Analysis Concept Proposal

Neurocognitive outcomes in survivors of childhood acute lymphoblastic leukemia treated with chemotherapy only

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Background and rationale

Landmark advances in treatment of childhood acute lymphoblastic leukemia (ALL) included cranial radiation for CNS-directed treatment, combination chemotherapy, and the addition of a re-intensification phase[1]. Quality of life *after* the cure became a prominent consideration in the treatment for ALL in the 1980s and 1990s, when a growing number of children became long-term survivors. Concerns over radiation-induced complications[2] motivated a transition away from prophylactic cranial radiation to prophylactic intrathecal chemotherapy and higher doses of intravenous methotrexate for targeting of the central nervous system. Follow-up studies confirmed that ALL survivors treated with chemotherapy-only had better neurocognitive outcomes and quality of life than survivors who had been exposed to cranial radiation[3–8], although cognitive impairments persisted. Compared with siblings, adolescent ALL survivors in the Childhood Cancer Survivor Study (CCSS) treated with chemotherapy alone and assessed with the Behavior Problem Index (BPI) were more likely to exhibit headstrong behaviors, symptoms of attention/deficit hyperactivity disorder, social withdrawal and learning disabilities[4]. Cognitive difficulties in working memory and mental efficiency have also been reported in survivors treated with contemporary therapy[9–11]. Over recent decades, chemotherapy-only regimens have

continued to evolve, including risk-adapted approaches to limit chemotherapy exposure, individualized methotrexate dose, leucovorin rescue, and substitution of prednisone with dexamethasone[12]. These adaptations may have contributed to changes in risk of neurocognitive impairments among ALL survivors; however, further investigation is required to establish treatment-related risk models for predicting neurocognitive outcomes. Using data from CCSS, we will identify demographic and treatment-related factors associated with increased risk of neurocognitive impairments among ALL survivors treated with chemotherapy alone across treatment periods (1970-1999). CCSS participants completed questionnaires regarding demographic characteristics, general health and well-being and chemotherapy exposures were abstracted from medical records. These parameters will be evaluated in the prediction models for neurocognitive impairments as measured with the CCSS Neurocognitive Questionnaire (CCSS-NCQ). Prediction models can shape surveillance strategies that help identify survivors who are at increased risk of developing neurocognitive challenges.

Specific Aims

Aim 1: To compare rates of neurocognitive impairment between sibling controls and ALL survivors who were either treated with chemotherapy or with cranial radiation

First, we will compare rates of neurocognitive impairment between ALL survivors and sibling controls. Using the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) to estimate neurocognitive abilities, we hypothesize that ALL survivors treated with chemotherapy-only will exhibit higher rates of impairments than sibling controls on Task Efficiency and Memory. We also expect that survivors treated with chemotherapy only will demonstrate lower rates of impairment than ALL survivors treated with cranial irradiation (CRT).

Aim 2: To determine if the relationship between chemotherapy treatment exposures and neurocognitive deficits is partially mediated by treatment era

Second, we will test the hypothesis that treatment era partially mediates the relationship between chemotherapy exposures and neurocognitive outcomes. In line with previous research[13], we hypothesize that treatment era will be a significant mediator of neurocognitive outcomes in ALL survivors.

Aim 3: To develop risk prediction models of neurocognitive impairments in ALL survivors treated with chemotherapy alone

The third aim is to leverage the CCSS cohort to develop clinically-relevant models that include demographic, chronic health conditions, and treatment parameters to predict risk of neurocognitive sequelae using an approach similar to that recently reported for predicting heart failure[14]. Risk scores will be validated in ALL survivors from the St Jude Lifetime Cohort Study (SJLIFE; approval for validation already provided by Melissa Hudson and Les Robison)[15]. We hypothesize that the following variables will confer increased risk of neurocognitive impairments among ALL survivors treated with chemotherapy only: female sex[16], younger age at diagnosis[6], earlier treatment era[13], higher dose of methotrexate, and presence of significant chronic health conditions (cardiovascular, endocrine and/or neurologic)[17].

Aim 4: To identify associations between neurocognitive outcomes, quality of life, and social attainment in ALL survivors treated with chemotherapy only

The final aim is to examine associations between neurocognitive outcomes, quality of life, and social attainment (employment, education and living independently) in survivors of ALL. Based on previous research[18], we expect that higher levels of neurocognitive impairment will be associated with decreases in both quality of life and social attainment.

Analysis framework

CCSS Study population

The proposed study population includes a sibling comparison group and survivors of ALL in the combined cohort who completed either Follow-up 2 (Original Cohort) or Follow-up 5 (Expansion Cohort). Approximately 40% of ALL survivors in the cohort received chemotherapy only (n= ~2600) and roughly 60% are expected to have completed follow-up assessments. We expect to have neurocognitive data on about 1,500 eligible ALL survivors treated with chemotherapy only and approximately 4000 ALL survivors treated with cranial radiation (range of 18 or 24 Gy). The original cohort could have participated in Follow-up 2 and Follow-up 5, while the expansion cohort participated in Follow-up 5 only. To ensure that time between diagnosis and follow-up is comparable between cohorts, we will use Follow-up 2 assessments for individuals from the original cohort. As an exploratory aim, we will determine if rates of neurocognitive impairments in the original cohort changed from Follow-up 2 to Follow-up 5.

<u>List of inclusion criteria</u>

- Diagnosis: Acute Lymphoblastic Leukemia
- Age at diagnosis: 1 - 20
- Original cohort completed Follow-up 2, Expansion cohort completed Follow-up 5
- Siblings completed Follow-up 2 or Follow-up 5 questionnaires

SJLIFE Validation cohort

The prediction models will be validated in the St Jude Lifetime Cohort (SJLIFE)[15], which was initiated in 2007 to facilitate prospective assessment of health outcomes in adults survivors of childhood cancer [15]. Similar to CCSS, treatment exposures were ascertained by medical record abstraction and chronic health conditions were determined using comparable methods (Common Terminology Criteria for Adverse Events). SJLIFE participants undergo neurocognitive assessments that include measures of executive functions comparable to the functions assessed as part of the CCSS-NCQ. They also complete the CCSS-NCQ. Thus, we will validate the model using the CCSS-NCQ in the SJLIFE cohort, but we will also examine prediction of impairment based on performance-based tests[15]. A recent report from the SJLIFE cohort showed that approximately 700 survivors were treated with chemotherapy only and ~30% of the sample had a primary diagnosis of ALL[13]. We expect approximately 400 potentially eligible ALL survivors in the validation cohort. CCSS participants who took part in SJLIFE will be excluded from the SJLIFE sample.

The CCSS and SJLIFE samples will be compared on demographics, and key treatment characteristics (Table 1).

Primary outcome of interest

Note that a summary of variables, definitions and sources are listed in Table 2.

Neurocognitive function and impairments

The primary outcome variable of interest is neurocognitive functioning, which will be assessed with the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ). The CCSS-NCQ was developed to screen for neurocognitive impairments in the CCSS population[19]. Participants rated 19 items on a Likert scale with three possible responses: "Never a problem" (score=1), "Sometimes a problem" (score=2) and "Often a problem" (score=3). Four factor scores were derived from these items, including Task Efficiency, Emotional Regulation, Organization and Memory. Factor scores were referenced to sibling norms to generate z-scores with a mean=0 and SD=1.0, where higher z-scores represent greater impairments. Neurocognitive impairment will be operationalized as CCSS-NCQ z-scores ≥ 1.28, corresponding to ≥ 90th percentile of the sibling sample.

Correlative factors

Demographic variables, treatment exposures and chronic conditions

Demographic variables include age at CCSS-NCQ evaluation, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), age at diagnosis, years since diagnosis, and year of diagnosis.

Chemotherapy treatment parameters include cumulative dose of intrathecal (IT) and intravenous (IV) methotrexate (MTX), use of cytarabine, anthracyclines, alkylating agents, and use of dexamethasone versus prednisone. Administration of high-dose IV MTX was not distinguished from standard-dose IV methotrexate in the CCSS medical record abstraction form (MRAF), nor was use of leucovorin rescue. These are two important factors to consider in examining MTX-related neurotoxicity. ALL protocol IDs provide basic information about key treatment parameters. For instance, review of protocol summaries could help establish if protocol A included HD IV MTX with leucovorin, or if protocol B included HD IV MTX without leucovorin. We propose to use the therapeutic protocol information recorded in the MRAF to abstract information on mode of IV MTX delivery (standard- vs high-dose) and administration of leucovorin rescue (yes/no) for the ALL survivors included in this study. Protocol abstraction and review will be performed by a Clinical Research Assistant. For Aim 1, we will also compare groups treated with cranial irradiation (18 or 24 Gy) to ALL survivors treated with chemotherapy only.

For chronic condition predictors, we will use current coding of Common Terminology Criteria for Adverse Events (CTCAE v4). We will examine severity of chronic conditions for categories that are associated with chemotherapy exposure[20], including: neurology, cardiac, pulmonary, and endocrine. Severity will be defined as absent or mild (Grades 0-1), Significant (Grade 2) and Severe/Life threatening (Grades 3-4). Additionally, we will examine the impact of severe, disabling or life-threatening chronic conditions (Grades 3-4) in relevant categories based on the frequency of occurrence of these conditions, as well as the impact of multiple chronic health conditions. We will also

explore associations with reproductive, musculoskeletal, hearing, ocular, and GI conditions, based on sufficient frequency of occurrence.

Quality of life and social attainment

The Short Form-36 (SF-36) will be used to evaluate self-perceived health-related quality of life (HRQOL)[21]. This instrument includes 36 questions about general health, well-being and quality of life in the previous four weeks and yields 8 scale scores and two summary scores: Mental Component Summary (MCS) and Physical Component Summary (PCS). The summary T-scores have a mean=50 and SD=10, where higher T-scores represent poorer health. Poor quality of life will be operationalized as T-scores ≤ 63, corresponding to ≥ 90th percentile of controls. Other indices of health will include the CCSS Health Status questionnaire and physical activity (meeting CDC requirements for weekly moderate or strenuous activity, yes/no).

Social attainment will be determined by several binary categories, including employment (yes/no), college education (yes/no), living independently (yes/no) and marriage (yes/no)[22]. These parameters are typically not applicable for younger participants who, for example, were too young to have had the opportunity to complete college at the time of follow-up. Social attainment assessments will be limited to participants who completed longitudinal follow-up surveys at ≥ 25 years of age. A summary social attainment core will be computed by assigning the number 1 to yes responses and 0 to no responses. The range of possible scores include 4 (all yes); 3 (three yes, one no); 2 (two yes and two no); 1 (1 yes and three no); and 0 (all no). For completeness, analyses will also be performed for each of the four social attainment categories separately.

Proposed analyses

Sample characteristics

Demographics, social attainment and chronic conditions will be compared between ALL survivors (chemo vs CRT) and sibling controls (Table 3). Chi square tests will be used to compare frequencies of categorical outcome variables and t-tests will be used to compare groups on continuous variables such as age at evaluation. We will analyze data to examine how individuals with missing data at Follow-Up 2 or Follow-Up 5 might differ from individuals with follow-up assessments. Missing data will be managed using full information maximum likelihood estimation to minimize bias.

Within-group comparisons for demographics, social attainment and chronic conditions will be performed for ALL survivors across treatment decades (1970-79; 1980-89; 1990-99) (Table 4). In addition to presenting p-values for the omnibus tests, we will also present p-values for each of the three pairwise comparisons. Treatment parameters will be described across treatment periods as well (Table 5).

Aim 1: Neurocognitive impairment in ALL survivors and sibling controls

We propose to conduct multivariable logistic regression to compare frequency (%) of neurocognitive impairments between ALL survivors (Follow-Up 2 for Original cohort, Follow-Up 5 for Expansion cohort) and sibling controls (Follow-Up 2 for Original cohort, Follow-Up 5 for Expansion cohort). Models will be run separately for each of the four CCSS-NCQ domains, using group (sibling controls vs ALL survivors

treated with chemotherapy only vs. ALL survivors treated with3 18 Gy or 24 Gy cranial irradiation), age, sex and race/ethnicity as predictor variables. The dependent variable–presence or absence of neurocognitive impairments–is operationalized as NCQ z-score ≥ 1.28 (present) versus NCQ z-score < 1.28 (absent). Results will be presented as age-, sex- and ethnicity-adjusted proportions along with 95% confidence limits for siblings and ALL survivors (Example shown in Figure 1).

For ALL survivors in the chemotherapy-only group, we propose within-survivor exploratory analyses to determine if we there is any change in neurocognitive impairments in ALL survivors from the original cohort who completed the NCQ at Follow-Up 2 and Follow-Up 5 (i.e., individuals with both data points). The purpose is to identify if scores are different between the two follow-ups. We will use multivariable logistic regression to establish if the frequency of neurocognitive impairments is predicted by follow-up (2 vs 5), age at assessment, age at diagnosis, sex, ethnicity, or treatment intensity. The model will include random intercepts to account for repeated observations. Results will be presented as age-sex- and ethnicity-adjusted proportions along with 95% confidence limits for Follow-Up 2 and Follow-Up 5 (Example shown in Figure 2).

Aim 2: Treatment era mediating the relationship between chemotherapy exposures and neurocognitive outcomes

For exploratory purposes, we will conduct multivariable logistic regression analyses to determine the relationship between chemotherapy exposures and presence or absence of neurocognitive impairments. Chemotherapy parameters include IT MTX dose (cumulative exposure); IV MTX (cumulative exposure); mode of IV delivery (standard dose vs high dose); leucovorin rescue (yes/no); cytarabine (yes/no); anthracycline (yes/no); alkylating agents (yes/no); dexamethasone (yes/no) (Table 2). Other predictor variables in the model will include age at diagnosis (continuous), sex (binary), race/ethnicity (categorical). Results will be presented as OR for each categorical predictor variable across the NCQ domains (Table 6). Note that if the prevalence of neurocognitive impairment is higher than 10% we will consider fitting log-binomial type models to directly estimate prevalence ratios rather than odds ratios. We will also explore relationships between chronic health conditions and neurocognitive impairments (See Table 7).

Mediation analyses will be conducted to test the hypothesis that treatment era mediates the relationship between chemotherapy exposures and neurocognitive impairments. Treatment period will be broken down into six 5-year intervals, i.e., 1970-74; 1975-79; 1980-84; 1985-89; 1990-94; 1995-99. The predictor variables include treatment parameters as defined previously (Table 2). Other predictor variables in the model will include age at diagnosis (continuous), sex (binary), race/ethnicity (categorical). Age at diagnosis, sex and age at follow-up will be used as covariates to neurocognitive outcomes. MPLUS will be used to examine the direct and indirect pathways illustrated in Figure 3. Results will be presented as adjusted rates of impairments across treatment periods (Figure 4).

Aim 3: Risk prediction models of neurocognitive impairments in ALL survivors treated with chemotherapy alone

A previous CCSS publication by Chow and colleagues demonstrated the utility of risk prediction models for cardiac outcomes[14]. We propose to use a similar approach to estimate risk of neurocognitive

impairments among ALL survivors treated with chemotherapy alone. Prediction models will be developed for each of the four CCSS-NCQ domains separately (See list of variables, sources and definitions). Initially, we will construct a prediction model including all predictors available at the 5-year anniversary of childhood cancer diagnosis, while excluding information available only *after* the 5-year mark. The purpose of the initial model is to construct a formula for predicting risk of neurocognitive impairments at the end of ALL treatment. We also aim to develop a follow-up prediction model that can be used at later time points in survivorship, e.g., 15 years after the cancer diagnosis. This follow-up model will include chronic health conditions that developed after the 5-year survival mark.

The following variables will be examined in our prediction models for neurocognitive impairments: sex, age at diagnosis, race/ethnicity (categorical), treatment period (continuous or 5-year categorical, where the use of the prediction model would involve a form of extrapolation if this is retained in the model), IT MTX dose (cumulative exposure), IV MTX (cumulative exposure), mode of IV delivery (standard dose vs high dose), leucovorin rescue (yes/no), cytarabine (yes/no), anthracycline (yes/no), alkylating agents (yes/no), dexamethasone (yes/no); age at testing. Categories of chronic health condition (Grade 2 vs Grade 0-1; Grade 3-4 vs Grade 0-1) will be included in the follow-up prediction model, where time at the development of chronic health conditions will be considered as described above. Logistic regression models will be used to construct risk prediction models between predictors and neurocognitive impairments. Backward selection or lasso will be used to identify the most influential predictors[14, 23]. The resulting regression estimated will be converted to risk scores to facilitate interpretation of risk.

Concordance statistics (C) and area under the curve (AUC) will be used to quantify the prediction performance of the models in the CCSS and validated in the SJLIFE cohort. Individuals in the validation cohort will be categorized into CCSS-based risk groups and the resulting cumulative incidence of neurocognitive impairments will be compared with those derived from the CCSS cohort. The R software package risksetROC will be used to calculate the AUCs and C statistics.

<u>Aim 4: Associations between neurocognitive outcomes, quality of life and social attainment in ALL survivors</u>

Logistic regression will be used to determine if poor quality of life is associated with neurocognitive outcomes in ALL survivors treated with chemotherapy only. The dependent variable—presence or absence of poor quality of life—is operationalized as SF-36 T-scores ≥ 63 (present) versus T-scores < 63 (absent). Models will be run separately for MCS and PCS. The independent variables will include: CCSS NCQ z-scores, health status (healthy/not healthy), physical activity, age at diagnosis, and sex. Results will be shown as ORs for each quality of life domain (Table 8).

We will conduct ordinal logistic regression to estimate if higher social attainment (ordinal variable) is predicted by CCSS NCQ z-scores, health status, physical activity, sex and age at diagnosis. The coefficients from the model will be converted from log odds to ORs for clarity (Table 8).

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Tables and figures

Table 1 CCSS and SJLIFE cohort demographics

ALL survivors treated with chemo only			
		CCSS	**SJLIFE**
Characteristic		N	N
Sex	Males	N (%)	N (%)
	Females	N (%)	N (%)
Age at diagnosis, years		Mean (SD)	Mean (SD)
Treatment era	Pre-1980	N (%)	N (%)
	1980-1989	N (%)	N (%)
	1990-1999	N (%)	N (%)
Time since treatment		Mean (SD)	Mean (SD)
Cumulative IT MTX	Median		
	IQR		
Cumulative IV MTX	Median		
	IQR		
	None	N (%)	N (%)
Mode IV delivery	Standard dose	N (%)	N (%)
	High dose	N (%)	N (%)
Leucovorin rescue	No	N (%)	N (%)
	Yes	N (%)	N (%)
Cytarabine	No	N (%)	N (%)
	Yes	N (%)	N (%)
Anthracycline	Median		
	IQR		
	No	N (%)	N (%)
	Yes	N (%)	N (%)
Alkylating agents	Median		
	IQR		
	No	N (%)	N (%)
	Yes	N (%)	N (%)
Dexamethasone	No	N (%)	N (%)
	Yes	N (%)	N (%)

Table 2 Variables, sources and definitions

		Source	Definition	
Outcome variable	Neurocognitive impairment	CCSS-NCQ • Task Efficiency • Emotional Regulation • Organization • Memory	Z ≥ 1.28	
Treatment exposures	Cumulative IV MTX	Treatment Data from Medical Record Abstraction	Cumulative exposure	0 vs >0 to 1 g/m^2 > 1 g/m^2
	Mode of IV MTX	To be abstracted*	Standard Dose High Dose	
	Leucovorin rescue	To be abstracted*	Administered	Yes No
	Cumulative IT MTX	Treatment Data from Medical Record Abstraction	Cumulative exposure	≤ 50 ml ≥ 50 ml
	Cytarabine	Treatment Data from Medical Record Abstraction	Administered	Yes No
	Anthracyclines	Treatment Data from Medical Record Abstraction	Administered	Yes No
	Alkylating agents	Treatment Data from Medical Record Abstraction	Administered	Yes No
	Use of dexamethasone versus prednisone	Treatment Data from Medical Record Abstraction	Administered	Prednisone Dexamethasone
Chronic conditions	Chronic health conditions • Neurology • Pulmonary • Endocrine • Reproduction • Musculoskeletal • Hearing • Ocular • Gastrointestinal	Common Terminology Criteria for Adverse Events (CTCAE v4)	Absent/mild: Significant Severe	Grade 0-1 Grade 2 Grade 3-4
Quality of life	Poor quality of life	Short Form-36 (SF-36)	Mental Component Summary Physical Component Summary	T ≤ 63 T ≤ 63
	Health			Yes

	CCSS Health Status questionnaire and physical activity	Any physical activity	No
		Moderate physical activity	Yes
			No
		Vigorous physical activity	Yes
			No
Social attainment	Employment status	Employed	
		Unemployed	
	Degree completed	College graduate	Yes
			No
	Living arrangements	Living as dependent	
		Living independently	
	Marriage or living with spouse	Not married/no spouse	
		Married/has spouse	

*Therapeutic protocol information from the MRAF will be used to abstract basic information on mode of IV MTX delivery and administration of leucovorin rescue

Table 3 Sample, demographics, social attainment and chronic conditions

			ALL survivors		Siblings	Pairwise comparison p-value	
			Chemo-only	CRT		chemo vs CRT	Chemo vs Sibs
Sample			N	N	N		
Sex		Males	N (%)	N (%)	N (%)		
		Females	N (%)	N (%)	N (%)		
Age at evaluation			Mean (SD)	Mean (SD)	Mean (SD)		
Race/ethnicity		White	N (%)	N (%)	N (%)		
		Black	N (%)	N (%)	N (%)		
		Hispanic	N (%)	N (%)	N (%)		
		Other	N (%)	N (%)	N (%)		
		Unknown	N (%)	N (%)	N (%)		
Social attainment*	**Employment Status**	Employed	N (%)	N (%)	N (%)		
		Unemployed	N (%)	N (%)	N (%)		
	Education	≥ college degree	N (%)	N (%)	N (%)		
		< college degree	N (%)	N (%)	N (%)		
	Living arrangements	Living independently	N (%)	N (%)	N (%)		
		Living as dependent	N (%)	N (%)	N (%)		
Chronic conditions	**Neurology**	Grades 0-1	N (%)	N (%)	N (%)		
		Grade 2	N (%)	N (%)	N (%)		
		Grades 3-4	N (%)	N (%)	N (%)		
	Pulmonary	Grades 0-1	N (%)	N (%)	N (%)		
		Grade 2	N (%)	N (%)	N (%)		
		Grades 3-4	N (%)	N (%)	N (%)		
	Endocrine	Grades 0-1	N (%)	N (%)	N (%)		
		Grade 2	N (%)	N (%)	N (%)		
		Grades 3-4	N (%)	N (%)	N (%)		
	Reproduction	Grades 0-1	N (%)	N (%)	N (%)		
		Grade 2	N (%)	N (%)	N (%)		
		Grades 3-4	N (%)	N (%)	N (%)		

Musculoskeletal	Grades 0-1	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)
Hearing	Grades 0-1	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)
Ocular	Grades 0-1	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)
Gastrointestinal	Grades 0-1	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)

* Includes participants ≥ 25 years old at Follow-up

Table 4 Demographics, social attainment, chronic conditions for ALL survivors across treatment periods

			ALL survivors						Pairwise comparison across treatment decades		
		Treatment decades	1		2		3		p-value		
			70-74	75-79	80-84	85-89	90-94	95-99			
Sample			N	N	N	N	N	N	**1 vs 2**	**2 vs 3**	**1 vs 3**
Sex		Males	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Females	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
Age at evaluation			Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
Race/ethnicity		White	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Black	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Hispanic	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Other	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Unknown	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
Social attainment	**Employment Status**	Employed	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Unemployed	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	Education	≥ college degree	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		< college degree	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	Living arrangements	Living independently	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Living as dependent	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
Chronic conditions	**Neurology**	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	Pulmonary	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	Endocrine	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	Reproduction	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			

	Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Musculoskeletal	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Hearing	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Ocular	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gastrointestinal	Grades 0-1	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grade 2	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Grades 3-4	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

*Grade 0-1 Absent/ Mild
*Grade 2 Moderate
*Grade 3-4 Severe

Table 5 Chemotherapy treatment exposures for ALL survivors across treatment periods

			ALL survivors						Pairwise comparisons across treatment decades		
	Treatment decades		1		2		3		p-value		
			70-74	75-79	80-84	85-89	90-94	95-99			
Sample			N	N	N	N	N	N	1 vs 2	1 vs 3	2 vs 3
Treatment factors	Age at diagnosis		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
	Time since treatment		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)			
	Intrathecal MTX	Median									
		IQR									
		< cutoff value based on median split	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		≥ cutoff value based on median split	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
	IV MTX	Median									
		IQR									
		None	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		< cutoff value based on median split	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			
		≥ cutoff value based on median split	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)			

Mode IV delivery	Standard dose	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	High dose	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Leucovorin rescue	No	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Yes	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cytarabine	No	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Yes	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Anthracycline	Median						
	IQR						
	No	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Yes	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Alkylating agents	Median						
	IQR						
	No	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Yes	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Dexamethasone	No	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
	Yes	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)

IQR = Interquartile range

Table 6: Multivariable Logistic regression models predicting domains of neurocognitive Impairment from treatment parameter

NCQ domain		Task Efficiency			Emotional Regulation			Organization			Memory		
Predictor Variables		**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Sex	Female	1			1			1			1		
	Male												
Race/ethnicity	White	1			1			1			1		
	Black												
	Hispanic												
	Other												
	Unknown												
Intrathecal MTX	≤ 50 mL of cumulative exposure	1			1			1			1		
	≥ 50 mL of cumulative exposure												
IV MTX	None	1			1			1			1		
	0 - 1 g/m^2 of cumulative exposure												
	> 1 g/m^2 of cumulative exposure												
Mode IV delivery	Standard dose	1			1			1			1		
	High dose												
Leucovorin rescue	No	1			1			1			1		
	Yes												
Cytarabine	No	1			1			1			1		
	Yes												
Anthracycline	No	1			1			1			1		
	Yes												
	No	1			1			1			1		

Alkylating agents	Yes				
Dexamethasone	No	1	1	1	1
	Yes				

Table 7: Multivariable Logistic regression models predicting domains of neurocognitive Impairment from chronic conditions

		NCQ domain	Task Efficiency			Emotional Regulation			Organization			Memory		
Predictor Variables			**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Race/ethnicity		White	1			1			1			1		
		Black												
		Hispanic												
		Other												
		Unknown												
Chronic conditions*	**Neurology**	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Pulmonary	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Endocrine	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Reproduction	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Musculoskeletal	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Hearing	Grades 0-1	1			1			1			1		
		Grades 2-4												
		Grades 3-4												
	Ocular	Grades 0-1	1			1			1			1		
		Grades 2-4												

	Grades 3-4				
	Grades 0-1	1	1	1	1
Gastrointestinal	Grades 2-4				
	Grades 3-4				

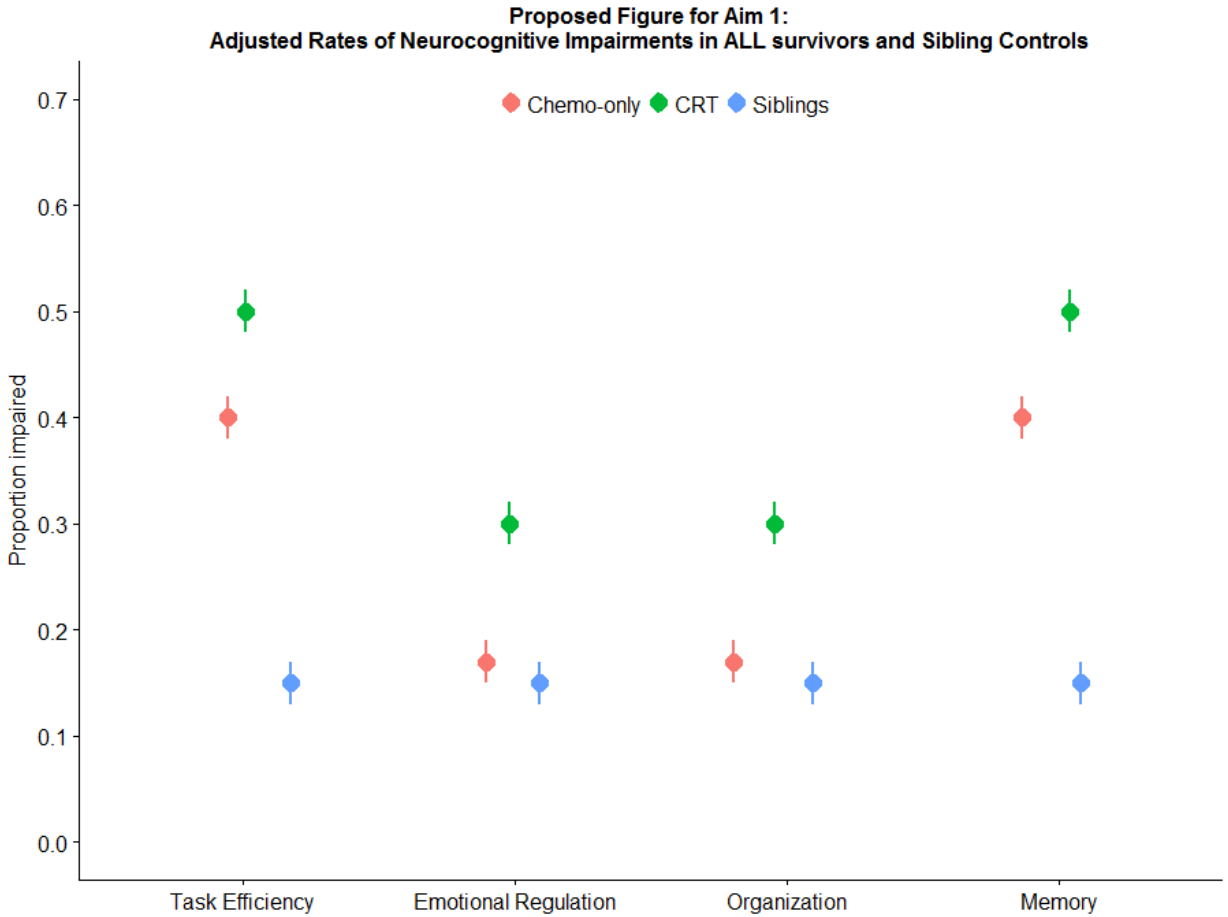
* Only chronic condition categories that occur with sufficient frequency will be included (e.g. if grade 3-4 GI conditions are too infrequent, this category will be dropped)

Table 8 Neurocognitive predictors of quality of life and social attainment

			Predictor variables							
			NCQ impairments				**Demographics**			
Outcome variables		**Stats**	Task Efficiency	Emotional Regulation	Organization	Memory	Sex	Age at diagnosis	Health status	Physical activity
Quality of life	General Health	OR								
		95% CI								
		p								
	Physical Functioning	OR								
		95% CI								
		p								
	Physical Role Limitations	OR								
		95% CI								
		p								
	Pain	OR								
		95% CI								
		p								
	Vitality	OR								
		95% CI								
		p								
	Mental Health	OR								
		95% CI								
		p								
	Emotional Role Limitations	OR								
		95% CI								
		p								
	Social Functioning	OR								
		95% CI								
		p								
Social Attainment	Educational attainment	OR								
		95% CI								

	p								
Employment	OR								
	95% CI								
	p								
Independent Living	OR								
	95% CI								
	p								

Figure 1: Proposed figure for showing rates of neurocognitive impairments (y-axis) for each CCSS-NCQ domain (x-axis) for ALL survivors treated with chemotherapy alone (pink), ALL survivors treated with cranial radiation (green) and sibling controls (blue circles).



Note that proportions will be adjusted for age at evaluation, sex and ethnicity

Figure 2: Proposed figure for showing adjusted rates of neurocognitive impairments (y-axis) across Follow-up assessments (x-axis) for the four NCQ domains (panels)

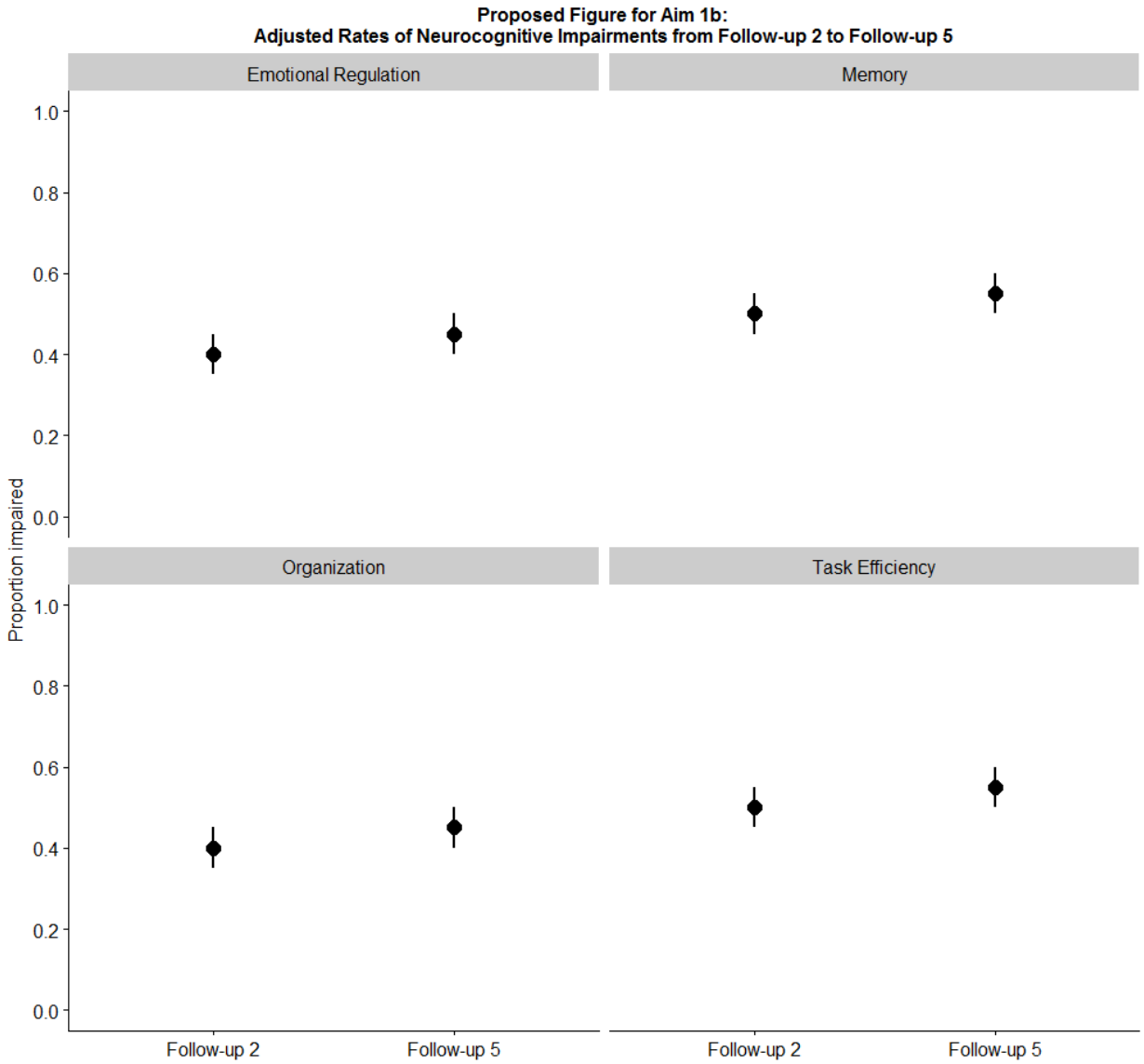


Figure 3 Mediation analyses to test if treatment era partially mediates the relationship between treatment parameters and neurocognitive outcomes

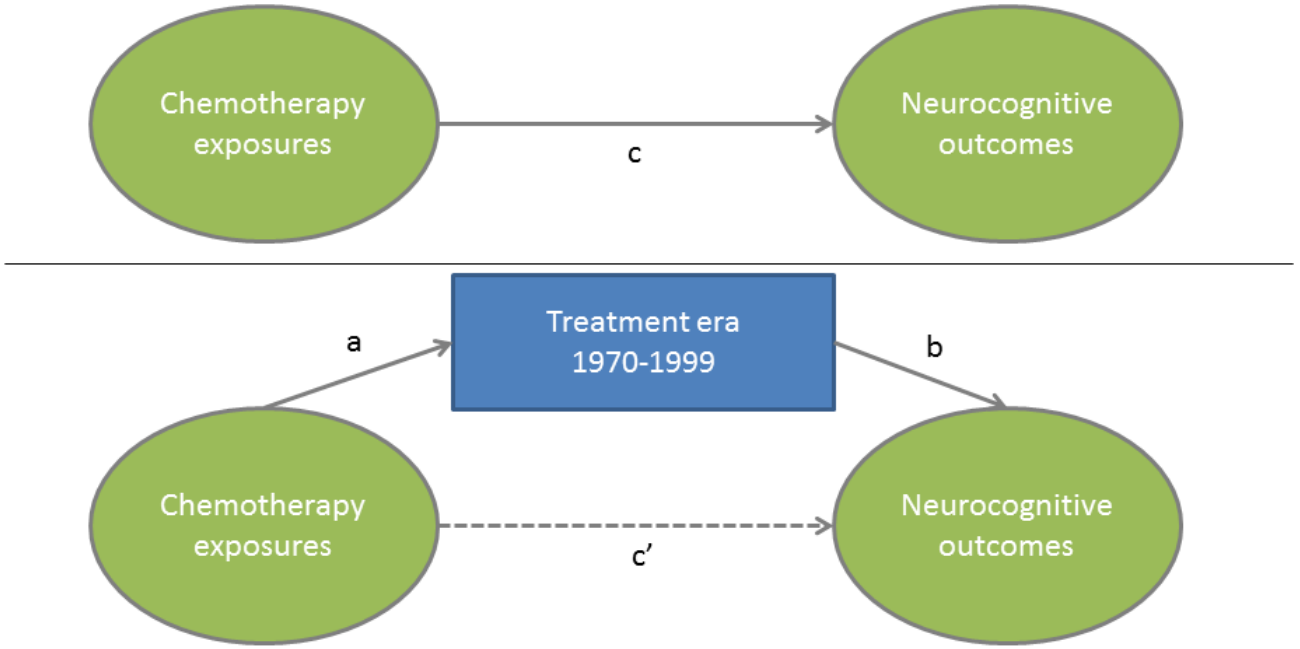
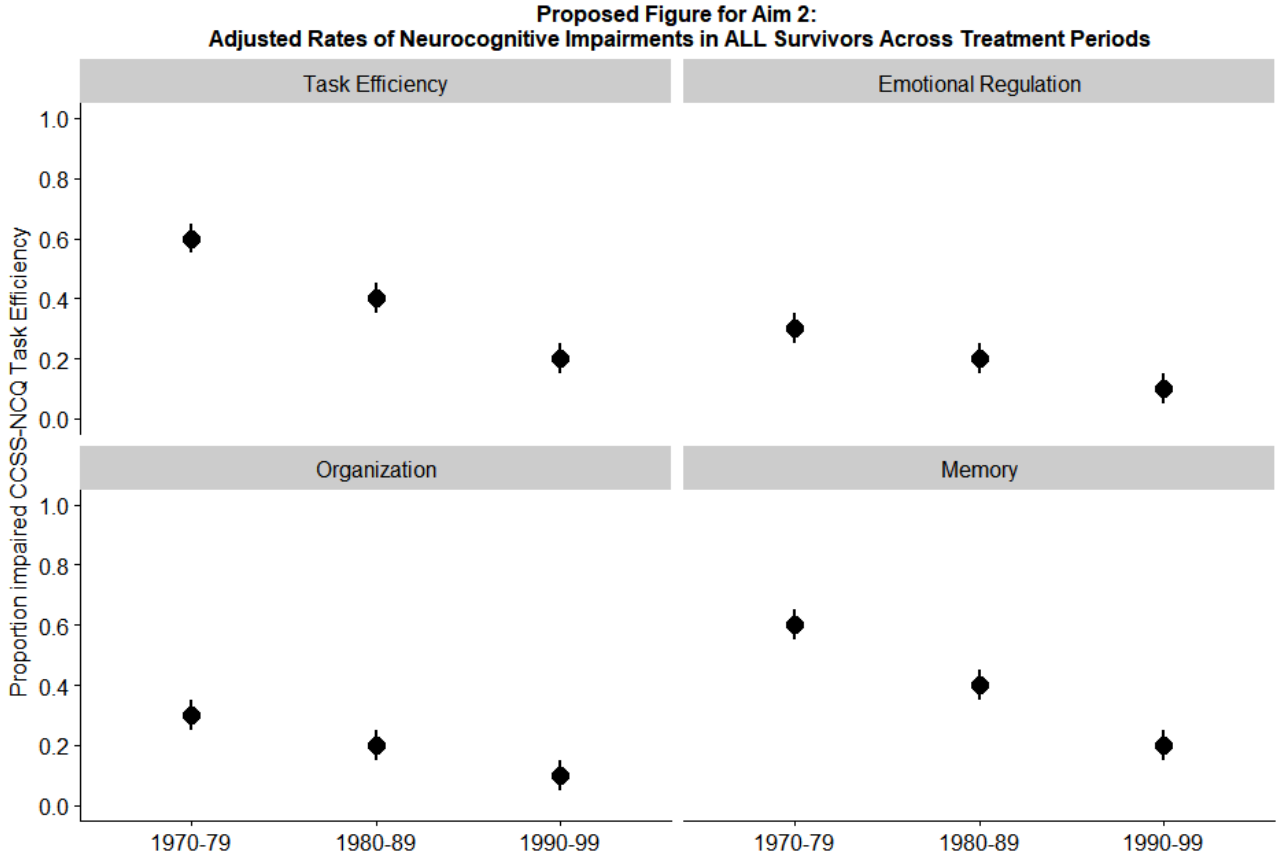


Figure 4: Proposed figure for showing adjusted rates of neurocognitive impairments (y-axis) across treatment periods (x-axis) for the four NCQ domains (panels)



Note that proportions will be adjusted for age at evaluation, sex and ethnicity