Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Analysis of Late Mortality by Treatment Era

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Background & Rationale:

Improvements in therapies for childhood cancer over the last four decades have resulted in significant increases in 5-year survival rates for most malignancies. The 5-year overall relative survival rate is now over 80%.[1] However, long-term survivors of childhood cancer are also at risk of late (>5 years from diagnosis) mortality.[2-8] During more recent decades, risk-stratification of therapeutic intensity has guided primary therapy. In general, primary therapeutic regimens have been intensified for patients with poor prognoses (high risk groups) in an attempt to reduce recurrence or progression of primary disease and, thus, improve five-year overall survival and event free survival. Likewise, among patients identified as having a good prognosis (low risk groups), efforts have been directed toward reduction in intensity to prevent long-term morbidity and mortality from treatment toxicity while maintaining excellent five-year overall and event free survival.

While detailed assessments of late mortality (>5 years from diagnosis) have been performed in selected cohorts of 5-year survivors, few have had survivors diagnosed and treated across a time span sufficiently broad to determine whether late mortality has improved among survivors of childhood cancer treated during more recent eras.[3-5] Therefore, in a recent analysis of SEER data among 26,643 five-year survivors of childhood cancer, we assessed temporal trends in cause-specific late mortality.[9] We identified that all-cause late mortality has improved in more recent treatment eras largely attributable to reduced mortality from recurrence/progression of the primary childhood malignancy. Thus, it was clear across the entirety of this SEER study population, and within most diagnostic subgroups, that intensification of therapy across this time

period, previously established to improve five-year survival, also resulted in durable, long-term remissions (long-term survival).

However, what was not clear in this previous analysis was whether nonrecurrence/nonexternal cause late mortality (i.e. late mortality attributable to health conditions other than progression of primary disease, such as death due to subsequent neoplasms, cardiac conditions and other medical conditions that are common therapeutic late effects) is reduced in more recent time periods. In our SEER analysis, there was no significant reduction in cumulative mortality attributable to nonrecurrence/nonexternal cause mortality (i.e. treatment related health conditions). However, multivariable analysis controlling for demographic characteristics suggested that there was a trend toward reduction in risk for nonrecurrence/nonexternal cause mortality (1974-80 HR 1.0; 1981-87 HR 0.87; 1988-94 HR 0.76; 1995-2000 HR 0.67; p for trend=0.007) across the entire population.

It is clear that reducing therapy to low-risk patients will reduce risk for certain specific late effects. However, it still remains unknown, whether the sum total of these efforts on a population level has ultimately reduced risk for late mortality attributable to late effects. In short, it is unknown whether our reductions in therapy have improved the life of survivors by extending their lifespan.

While the previous SEER analysis was able to assess temporal trends in mortality it lacked specific treatment information needed to truly assess whether changes (reduction) in therapeutic intensity have improved late mortality. The CCSS cohort, with the addition of the expansion population, now includes over 35,000 eligible survivors across thirty years of diagnostic time (1970-1999) and detailed abstraction of both radiation and chemotherapeutic exposure can be utilized to fill this gap in knowledge. Fundamental changes in therapy across this period included reduction in dose and eventual elimination of prophylactic cranial RT in treatment of ALL, reduction and in some cases elimination of RT for treatment of Hodgkin lymphoma, and reduction in radiation and anthracycline exposure for treatment of Wilms tumor, among others. Many of these therapeutic reductions were to reduce risk for subsequent neoplasms and cardiotoxicity, the most common causes of treatment-related late mortality. Completion of this analysis will allow us to understand whether these fundamental changes in treatment ultimately improved the long-term survival of children with cancer.

Specific Aims & Hypotheses:

1) To compare cumulative mortality (all cause and cause-specific) and standardized risk of mortality (all cause and cause-specific) by treatment era.

2) To evaluate temporal patterns in mortality (all cause and cause-specific) according to treatment exposure (modality specific and intensity of exposure)

Hypotheses:

-Cumulative mortality rates will be lower in more recent treatment eras, largely attributable to lower mortality from recurrence/progression of primary disease. These data should establish that historical improvements in early (first 5 years from diagnosis) disease control were durable well beyond the 5 year time point.

-Reduced rates of treatment related mortality (i.e. non-recurrence, non-external cause) may be identified within certain cancer diagnoses where historical reduction in therapeutic intensity has occurred including ALL. Hodgkin lymphoma and Wilms tumor.

Analysis Framework:

A) Population of Interest: All patients eligible to participate in the CCSS cohort (diagnosed 1970-1999, n=35,990).

B) Outcome Measures: Vital status (alive/dead) to identify a) cumulative mortality, and 2) standardized mortality ratios (SMR). The National Death Index will be the source for vital status. The CCSS currently has NDI data updated through 2008. This is the same NDI data used during the recruitment of the expansion cohort. Standardized mortality rates will be calculated using age- and sex-specific mortality rates for the U.S. population from the National Center for Health Statistics as per the method established by Dr. Mertens for previous CCSS publications.

Information on the underlying cause of death was obtained from death certificates for cases that resided in the U.S. Cause of death has been determined from death certificates and for this analysis will be categorized as:

1) Recurrence/progression of primary childhood malignancy
2) External cause (e.g. accidents, injuries, suicide)
3) Nonrecurrence/nonexternal cause (attributable to chronic health conditions)
    a. SMN cause
    b. Cardiac cause
    c. Pulmonary cause
    d. other

C) Explanatory Variables: Treatment era. We propose to break the current cohort diagnosed between 1970-99 into 3 treatment eras of 10 years each (i.e. 1970-79, 1980-89, and 1990-99) and assess mortality by treatment era. Shorter treatment eras blocks (five year blocks) will be considered if sufficient power exists with diagnostic sub-groups. Patients will be assigned to a given treatment era based on their date of diagnosis.

Additionally, we will evaluate mortality within primary treatment groups (ALL, AML, HD, NHL, etc.) based on:

1) Historical changes in therapy intended to reduce risk for late effects

2) Stage (risk status) of primary cancer (for expansion cohort only)

D) Statistical approach: To accomplish the primary aim of assessment of mortality by treatment era, a descriptive analysis of the entire cohort based on treatment era, and to include vital status (life table) will be performed (Table 1). The 10-year cumulative mortality (all cause, recurrence/progression, nonrecurrence/nonexternal cause) will be reported by treatment era (Table 2 and Hypothetical Figure 1) accounting for competing risk of death from other causes. Standardized mortality ratios (SMR) and excess absolute risk (EAR) (Tables 3 and 4) by treatment era will be calculated for all cause and cause specific mortality. To compare CCSS mortality with that expected in the US population, an expected number of deaths each year since diagnosis will be calculated based on US age-, year- and sex-specific mortality rates. To assess the trend over time of all-cause mortality and cause-specific mortality rates, we will use joinpoint methods similar to linear splines .[10] Multivariable Poisson regression will be used to assess the simultaneous impact of multiple factors on the cause-specific SMRs, potentially adjusting for sex, age at diagnosis, year of diagnosis, and/or years since diagnosis (Table 5). With the logarithm of expected numbers of deaths from the US mortality rates incorporated in the models as offset terms, these models will allow for comparisons between SMRs between levels of specific factors of interest, such as treatment era.

Since treatment era is really just a surrogate for changes in therapy over time, to truly assess whether changes in therapy resulted in improved treatment-related late mortality, we will examine mortality (all cause, recurrence/progression, nonrecurrence/nonexternal cause) within each primary cancer diagnosis and within therapeutic strata specific for the given diagnosis (Table 6). These specific therapeutic strata were selected as they represent specific examples of where treatment intensity was reduced with the goal of reducing risks of late effects (including SMNs and cardiotoxicity in many cases). Treatment data is available for all eligible subjects in the expansion cohort, but is only available for participating members of the original CCSS cohort who signed a medical release. It is therefore missing completely, or in part, for approximately 8,000 subjects. Using similar methods to those used for the Mertens 2010 JNCI paper, multiple imputation methods will be carried out to impute medical record information for these subjects[4]. Sensitivity analyses will be carried out to evaluate the robustness of the imputation, particularly since relatively specific treatment data are required. If the method is not robust, treatment variables will be collapsed to more crude levels.

For each primary cancer diagnosis, a specific multivariable Poisson model (Tables 7a-x) will be constructed to include therapeutic exposures and demographic characteristics. It is important to note that changes in race/ethnicity over time had a significant impact on our previous SEER analysis.[9] Additionally, SMRs will be calculated within each diagnostic group for therapeutic exposures (Table 8). A second approach will be to assess 10-year cumulative incidence of mortality based on initial staging (risk) for each patient within primary cancer diagnoses (Table

9). As stage information only exists for the expansion cohort this will be an exploratory analysis in a subset of the entire CCSS population. Finally, using the full population, RRs for cause specific mortality will be estimated (Table 10).

Table 1. Demographic and treatment characteristics by treatment era and life status of five year survivors of childhood cancer									
	1970-1979		**1980-1989**		**1990-1999**		**Total**	**Alive**	**Dead**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**N**	**N**
All Survivors									
Sex									
Male									
Female									
Race/Ethnicity									
Non-Hispanic white									
Non-Hispanic black									
Hispanic									
Non-Hispanic Asian or Pacific Islander									
Non-Hispanic American Indian/Alaskan Native									
Age at Diagnosis (years)									
0-4									
5-9									
10-14									
15-20									
Survival after diagnosis (years)									
5-9	-	-	-	-	-	-	-	-	
10-14	-	-	-	-	-	-	-	-	
15-19	-	-	-	-	-	-	-	-	
20-24	-	-	-	-	-	-	-	-	
25=29	-	-	-	-	-	-	-	-	
30-34	-	-	-	-	-	-	-	-	
Diagnosis									
Leukemia									
Acute lymphoblastic leukemia									
Acute myeloid leukemia									
Other leukemia									
Hodgkin lymphoma									
Non-Hodgkin lymphoma									
CNS tumors									
Medulloblastoma									
Ependymoma									
Glioma									
Other CNS									
Kidney tumors									
Neuroblastoma									
Soft tissue sarcoma									
Bone tumors									
Ewing sarcoma									
Osteosarcoma									
Other bone tumors									
Treatment exposure									
Any radiation									
Yes									
No									
Chest radiation									
Yes									
No									
Central nervous system radiation									

Yes									
No									
Abdominal radiation									
Yes									
No									
Pelvic radiation									
Yes									
No									
Alkylating agent (CPM equivalents, mg/m^2)									
None									
0 - <4,000									
≥4000-<8000									
≥8000-12,000									
≥12,000-<16,000									
≥16,000-<20,000									
≥20,000									
Anthracycline (mg/m^2)									
None									
0-100									
101-250									
251-400									
>400									
Epipodophyllotoxin(mg/m^2)									
Yes									
No									
Bleomycin									
Yes									
No									
Platinum									
Yes									
No									

Table 2. 10-year cumulative mortality among five year survivors of childhood cancer										
	1970-1979			1980-1989			1990-1999			
	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	P*
All Cause										
All diagnoses										
All leukemias										
Acute lymphoblastic leukemia										
Acute Myeloid leukemia										
Other leukemia										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										
All CNS tumors										
Medulloblastoma										
Ependymoma										
Glioma										
Other CNS										
Kidney tumors										
Neuroblastoma										
Soft tissue Sarcoma										
All Bone tumors										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										
Recurrence/Progression										
All diagnoses										
All leukemias										
Acute lymphoblastic leukemia										
Acute Myeloid leukemia										
Other leukemia										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										
All CNS tumors										
Medulloblastoma										
Ependymoma										
Glioma										
Other CNS										
Kidney tumors										
Neuroblastoma										
Soft tissue Sarcoma										
All Bone tumors										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										
Nonrecurrence/Nonexternal cause										
All diagnoses										
All leukemias										
Acute lymphoblastic leukemia										
Acute Myeloid leukemia										
Other leukemia										
Hodgkin lymphoma										
Non-Hodgkin lymphoma										

All CNS tumors										
Medulloblastoma										
Ependymoma										
Glioma										
Other CNS										
Kidney tumors										
Neuroblastoma										
Soft tissue Sarcoma										
All Bone tumors										
Ewing sarcoma										
Osteosarcoma										
Other bone tumors										

***P value based on the comparison of the cumulative mortality curves for the three time periods**

Figure 1. Hypothetical example of figure to display cumulative incidence of mortality by treatment era

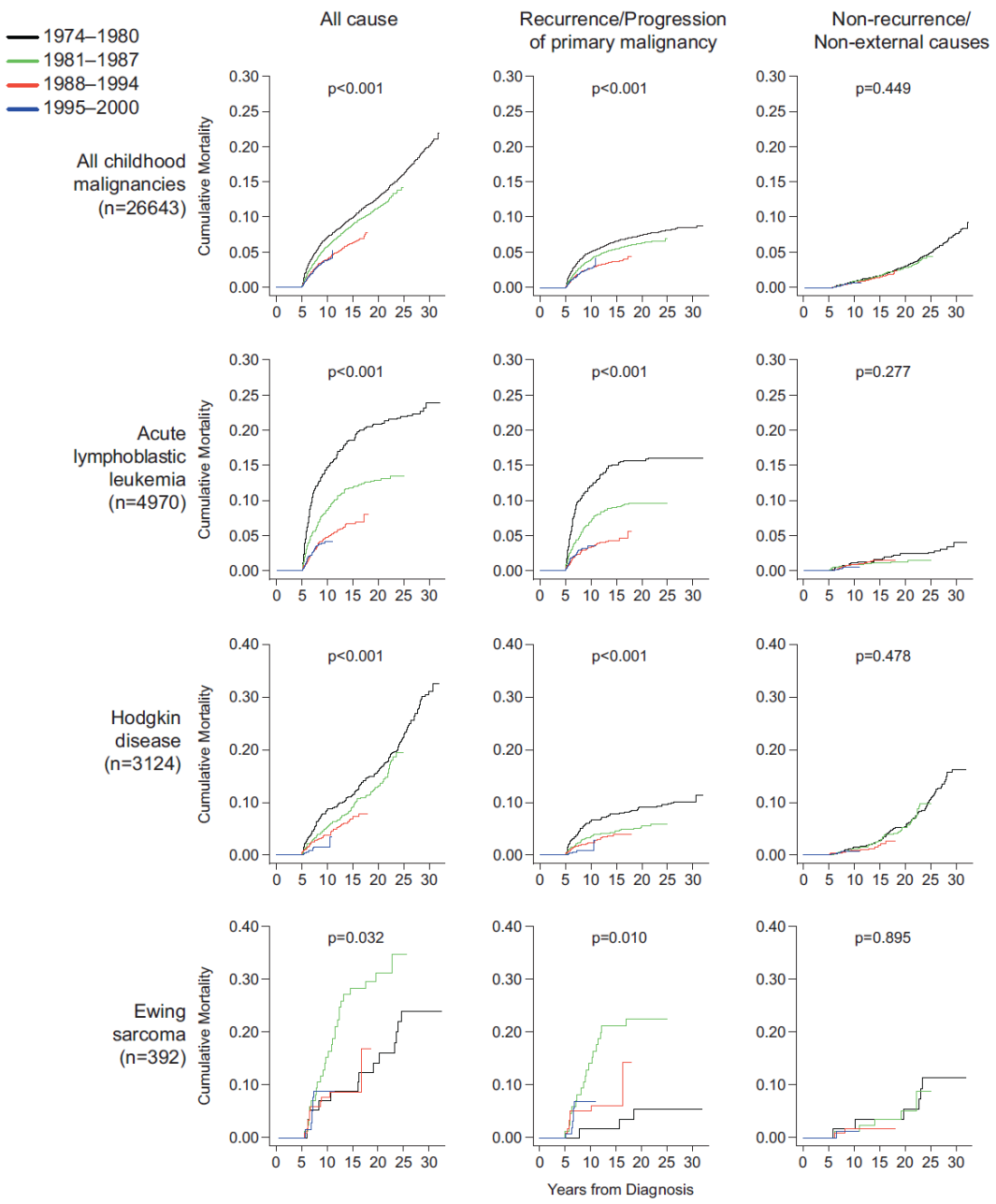

	Table 3. All cause and cause specific standard mortality ratios in five year survivors of childhood cancer by treatment era and by demographic status																	
	All Causes			Nonrecurrence/ Nonexternal Cause			Subsequent Malignancy			Cardiac Causes			Pulmonary Causes			Other nonrecurrent/nonexternal causes		
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All survivors																		
Treatment Era																		
1970-79																		
1989-89																		
1990-99																		
Sex																		
Male																		
Female																		
Race/Ethnicity																		
Non-Hispanic White																		
Non-Hispanic Black																		
Hispanic																		
Non-Hispanic Asian or Pacific Islander																		
Non-Hispanic American Indian/Alaskan Native																		

Table 4. Absolute excess risk per 1000 person-years compared with the US population					
	Subsequent Malignancy	Cardiac	Pulmonary	Other Causes	External Causes
All Cases					
Sex					
Male					
Female					
Diagnosis					
Acute lymphoblastic leukemia					
Acute myeloid leukemia					
Other leukemia					
Astrocytomas					
Medulloblastoma/PNET					
Other CNS tumors					
Hodgkin lymphoma					
Non-Hodgkin lymphoma					
Kidney tumors					
Neuroblastoma					
Soft tissue sarcoma					
Ewing Sarcoma					
Osteosarcoma					
Other bone tumors					
Years since original diagnosis					
5-9					
10-14					
15-19					
20-24					
≥25					

Table 5. Relative Risk for mortality among five year survivors of childhood cancer by treatment era												
	All Cause		Recurrence/Progression of Primary Malignancy		Nonrecurrence/Non-external cause		Cardiac cause		Pulmonary Cause		Other Causes	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age (continuous)												
Treatment Era												
1970-79												
1989-89												
1990-99												
Sex												
Male												
Female												
Race/Ethnicity												
Non-Hispanic White												
Non-Hispanic Black												
Hispanic												
Non-Hispanic Asian or Pacific Islander												
Non-Hispanic American Indian/Alaskan Native												
All survivors												

Table 6. 10-year cumulative incidence of mortality among five year survivors of specific childhood cancers based on historical changes in treatment										
	All Cause			Recurrence/Progression of primary malignancy			Nonrecurrence, Nonexternal Cause			
	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	P*
Acute lymphoblastic leukemia										
Cranial RT										
≥20 Gy										
<20 Gy										
None										
Epipodophyllotoxin										
Any										
None										
Steroid										
Prednisone										
Dexamethasone										
Both										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Duration of therapy										
≥4 years										
≥3-4 years										
≥2-3 years										
Acute Myeloid leukemia										
Cranial RT										
Yes										
No										
Anthracycline (mg/m^2)										
BMT										
Yes										
No										
BMT										
Yes, with TBI										
Yes, non-TBI										
No										
Hodgkin lymphoma										
Multimodal therapy										
RT≥30 Gy, no chemo										

RT<30 Gy, with chemo										
Chemo only, no RT										
Chemo regimen										
MOPP (no ABVD)										
MOPP + ABVD										
COPP										
COPP + ABVD										
ABVD alone										
Other										
Splenectomy										
Yes										
No										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Alkylator (CPM equiv. in grams)										
≥20										
≥16 - <20										
≥12 - <16										
≥8 - <12										
≥4 - <8										
0 - <4										
None										
RT										
≥30 Gy										
≥20-30 Gy										
1-20 Gy										
None										
Non-Hodgkin lymphoma										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Alkylator (CPM equiv. in grams)										
≥20										
≥16 - <20										
≥12 - <16										
≥8 - <12										
≥4 - <8										
0 - <4										
None										
Medulloblastoma										

>30 Gy Craniospinal										
<30 Gy Craniospinal										
Is none included in <30, or no one gets "none"?										
Neuroblastoma										
Surgery alone										
Surgery + RT										
Surgery + RT + Chemo										
S + RT + Chemo +BMT										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Alkylator (CPM equiv. in grams)										
≥20										
≥16 - <20										
≥12 - <16										
≥8 - <12										
≥4 - <8										
0 - <4										
None										
Cisplatinum										
≥800										
≥400 - <800										
1 - <400										
None										
Carboplatinum										
Yes										
No										
Kidney tumors										
RT Dose										
≥30 Gy										
≥18-30 Gy										
1 - <18 Gy										
None										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Rhabdomyosarcoma										
Anthracycline										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										

None										
RT										
≥50 Gy										
1-<50 Gy										
None										
Osteosarcoma										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										
Cisplatinum										
≥800										
≥400 - <800										
1 - <400										
None										
Ewing sarcoma										
RT (local control)										
Yes										
No										
Anthracycline (mg/m^2)										
≥600										
≥450-<600										
≥300-<450										
≥150-<300										
1-<150										
None										

*p value for no recurrence, nonexternal cause mortality

Table 7a. Relative risk for mortality among five year survivors of ALL based on historical changes in therapy to reduce risk of late effects												
	All Cause		Recurrence/Progression of Primary Malignancy		Nonrecurrence/Non-external cause		Cardiac cause		Pulmonary Cause		Other Causes	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age (continuous)												
Cranial RT												
≥20 Gy												
<20 Gy												
None												
Epipodophyllotoxin												
Any												
None												
Steroid												
Prednisone												
Dexamethasone												
Both												
Anthracycline (mg/m^2)												
≥600												
≥450-<600												
≥300-<450												
≥150-<300												
1-<150												
None												
Sex												
Male												
Female												
Race/Ethnicity												
Non-Hispanic White												
Non-Hispanic Black												
Hispanic												
Non-Hispanic Asian or Pacific Islander												
Non-Hispanic American Indian/Alaskan Native												

Table 7b. Relative Risk for mortality among five year survivors of Hodgkin lymphoma based on historical changes in therapy to reduce risk of late effects												
	All Cause		Recurrence/Progression of Primary Malignancy		Nonrecurrence/Non-external cause		Cardiac cause		Pulmonary Cause		Other Causes	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Age (continuous)												
Splenectomy												
Yes												
No												
Anthracycline (mg/m^2)												
≥600												
≥450-<600												
≥300-<450												
≥150-<300												
1-<150												
None												
Alkylator (CPM equiv. in grams)												
≥20												
≥16 - <20												
≥12 - <16												
≥8 - <12												
≥4 - <8												
0 - <4												
None												
RT												
≥30 Gy												
≥20-30 Gy												
1-20 Gy												
None												
Race/Ethnicity												
Non-Hispanic White												
Non-Hispanic Black												
Hispanic												
Non-Hispanic Asian or Pacific Islander												
Non-Hispanic American Indian/Alaskan Native												

Table 8. All cause and cause specific standard mortality ratios in five year survivors of childhood cancer by diagnosis-specific and treatment exposure															
	All Causes			Subsequent Malignancy			Cardiac Causes			Pulmonary Causes			Other nonrecurrent/nonexternal causes		
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All Acute lymphoblastic leukemia															
Cranial RT															
≥20 Gy															
<20 Gy															
None															
Epipodophyllotoxin															
Any															
None															
Steroid															
Prednisone															
Dexamethasone															
Both															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Duration of therapy															
≥4 years															
≥3-4 years															
≥2-3 years															
Acute Myeloid leukemia															
Cranial RT															
Yes															
No															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															

≥150-<300															
1-<150															
None															
BMT															
Yes															
No															
Hodgkin lymphoma															
Multimodal therapy															
RT≥30 Gy, no chemo															
RT<30 Gy, with chemo															
Chemo only, no RT															
Chemo regimen															
MOPP (no ABVD)															
MOPP + ABVD															
COPP															
COPP + ABVD															
ABVD alone															
Other															
Splenectomy															
Yes															
No															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Alkylator (CPM equiv. in grams)															
≥20															
≥16 - <20															
≥12 - <16															
≥8 - <12															
≥4 - <8															
0 - <4															
None															
RT															

≥30 Gy															
≥20-30 Gy															
1-20 Gy															
None															
Non-Hodgkin lymphoma															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Alkylator (CPM equiv. in grams)															
≥20															
≥16 - <20															
≥12 - <16															
≥8 - <12															
≥4 - <8															
0 - <4															
None															
Medulloblastoma															
>30 Gy Craniospinal															
<30 Gy Craniospinal															
Neuroblastoma															
Surgery alone															
Surgery + RT															
Surgery + RT + Chemo															
S + RT + Chemo +BMT															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Alkylator (CPM equiv. in grams)															

≥20															
≥16 - <20															
≥12 - <16															
≥8 - <12															
≥4 - <8															
0 - <4															
None															
Cisplatinum															
≥800															
≥400 - <800															
1 - <400															
None															
Carboplatinum															
Yes															
No															
Kidney tumors															
RT Dose															
≥30 Gy															
≥18-30 Gy															
1 - <18 Gy															
None															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Rhabdomyosarcoma															
Anthracycline															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
RT															
≥50 Gy															

1-<50 Gy															
None															
Osteosarcoma															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															
Ewing sarcoma															
RT (local control)															
Yes															
No															
Anthracycline (mg/m^2)															
≥600															
≥450-<600															
≥300-<450															
≥150-<300															
1-<150															
None															

Table 9. 10-year cumulative incidence of mortality among five year survivors of specific childhood cancers based on stage and risk status at time of diagnosis (expansion cohort only)										
	All Cause			Recurrence/Progression of primary malignancy			Nonrecurrence, Nonexternal Cause			
	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	N	Cumulative incidence	95% CI	P*
Hodgkin lymphoma										
Ann Arbor Stage										
I										
II										
III										
IV										
Stage not available										
Other staging system										
Non-Hodgkin lymphoma										
Murphy Stage										
I										
II										
III										
IV										
Stage not available										
Other staging system										
Medulloblastoma										
Localized, complete resection										
Localized, incompletely resected										
Disseminated										
Neuroblastoma										
INSS										
I										
II										
III										
IV										
V										
Stage not available										
Other staging system										
Kidney tumors										
NWTS stage										
I										
II										
III										
IV										
V										
Stage not available										
Other staging system										
Rhabdomyosarcoma										
IRS										
I										

II										
III										
IV										
V										
Localized, Stage not available										
Disseminated, Stage not available										
Other staging system										
Osteosarcoma										
Localized										
Disseminated										
Not Available										
Ewing sarcoma										
Localized										
Disseminated										
Not Available										

Table 10. Relative Risk for cause specific mortality among five year survivors of childhood cancer based on therapeutic exposure								
	Nonrecurrence/Non-external cause		Cardiac cause		Pulmonary Cause		Other Causes	
	RR	95%CI	RR	95%CI	RR	95%CI	RR	95%CI
Treatment Era								
1970-79								
1989-89								
1990-99								
Sex								
Male								
Female								
Any RT								
Yes								
No								
Chest RT								
Yes								
No								
Cranial RT								
Yes								
No								
Abdominal RT								
Yes								
No								
Pelvic RT								
Yes								
No								
Alkylating agents								
None								
0-<4,000								
≥4,000-<8,000								
≥8,000-<12,000								
≥12,000-16,000								
>16,000-20,000								
>20,000								
Anthracyclines								
None								
1-100								
101-250								

251-400								
>400								
Epipodophyllotoxin								
Yes								
No								
Bleomycin								
Yes								
No								
Platinum								
Yes								
No								

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