy having three non-viable pregnancies [38].

7. Mitigation strategies and surveillance guidelines

Given the young age of most WT patients, it is imperative to counsel caregivers of the late fertility risks of therapy and to involve endocrinology specialists early in the care of these patients [39]. With the continued advances in novel biomarker discovery and revised tumor-risk based stratifications, RT technology, including improvements in image-guidance and increased availability of proton beam therapy, it may be possible to further reduce radiation exposure to organs-at-risk involved in fertility and gestation and thereby reduce the undesired late effects of RT on fertility in WT survivors.

	Factors that may increase risk	Recommendation
Ovarian dysfunction	The ovaries are included in flank/hemiabdomen RT fields only if the fields extended below iliac crest. Patient factors: Older age at RT Treatment factors: RT dose ≥5 Gy if pubertal (especially dose ≥10 Gy), RT dose ≥10 Gy if prepubertal (especially dose ≥15 Gy), combination with alkylating agent chemotherapy, longer time since treatment, combination with cyclophosphamide conditioning for high dose chemotherapy regimens.	Yearly evaluation for: Onset and tempo of puberty Menstrual history Sexual function (vaginal dryness, libido) Menopausal symptoms Medication use Sexual function (vaginal dryness, libido) Menopausal symptoms Medication use Tanner staging until sexually mature Yearly Monitor growth until mature FSH and estradiol and/or endocrine/gynecology referral for patients with no signs of puberty at age 13, failure of pubertal progression, abnormal menstrual patterns or menopausal symptoms. Bone density evaluation in patients with ovarian hormone deficiencies.
Reduced ovarian follicular pool Infertility	The ovaries are included in the left and right flank RT fields only if they extended below iliac crest. Patient factors: Older age at RT Treatment factors: RT dose ≥5 Gy if pubertal (especially dose ≥10 Gy), RT dose ≥10 Gy if prepubertal (especially dose ≥15 Gy), combination with alkylating agent chemotherapy, longer time since treatment, combination with cyclophosphamide conditioning for high dose chemotherapy regimens.	Yearly evaluation for: Menstrual and pregnancy history Hormonal Therapy Tanner staging until sexually mature FSH and estradiol for patients with menstrual cycle dysfunction suggestive of premature ovarian insufficiency or those who desire information about potential for future fertility. AMH (anti-Mullerian hormone) to assess for diminished ovarian reserve. Reproductive endocrinology referral for assisted reproductive and interventions to preserve future fertility.
Uterine vascular insufficiency resulting in adverse pregnancy outcomes like spontaneous abortion, neonatal death, low-birth weight infant, fetal malposition and premature labor	The uterus is included in the left and right flank RT fields only if they extended below iliac crest. Patient factors: Wilms tumor and associated Müllerian anomalies, prepubertal at time of treatment Treatment factors: Total body Irradiation, higher RT dose to pelvis, or RT dose ≥30 Gy	Yearly evaluation for: Pregnancy and Childbirth history High-level ultrasound evaluation of genitourinary tract after pubertal development as clinically indicated in patients contemplating pregnancy. High-risk obstetrical care during pregnancy
Pulmonary Toxicity	Patient factors: Younger age at RT. Pre-morbid/Co-morbid medical conditions: Atopic history—Health behaviors: Smoking, inhaled illicit drug use Treatment factors: RT dose >10 Gy, especially RT dose ≥15 Gy, Total body Irradiation ≥6 Gy in single fraction, TBI ≥12 Gy fractionated, RT combined with bleomycin, busulfan, carmustine (BCNU), or lomustine (CCNU), radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin)	Clinical Pulmonary exam Yearly PFTs (including DLCO and spirometry) Baseline at entry into long-term follow-up, repeat as clinically indicated. Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations.

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	Factors that may increase risk	Recommendation
Musculoskeletal growth problems: Hypoplasia, fibrosis, Kyphosis, Scoliosis	Patient factors: Younger age at treatment, especially prepubertal at treatment Treatment factors: Higher RT dose, especially dose ≥20 Gy, larger RT field, higher radiation dose per fraction, orthovoltage radiation	Yearly Height Weight Sitting height for patients who had trunk radiation Orthopedic consultation for any deficit noted in growing child. Plastic surgery consult for reconstruction.
Renal dysfunction	Patient factors: congenital syndromes (WAGR, DDS, hypospadias, cryptorchidism), Diabetes mellitus, hypertension, congenital absence of kidney Treatment factors: Bilateral Wilms tumor, nephrectomy, radiomimetic chemotherapy (e.g., doxorubicin, dactinomycin), combination with other nephrotoxic agents (e.g., cisplatin, carboplatin, ifosfamide, aminoglycosides, amphotericin, immunosuppressants), RT dose ≥10 Gy, especially RT dose ≥15 Gy, TBI ≥6 Gy in single fraction, TBI ≥12 Gy fractionated, TBI combined with radiation to the kidney	Blood pressure Yearly BUN Creatinine Na, K, Cl, CO2, Ca, Mg, PO4 Baseline at entry into long-term follow-up, repeat as clinically indicated.
Diabetes Mellitus Impaired glucose metabolism may occur as part of a metabolic syndrome that includes central obesity with at least 2 or more of the following: hypertension, atherogenic dyslipidemia, and abnormal glucose metabolism.	Patient factors: Family history of diabetes mellitus, Obesity Treatment factors: Abdomen RT, TBI Prolonged corticosteroid therapy	Fasting blood glucose OR HbA1c Every 2 years Diet and Physical Activity Cardiovascular Risk Factors Endocrine consultation Evaluate for other co-morbid conditions, including dyslipidemia, hypertension, and overweight/obesity. Refer to dietician for blood sugar management.

Table 3.
The Children's oncology group long-term follow-up guidelines recommendations for surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors.

The International Late Effects of Childhood Cancer Guideline Harmonization Group have recently published evidence-based consensus recommendations for fertility preservation, including testicular and ovarian cryopreservation, in young cancer patients [40]. Currently, fertility preservation for WT patients is largely experimental, expensive and not widely available. Most patients are prepubertal, and there are no established criteria and standard guidelines for fertility preservation in males and ovarian cryopreservation in prepubertal females. Clinicians should proactively initiate conversations around standard and experimental options for fertility preservation in high risk WT children. Other options that exist for WT survivors of both genders include adoption, surrogacy, and the use of donor sperm/eggs or embryos.

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 3**.

8. Pulmonary disease

Pulmonary disease is an uncommon but important late effect observed in survivors of WT. In a report from the NWTS on 6449 survivors WT survivors from NWTS 1–4 after a median follow up of 17.9 years, 64 fully evaluable and 16 partially evaluable cases of pulmonary disease were identified. The 15-year cumulative incidence of pulmonary disease was 4.0% among fully evaluable and 4.8%among fully and partially evaluable patients who received WLI for pulmonary metastases at initial diagnosis. In contrast, 15-year cumulative incidence of pulmonary disease was much lower (<0.5%) among those who did not receive WLI. Survivors who had lung RT for relapse treatment had higher rates of pulmonary disease than those who had lung RT at initial treatment (hazard ratio [HR] 1.7). Survivors who received abdominal RT only had higher rates than those who received no RT at all (HR 3.5) [41]. Foster et al. reported on 280 WT survivors compared to 625 age and sex-matched controls for childhood cancer from St. Jude Children's Hospital [42]. At a median follow up of 26 years, compared to controls, survivors had an excess grade 2 to 4 obstructive (11.7 vs. 2.9%, $P < 0.01$), restrictive (9.6 vs. 0.2%, $P < 0.01$), and diffusion (10.4 vs. 0.3%, $P < 0.01$) pulmonary impairments. Adjusting for smoking status, pulmonary diffusion defects were associated with doxorubicin (RR 3.9) and restrictive deficits with chest radiation (RR 12.3).

9. Mitigation strategies and surveillance guidelines

The avoidance of lung RT in children with good response to chemotherapy and lack of adverse biomarkers can significantly reduce the risks for pulmonary toxicity. Modern protocols with IMRT in COG use lower doses of RT (12Gy) with lung heterogeneity compared to SIOP protocols.

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10. Musculoskeletal effects

Musculoskeletal toxicity may occur from RT in young children, the severity of which depends on the patient's age at treatment, RT dose, fractionation and RT fields. Growth of normal tissues can be impaired, resulting in reduced spinal growth and sitting height after RT for WT [43]. Scoliosis and kyphosis are other possible complications WT therapy, which may be a result of reactive myocontracture and shortened soft tissues from RT [44, 45], or nerve injury related to surgery [46]. At a median follow-up of 12–13 years, WT survivors have reported scoliosis in 54–67% and kyphosis in 14%, with 10–20% experiencing symptoms or requiring intervention [46, 47]. A higher scoliosis rate of 88% was observed by Mäkipernaa et al., potentially related to a longer median follow-up of 19 years and more complete radiologic follow-up; nevertheless, the vast majority of patients were still mild and asymptomatic, with 3 of 21 having a scoliosis curvature greater than 10° and only 1 being symptomatic. It is noteworthy that the available data on musculoskeletal complications involved WT patients treated to higher RT doses (median doses >30Gy) than are typically used in the current era [46–48]. Thus, it is likely that the incidence and severity of scoliosis after modern WT therapy are lower than previously published. Slipped femoral capital epiphyses can occur after RT for WT that includes the hip joint. The incidence is higher in children <4 years of age and after RT doses >25 Gy to the hip [49].

11. Mitigation strategies and surveillance guidelines

A number of strategies including avoidance of RT, use of lower doses of RT (10–20Gy) in modern COG and SIOP protocols, inclusion of the entire vertebral body during RT and blocking the hip joint completely can reduce musculoskeletal toxicity among WT survivors.

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 3**.

12. Renal failure

Renal function is an important consideration in survivors of WT, particularly in those who develop progression of bilateral WT or receive RT to the opposite kidney in unilateral disease. Non-syndromic children with unilateral WT treated with radical nephrectomy without nephrotoxic chemotherapy or RT are at low risk for significant long-term renal dysfunction [50]. Although a significant number of survivors have subclinical glomerular and tubular damage [51, 52], the risk of end-stage renal disease (ESRD) is very low in most patients with unilateral WT. A study on 5910 patients enrolled in NWTS showed that the 20-year cumulative incidence of end-stage renal disease (ESRD) after unilateral WT was 74% in children with Denys Drash syndrome, 36% in children with WAGR syndrome, 7% in male patients with hypospadias or cryptorchidism and 0.6% in non-syndromic WT patients. Twenty-year cumulative incidence of ESRD after bilateral Wilms tumor was 50% in children with Denys Drash syndrome, 90% in children with WAGR syndrome, 25% in male patients with

hypospadias and cryptorchidism and 12% in other non-syndromic patients [53]. A subsequent NWTS study assessed risk factors for ESRD in those without known WT1-related syndromes; it was found that patients with characteristics associated with a WT1 etiology (stromal predominant histology, intralobar nephrogenic rests and WT diagnosis at <24 months) had a higher risk of ESRD due to chronic renal failure [54]. In other reports from the CCSS and Denmark, renal tumor survivors after 18–20 years after treatment with nephrectomy and abdominal RT, had good renal function based on estimated glomerular filtration rates, although eGFR was significantly lower than in the normal population. WT survivors also had higher rates of albuminuria and hypertension [55, 56].

13. Mitigation strategies and surveillance guidelines

A number of strategies including avoidance of RT, use of lower doses of RT and modern RT technologies including IMRT and proton therapy may reduce the risks of renal toxicity in WT survivors.

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 3**.

14. Diabetes mellitus

The increased risk of diabetes mellitus (DM) from abdominal RT has been increasingly recognized over the past two decades, the pathophysiology of which is not completely clear, but likely related to the damage of insulin-producing ß cells concentrated in the tail of the pancreas [57]. In a study of Scandinavian childhood cancer survivors, the relative risks for DM were significantly increased in patients with WT, with an observed-to-expected first hospitalizations for DM of 2.9 [58]. A report from the Childhood Cancer Survivor Study demonstrated that WT survivors were more likely to be diabetic than siblings (RR 3.77), and this association remained significant when adjusted for body mass index. Among cancer survivors treated with abdominal RT, greater attained age, higher body mass index and increasing pancreatic tail dose were associated with increased DM risk [59]. In addition, a statistically significant interaction was noted between younger age at cancer diagnosis and mean pancreatic tail dose, with greater differences in DM risk noted among those diagnosed at the youngest ages. Among survivors diagnosed at age 5 years, relative risk of DM was 2.98 after a mean pancreatic dose of 10–19.9 Gy, 3.62, after 20–29.9 Gy, and 4.66 after 30+ Gy, with reference group being 0.1–9.9 Gy [59].

15. Mitigation strategies and surveillance guidelines

A number of strategies including avoidance of RT, use of lower doses of RT and modern RT technologies including IMRT and proton therapy may reduce the risks of diabetes mellitus among WT survivors.

The COG LTFU guidelines, version 5.0, provide extensive recommendations for the appropriate surveillance of childhood cancer survivors for common RT-induced

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toxicities observed in WT survivors (http://survivorshipguidelines.org). A summary of these guidelines is provided in **Table 3**.

16. Conclusions and future directions

The cure rates of WT patients following multimodality therapy including RT are excellent. However, RT is an important cause of late toxicity. Novel RT techniques such as IMRT for abdominal and lung RT and proton therapy are currently being studied in SIOP and COG in prospective clinical trials and may reduce the incidence of late toxicity. Currently WT biomarkers are only utilized for defining high-risk tumors to be treated with chemotherapy. Their utilization for potentially refining indications for RT in certain risk groups remains to be studied. Detailed studies of late toxicities specifically by analyzing the effects of RT doses to target organs is critical to improve our understanding of the relationship between RT and a variety of toxicities such as infertility, hypogonadism, congestive heart failure and secondary malignancies [60]. International collaborations like the Pediatric Normal Tissue Effects in the Clinic (PENTEC), are systematically analyzing the association between RT doses and volumes and organ toxicities by reviewing published reports of late toxicities following RT in children. However, a large number of reports lack detailed RT doses and organ dose-volume correlations for these reported toxicities. Another approach, as used by the CCSS, is to perform retrospective dosimetry using patient age and sex-matched phantoms to recreate multiorgan dosimetry from past treatments for correlation with late toxicities [61]. A similar approach using patient-matched 3D University of Florida/National Cancer Institute (UF/NCI) phantoms is currently being completed by the NWTS Late Effects Study [60]. A better understanding of the RT dose thresholds for these toxicities will help promote the adoption of interventions for their prevention and mitigation. The revision of previous RT dose thresholds (>20 Gy) for breast cancer surveillance to 12 Gy following reports by the NWTS is an important example of the critical value of such studies [62].

There are many preclinical and clinical reports that describe novel biomarkers that could detect RT injury in various organs more accurately and earlier in the time course after treatment. These biomarkers could greatly improve our understanding of risks of RT and refine surveillance guidelines for high-risk survivors to mitigate late toxicity [63, 64]. Another area of importance that deserves further study is the assessment of risk for late toxicities based on individualized genetic susceptibility to cancer treatment. Currently, while there are no established genetic biomarkers for RT induced toxicities, there are few reports of large-scale genome wide association studies (GWAS) that have identified several single nucleotide polymorphisms (SNPs), linked to breast cancer after RT exposure, cardiovascular toxicity and ovarian failure after cancer therapy [65–67]. The identification of predictive genetic biomarkers that may interact with RT or chemotherapy and increase the likelihood of these toxicities may permit individualized treatment and surveillance guidelines to minimize these risks and maximize long-term quality of life. Currently, the NIH is providing funding opportunities to advance understanding of mechanistic interactions and biologic consequences of RT prioritizing a comprehensive study of patient (genomic and epigenomics), tumor and treatment (chemotherapy, RT, dosimetry) factors, together with longitudinal multiomics (pre and post-therapy) to improve our understanding of the effects of RT on normal tissues (RFA-CA-21-040). Such novel studies could lead to the discovery of new biomarkers and novel therapeutics that could mitigate RT induced complications and improve tumor control rates in children with cancer.

Despite all these advances, there are significant challenges facing health care providers in their efforts to improve the long-term health and quality of life of childhood cancer survivors. The Academy of Medicine (AOM) recommends that cancer survivors be provided survivorship care plans (SCPs) that include treatment summaries and follow-up plans [68]. The '*Passport for Care*®' (PFC) program is a free interactive internet resource for global use that addresses the need to provide childhood cancer survivors and primary care physicians with accurate and individualized health care information based on patients' age, sex, diagnosis, chemotherapy, RT, surgery, clinical history and other related data. The PFC program provides recommendations derived from the long-term COG follow-up guidelines [69]. However, SCPs have not been shown to improve patient reported outcomes due to notable barriers to routine implementation relating to health care providers and survivors such as lack of family and social support for survivors especially among minorities, lack of transition of care, lack of interest and knowledge among primary care providers, knowledge gap among survivors, lack of financial support and psychologic issues including addictions among survivors, among others [70–73]. All of these issues need to be addressed by the global medical community, and new health care models with improved collaboration, better coordination and more communication among survivors and their clinicians will be required to translate the benefits of many of these innovations in late effects research to individual childhood cancer survivors [68, 74].

Author details

Samir Patel[1], Andrea Lo[2], Luke E. Pater[3], Mary Frances McAleer[4], Arnold Paulino[4] and John A. Kalapurakal[5*]

1 Department of Radiation Oncology, Cross Cancer Institute, Edmonton, AB, Canada

2 Division of Radiation Oncology, University of British Columbia, Vancouver, BC, Canada

3 Department of Radiation Oncology, University of Cincinnati Medical Center, Cincinnati, OH, USA

4 Department of Radiation Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA

5 Department of Radiation Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

*Address all correspondence to: j-kalapurakal@northwestern.edu

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