Childhood Cancer Survivor Study: Analysis Concept Proposal

STUDY TITLE:
Development and validation of a prediction model for end-stage renal disease in childhood cancer survivors

WORKING GROUP AND INVESTIGATORS:
Working Group

- Primary: Chronic Disease
- Secondary: Epidemiology & Biostatistics

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BACKGROUND AND RATIONALE:

As therapy for various childhood cancers has improved over the decades, increasing numbers of cancer survivors are being seen. Childhood cancer survivors are at risk for many late effects due to inherent risk factors and treatment-related exposures.[1-3] Impaired renal function can be seen both acutely during treatment and chronically years later. Development of end-stage renal disease (ESRD) is a significant concern in many cancer survivors due to the use of nephrotoxic chemotherapy, irradiation, and surgery such as nephrectomy.[1,4,5] ESRD requiring chronic dialysis or kidney transplant carries significant risk of morbidity and mortality,[6] and also has a major impact on overall quality of life.[7]

In the general population, certain factors are known to affect development of ESRD, including sex and ethnicity. In one study that used the National Health and Nutrition Examination Surveys (NHANES) data to examine the prevalence of chronic kidney disease (CKD), females and non-Hispanic whites had a higher prevalence of CKD.[8] Co-morbid conditions such as hypertension and diabetes are also associated with lower renal function and CKD.[8]

In childhood cancer survivors, several studies have explored the demographic and treatment-related factors associated with long-term nephrotoxicity. Age at cancer diagnosis may play a role, although evidence appears mixed, with younger patients experiencing more nephrotoxicity in several

studies[9-11] and older patients in another.[12] Other studies have not found age at diagnosis to be a significant independent contributing factor.[13,14] Male sex has been associated with renal dysfunction, including hypertension.[15] Patients with congenital anomalies such as Denys-Drash syndrome, Wilms tumor-aniridia syndrome (WAGR), or other genitourinary anomalies are at higher risk for development of ESRD.[4] Certain chemotherapy agents such as platinum-based agents, ifosfamide, and high-dose methotrexate are known to be particularly nephrotoxic, however studies of long-term effects are varied in terms of renal outcome measures and time elapsed since chemotherapy exposure. The majority of studies that examine chronic renal toxicity are performed within a few years of exposure, with few very long-term (>20 years) follow-up studies.[4,16,17]

Cisplatin is a known cause of acute kidney injury and dosing of this medication on treatment protocols is often adjusted with decreasing glomerular filtration rate (GFR). Chronic nephrotoxicity is typically a result of tubular dysfunction with a particular effect on magnesium retention,[18] as well as glomerular dysfunction. Both cumulative cisplatin dose[18,19] and dose rate[20] have been significantly associated with nephrotoxicity. Total cisplatin dose of $\geq$200mg/m^2 is the acknowledged dose of concern determined by the Children's Oncology Group (COG) in their Long-Term Follow-Up (LTFU) Guidelines, most recently updated in 2018.[21] Of note, higher total cisplatin doses have been used in studies of chronic nephrotoxicity, including median/mean doses of 360mg/m,[2,22] 400mg/m,[2,23] and 568mg/m.[2,20] Carboplatin is typically regarded as less nephrotoxic compared to cisplatin but several studies have also found it to be a risk factor for late nephrotoxicity.[22,24]

Ifosfamide is another agent that can cause chronic nephrotoxicity, which is related to both proximal tubular dysfunction, particularly Fanconi syndrome, and glomerular impairment.[13] Higher cumulative dose appears to be the most important contributing risk factor,[25] with significantly increased risk for toxicity seen at cumulative $\geq$60g/m^2 dosing,[11,26] $\geq$70g/m^2 dosing,[27] and $\geq$80g/m^2 dosing[13] in the literature. These studies are in line with total ifosfamide dose $\geq$60g/m^2 associated with higher risk for long-term nephrotoxicity noted in the COG LTFU guidelines.[21] However, other studies have demonstrated severe nephrotoxicity at lower median cumulative doses of 50g/m.[2,10] Previous or concurrent administration of cisplatin has also been shown to be a risk factor for ifosfamide-induced nephrotoxicity.[10,14]

Methotrexate at high doses, defined as $\geq$1000mg/m^2/dose, has also been studied and shown to contribute to acute renal toxicity.[28,29] There is a lack of study on the long-term sequelae of methotrexate, but several studies have not demonstrated association with chronic nephrotoxicity in multivariable regression analyses.[15,17] The COG LTFU Guidelines downgraded methotrexate in its most recent version,[21] now noted as having no known renal late effects (score 2A, uniform consensus of the panel based on lower-level evidence).

In addition to chemotherapy, surgery and radiation therapy have been studied as contributors to chronic renal dysfunction. After nephrectomy, there can be inadequate renal function due to volume loss.[16] Another mechanism is that the remaining kidney can undergo compensatory hypertrophy and develop eventual injury due to hyperfiltration.[30] Focal glomerulosclerosis can also develop[31] and contribute to further renal injury. Nephrectomy has been associated with long-term nephrotoxicity, as defined by both measures of glomerular function and tubular function.[15,17] However, long-term follow-up studies in patients with Wilms tumor who have undergone unilateral nephrectomy have demonstrated that the overall incidence of ESRD, as defined by dialysis or renal transplant, is low.[4] Patients with bilateral Wilms tumor requiring further surgical resection or bilateral nephrectomies are, as expected, at higher risk for development of ESRD.[32]

Abdominal irradiation is associated with long-term nephrotoxicity, especially after nephrectomy.[17,33] Several clinical syndromes following renal irradiation have been described, including acute radiation nephropathy, chronic radiation nephropathy, and hypertension (benign, malignant, hyperreninemic).[34] The COG LTFU guidelines[21] outline radiation dose specifications that indicate the

minimum dose of radiation believed to put patients at risk for certain late effects. Specifically for the kidney, cumulative prescribed radiation to the abdomen (which encompasses traditional flank or renal radiation fields) and/or total body irradiation (TBI) ≥10Gy, especially ≥15Gy, meets the threshold of concern.[21] In two studies of patients following nephrectomy for malignancy, patients who received calculated total cumulative doses ≥12Gy to the remaining kidney had a higher incidence of renal dysfunction.[9,35] Generally, the threshold for renal tolerance has been regarded as 20Gy (i.e. irradiation to both kidneys in daily fractions over 3-5 weeks).[34]

The Childhood Cancer Survivor Study (CCSS) is the largest cohort of 5-year-survivors of childhood cancer with over 24,000 participants who have been closely followed over decades.[36,37] There are many advantages to utilizing this large multidisciplinary cohort, including the ability to study chronic conditions and rare long-term outcomes[2] as well as establish the contributing risk factors. Cardiovascular risk factors have been previously examined in the CCSS population with the subsequent development of a prediction model for serious cardiovascular outcomes, such as heart failure, ischemic heart disease, and stroke.[38] Risk prediction models have been used to predict the probability of an adverse outcome given certain identified risk factors. While certain risk factors have been identified in multivariate regression analyses as significant to the development of ESRD, studies are lacking in terms of identifying the combination of risk factors and the relative contribution of each to predict serious nephrotoxicity. Development of validated risk prediction models specifically for predicting serious renal outcomes based on baseline demographic variables and cancer treatment exposures would help guide clinical decision making and personalize surveillance plans for these high-risk individuals.

SPECIFIC AIMS:

1. Identify the demographic factors, disease or treatment-specific characteristics, and co-morbidities that predict the risk of dialysis and end-stage renal disease (ESRD) per the chronic disease matrix's common terminology criteria for adverse events (CTCAE) grades 4 and 5 classifications.
2. Develop a prediction algorithm using the identified risk factors to predict individual risk of serious renal outcomes.
3. Validate the prediction algorithm with use of external data from the National Wilms Tumor Study Group (NWTSG), the St. Jude Lifetime Cohort Study (SJLIFE), and possibly other sources.

Approach for Aim 1

- Summarize the existing literature to identify *a priori* factors (demographic, disease, treatment-related, additional co-morbidities) as possible predictors of ESRD.
- Select the variables that would be considered significant risk factors based on regression analyses.

Approach for Aim 2

- Build a prediction model to determine the absolute risk of developing ESRD utilizing risk scores for each significant variable.
- Based on distribution of overall risk scores, divide into distinct risk groups (e.g. low, moderate, and high).

Approach for Aim 3

- Use outside data to validate the prediction algorithm by examining CCSS-based model performance in external datasets.
- Support has been confirmed by Wendy Leisenring to use NWTSG data; 119 patients with ESRD are preliminarily available in the cohort.

- Explore validation in the St. Jude LIFE cohort, with support confirmed by Melissa Hudson for this collaboration.
- Approach additional cohorts if needed, including the Dutch LATER cohort, which has been a successful collaborator in previous CCSS projects.[39]
- If the external datasets are insufficient, will plan to randomly divide the CCSS group into two for use as discovery sample and subsequent cohort for validation, which has been done previously.[38]

ANALYSIS FRAMEWORK:

Subject population available for model discovery:

- Entire CCSS survivor cohort (both baseline and expanded, n = 25,664)
- Sibling population would serve as an unexposed referent group
- Analysis would exclude patients who developed Grade 4 renal disease within 5 years of initial diagnosis

Cohort	Type	Grade					
		1	2	3	4	5	4 or 5
Expanded cohort	After 5 years of cancer diagnosis	16 (0.14%)	5 (0.04%)	3 (0.03%)	83 (0.73%)	1 (0.01%)	84 (0.74%)
	Any time after cancer diagnosis	21 (0.19%)	6 (0.05%)	3 (0.03%)	153 (1.35%)	1 (0.01%)	154 (1.35%)
Original cohort	After 5 years of cancer diagnosis	34 (0.24%)	7 (0.05%)	10 (0.07%)	118 (0.82%)	26 (0.18%)	144 (0.98%)
	Any time after cancer diagnosis	58 (0.40%)	7 (0.05%)	10 (0.07%)	174 (1.21%)	26 (0.18%)	200 (1.37%)

CCSS renal disease - preliminary data provided by Yan Chen on 7/4/2019, updated by Daniel Mulrooney on 10/19/2019.

Outcomes of interest:

- Incidence of late end-stage renal disease (age at initial classification of Grade 4 or 5 renal disease by age 50 (if data sparse after age 40, will consider modeling out to age 40 instead).
- Grade 4 chronic renal disease per CTCAE classification includes patient indication of dialysis or kidney transplant on specific survey questions and/or coding designation of Grade 4 disease based on write-in responses (by St. Jude nosologists).
- Grade 5 chronic renal disease per CTCAE classification signifies patient death due to renal disease (determined from National Death Index records).
- Only outcomes reported after 5 years of cancer diagnosis will be studied (n = 225 per table above).

Exploratory variables:

- Age at cancer diagnosis
- Sex
- BMI
- Race/ethnicity
- Socioeconomic status
- Medications (“medications for high blood pressure or hypertension”) - Y/N and exploration of individual medications (although numbers may be low)

- Congenital anomalies ("any kidney, bladder, or genital abnormalities") - Y/N
- Chemotherapy within the first 5 years - Y/N and exploration of dose (based on tertiles and/or dose thresholds as suggested by the literature – see background above)
    - Cisplatin/carboplatin
    - Ifosfamide
    - Methotrexate (high-dose only)
- Surgery within the first 5 years (unilateral nephrectomy, bilateral partial nephrectomy) Y/N (of note, complete bilateral nephrectomies as part of upfront therapy would result in immediate grade 4 ESRD and thus would not be relevant to this study)
- Radiation within the first 5 years - Y/N and abdomen/kidney doses
    - Abdomen maximum treatment dose (maxTD)
    - Mean dose to right and left kidneys (NWTSG will have whole abdomen in addition to left or right flank radiation exposure; this information will not be available in SJLIFE validation dataset)
- Other potential comorbid conditions (prevalence of these conditions at 5 years after cancer diagnosis may be low; inclusion may also depend on their presence in the validation datasets at the same time point)
    - Hypertension at 5 years after diagnosis - Y/N
    - Diabetes at 5 years after diagnosis - Y/N

STATISTICAL METHODS:

Approach for Aim 1

- The following variables are selected *a priori* for statistical testing: age at diagnosis, sex, race/ethnicity, presence of congenital GU/renal anomalies, and treatment exposures to platinum agents (cisplatin/carboplatin), ifosfamide, high-dose methotrexate, radiation therapy to the abdomen/kidney, and surgery (nephrectomy).
- For chemotherapy agents and radiation, dose will be explored as a contributing factor to the outcomes of interest.
- Piecewise exponential or Poisson regression will be used to determine the relationship between each independent variable and the outcomes.

Approach for Aim 2

- Backward selection will be used to determine the most influential treatment predictors and to eliminate any variables that are not statistically significant to the risk prediction model. Based on previous literature, we will *a priori* explore potential interactions between age at diagnosis and treatment exposures.
- Internal 10-fold cross-validation will be performed to evaluate the performance of the prediction model.
- Using the regression coefficients associated with the selected variables, integer risk scores can be determined.
- Points will be summed to compute an overall risk score with the corresponding risk of serious renal outcomes.
- Based on distribution of overall risk scores, we will divide into several risk groups (low, moderate, high risk) associated with a differential absolute risk of ESRD by age 50; siblings will serve as a referent group for ESRD risk in the non-cancer population.

Approach for Aim 3

- Use the validation datasets to validate the CCSS risk prediction model by determining area under the curve (AUC) and concordance (C). Would identify any patients in multiple cohorts and determine if they should be included in the discovery or validation datasets.
- Each individual in the validation cohorts would be assigned a CCSS-based risk score using the risk prediction model developed in Aims 1 and 2.
- Cumulative incidence of ESRD by age 50 in the validation cohorts would be compared against the CCSS cohort.
- The difference of the AUC and C-statistics of each model between the CCSS and external cohorts would be assessed using 1000 bootstrap iterations.

TABLES:

Table 1: Baseline characteristics of childhood cancer survivors in included study cohorts

Cohort	CCSS (#)	NWTSG (#)	SJLIFE (#)
Demographic information			
Treatment characteristics			
Outcome measures			

Table 2: Multivariable exponential regression results for ESRD outcome in the CCSS cohort

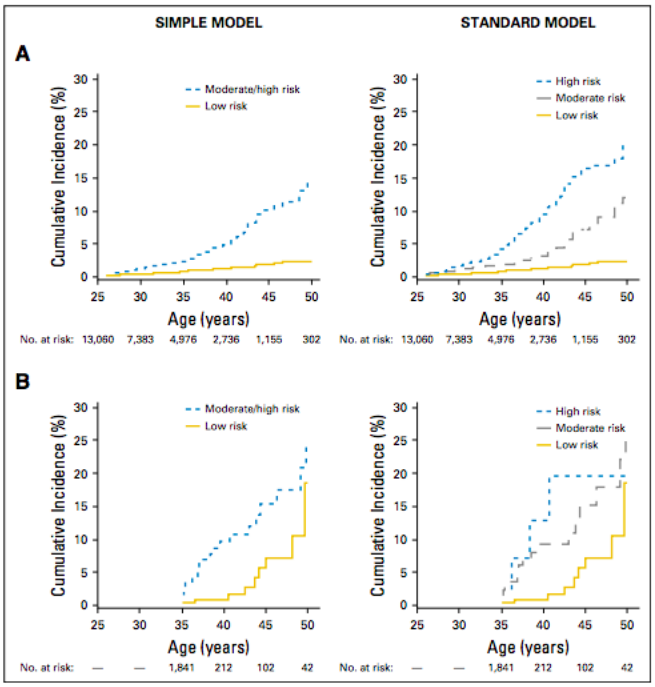
Exploratory variable	Grade 4/5 ESRD Rate ratios (95% CI)
Age at cancer diagnosis	
Sex	
BMI	
Race/ethnicity	
Socioeconomic status	
Medications	
Congenital anomalies	
Cisplatin Any vs none Dose	
Carboplatin Any vs none	
Ifosfamide Any vs none Dose	
High-dose methotrexate Any vs none	
Radiation Any vs none Abdomen Kidney-specific	
Unilateral or partial bilateral nephrectomy	
Hypertension	

Diabetes	

Table 3: Classification of ESRD event risk and incidence in the study cohorts

Risk group	Risk score	No. of events/ No. at risk in CCSS	Cumulative Incidence in CCSS	No. of events/ No. at risk in NWTSG	Cumulative Incidence in NWTSG	No. of events/ No. at risk in SJLIFE	Cumulative Incidence in SJLIFE
Low							
Moderate							
High							

Figure 1: Cumulative incidence of ESRD by risk group for the study cohorts
Sample figure taken from Chow, et al. 2017



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