

## CHILDHOOD CANCER SURVIVOR STUDY

### Analysis Concept Proposal

**Draft:** September 22, 2003

**Title:** Growth and neuroendocrine sequelae associated with central nervous system irradiation in childhood acute lymphoblastic leukemia survivors

#### **Working Group and Investigators:**

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#### **Background and Rationale:**

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with an incidence of 3.5/100,000. While fewer than 5% of children presenting with ALL have central nervous system (CNS) involvement, the CNS is a common site of relapse. CNS radiation was widely adopted in the 1970s as an effective means to decrease this relapse risk. Studies showed that 24 Gy of "prophylactic" craniospinal radiation reduced the incidence of CNS relapse from roughly 50% to 10%. Because of increased growth retardation and myelosuppression associated with spinal radiation, it was replaced by comparably effective intrathecal methotrexate. However, cranial radiation alone was still associated with adverse neurocognitive and neuroendocrine sequelae. Doses of 18 Gy cranial radiation with intrathecal chemotherapy was subsequently shown to be as effective as 24 Gy in reducing CNS relapse, becoming the standard treatment during the 1980s. However, concerns have arisen that even an 18 Gy radiation dose may cause unacceptable long-term effects, and currently only high-risk ALL patients receive cranial radiation as part of frontline therapy. Standard-risk patients are now effectively treated with systemic and intrathecal chemotherapy without cranial radiation. Children with CNS leukemia at diagnosis or with CNS relapse often still receive some form of craniospinal radiation.

Multiple studies have examined growth retardation and changes in pubertal timing associated with CNS radiation in ALL survivors. Studies have been fairly consistent in finding significantly decreased height in children exposed to 24 or more Gy cranial radiation compared with population norms or predicted adult height.<sup>1,2,3,4,5,6</sup> These children had on average one or more standard deviation decrease in their adult height. Children who also received spinal

radiation had even greater stature loss.<sup>7</sup> However, while some studies reported similar degrees of height retardation associated with 18 Gy cranial radiation,<sup>1,8</sup> others reported smaller decreases with the lower dose.<sup>3,5,6</sup> A few papers examined the impact of chemotherapy alone and generally found that exposed patients appeared to have significant growth suppression during treatment, but exhibited catch-up growth afterwards, achieving normal or near-normal adult heights.<sup>2,3,4,9</sup>

It is hypothesized that shorter stature associated with cranial radiation may be secondary to radiation induced growth hormone insufficiency and changes in pubertal timing. Growth hormone secretion can be depressed in a dose-dependent manner, even at relatively low levels of radiation, such as 18 Gy.<sup>6</sup> Nevertheless, most ALL patients who receive prophylactic cranial radiation do not have detectable growth hormone insufficiency, and of those who do, the degree of insufficiency does not always correlate with the degree of growth retardation. Higher doses of cranial radiation have been shown to be associated with subsequent precocious puberty in children with brain tumors, particularly girls.<sup>10,11</sup> Earlier puberty following prophylactic cranial irradiation in ALL patients has been reported,<sup>12,13</sup> but not consistently.<sup>1,2</sup> Earlier pubertal onset in conjunction with growth hormone insufficiency often leads to short adult stature.

There may be other endocrine sequelae following cranial radiation. In addition to possible effects on the pituitary-thyroid axis, dosimetry studies have found that up to 7% of the prophylactic cranial radiation dose is scattered to the thyroid itself.<sup>14</sup> In malignancies where higher cranial radiation doses have been used, there has been a significantly increased risk of both primary and central hypothyroidism.<sup>15</sup> However, in many small studies of childhood ALL survivors exposed to cranial radiation, clinical hypothyroidism has been rare, although TSH abnormalities with “compensated” thyroid function was more common.<sup>16,17,18,19</sup> It is controversial whether patients with subclinical hypothyroidism need to be treated. Negative findings may reflect small numbers of patients reviewed and also limited follow-up time, as thyroid dysfunction can develop decades after exposure.<sup>20</sup> There is less data on other neuroendocrine sequelae. At high doses reserved for brain tumors, cranial radiation was associated with a significant risk of central hypogonadism in a small case series.<sup>21</sup> Adrenal insufficiency has also been reported, although symptomatic disease appears to be rare.<sup>21,22</sup>

Spinal radiation causes growth retardation via inhibition of vertebral growth. In addition, there is scatter to the thyroid and gonads. While thyroid disease following craniospinal radiation in ALL survivors has not been well studied, studies have found an increased risk of ovarian<sup>23</sup> and testicular<sup>24</sup> dysfunction associated with craniospinal radiation compared with cranial exposure alone. Depending on the dose, craniospinal radiation has been associated with both delayed and early menarche.<sup>13</sup>

**Specific Aims:**

In survivors of childhood ALL treated with CNS radiation or chemotherapy alone:

- To determine the prevalence and spectrum of adult growth retardation.
- To determine the prevalence, spectrum and cumulative incidence of clinical growth hormone deficiency, thyroid dysfunction, and other potential neuroendocrine sequelae.

**Hypotheses:**

- Children treated for ALL without cranial radiation do not have an increased risk of growth retardation, growth hormone deficiency, thyroid dysfunction, or other neuroendocrine sequelae compared to sibling controls.
- Risk of growth retardation, growth hormone deficiency, thyroid dysfunction, and other neuroendocrine sequelae following treatment for childhood ALL is associated with cranial radiation in a dose-dependent fashion, and highest in those receiving additional spinal radiation.

**Analysis Framework:**

- (a) Outcomes of interest (baseline questionnaire items, unless otherwise specified)
- Adult height: self-reported height of men and women 18 years and older (A.10).
  - Growth hormone deficiency: self-reported diagnosis of growth hormone deficiency (E.8) or history of growth hormone supplementation (E.9).
  - Thyroid dysfunction: self-reported history of hyper- (E.1) or hypothyroidism (E.2), thyroid nodules (E.3), or thyroid enlargement (E.4), cross-referenced with self-reported usage of thyroid medications (B.8.5).
  - Pubertal timing: self-reported menarche (first follow-up questionnaire 19.a). There was no question specific for pubertal onset in males. History of medications given for delayed puberty (E.11) may provide additional information.
  - Other neuroendocrine dysfunction: e.g. central hypogonadism and adrenal insufficiency: review self-reports of estrogen/progesterone (B.8.3) or testosterone (B.8.4), as well as “other hormonal problems” (E.12) and “other prescribed drugs” (B.8.16). There may not be sufficient numbers to analyze, and it may be impossible to distinguish central from primary dysfunction.
- (b) Subject population
- Cases: ALL patients without CNS involvement who received prophylactic cranial irradiation.
  - Controls: ALL patients without CNS involvement who were not exposed to cranial irradiation.
  - Controls: Siblings of ALL cases (or potentially all CCSS siblings, depending on available numbers).

## (c) Exploratory Variables:

- Outcome variables: see above
- Exposure variables:
  - CNS radiation dose
  - Chemotherapy intensity (standard versus intensive)
- Potential confounders and effect modifiers:
  - Gender
  - Ethnicity
  - Current age
  - Age at diagnosis
  - Time interval between ALL diagnosis and late-effect occurrence
  - Pubertal status (menarche)
  - Growth hormone treatment

## (d) Analyses

- Calculate the mean adult height of ALL survivors, stratified by CNS radiation dosage and gender, compared to sibling controls and period-specific national standards.
- In the case of female patients, determine if prepubertal (premenarchal) CNS radiation exposure is associated with increased adult height loss.
- Calculate the incidence rates of and the relative risks of developing other neuroendocrine sequelae, e.g. growth hormone deficiency, growth hormone usage, thyroid disease, usage of puberty inducing medicines, following different levels of CNS radiation.
- Depending on the quality of the data, will attempt to determine the time interval in which these late effects are most likely to be diagnosed.
- Depending on the quality of the data, will create Kaplan-Meier curves to illustrate when various neuroendocrine sequelae occur, stratified by CNS radiation dosage.
- Analyses will be adjusted for age at diagnosis, gender, and other variables as appropriate.

**Specific Tables/Figures:**

(a) Case and control characteristics

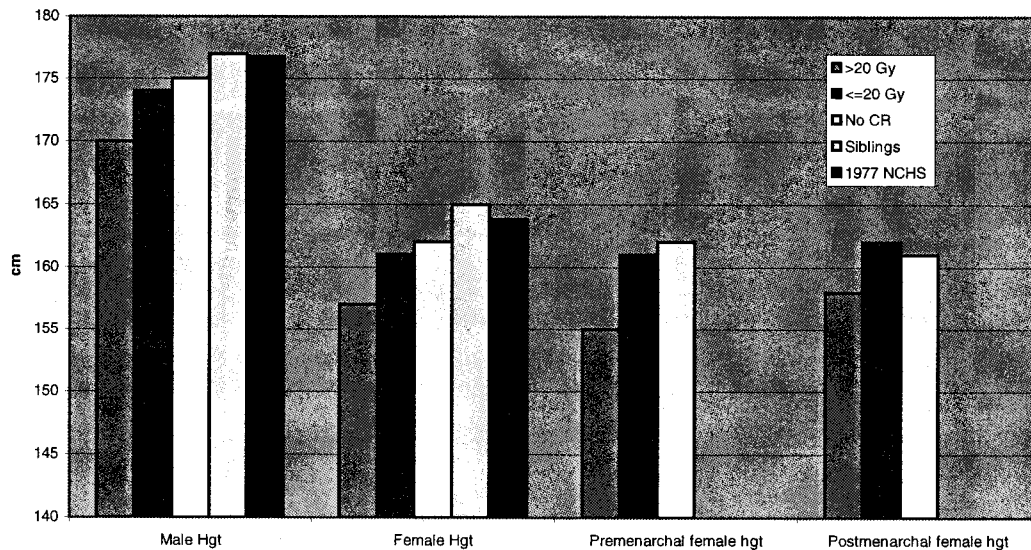
	ALL survivors					Sibling Controls (n=)
	No cranial radiation (n=)	≤ 20 Gy (n=)	> 20 Gy (n=)	≤ 20 Gy +spinal (n=)	> 20 Gy +spinal (n=)	
Interview age						
Diagnosis age						
% female						
% premenarchal at diagnosis						
Age at menarche						
Adult height						
Males						
Females						
Premenarchal at diagnosis						
Postmenarchal at diagnosis						

(b) Incidence and risk of endocrine effects.

	No. among cases*	Rate among cases*	RR	95% CI
Growth hormone deficiency				
No radiation				
≤ 20 Gy cranial				
≤ 20 Gy craniospinal				
> 20 Gy cranial				
> 20 Gy craniospinal				
Sibling control				
Hypothyroidism				
No radiation				
≤ 20 Gy cranial				
≤ 20 Gy craniospinal				
> 20 Gy cranial				
> 20 Gy craniospinal				
Sibling control				
Medications to induce puberty				
No radiation				
≤ 20 Gy cranial				
≤ 20 Gy craniospinal				
> 20 Gy cranial				
> 20 Gy craniospinal				
Sibling control				
Etc.				

\* Unless otherwise specified, i.e. sibling control.

(c) [SAMPLE] Mean adult height in ALL survivors, stratified by cranial radiation (CR), and compared with sibling controls and the 1977 National Center for Health Statistics (NCHS) data.



(d) Kaplan-Meier curves showing the probability of developing [\*] after ALL diagnosis. Patients are grouped according to prophylactic cranial irradiation dose.

\* Possibilities include growth hormone deficiency and hypothyroidism, depending on the data quality.

**Special Considerations:**

Two other CCSS analyses have been published recently that are related in topic with this proposal. These studies, focusing on obesity in ALL survivors<sup>25</sup> and cardiovascular and endocrine late effects in brain tumor survivors,<sup>26</sup> were reviewed during the formulation of this concept proposal and were used as models for our proposed analysis. Dr. Oeffinger was contacted to ensure that this proposal does not overlap substantially with his group’s ALL analyses. Oeffinger et al has focused primarily on BMI and diabetes risk while we will be looking only at height and other endocrine outcomes, excluding diabetes. In the event that the review committee feels that significant overlap exists, we would be willing to reformulate parts of this proposal in collaboration with Oeffinger et al. With regards to Gurney et al, while some of our proposed outcomes are similar we focus on a different cancer with different treatment regimens. Direct and scattered radiation dosages to the brain and thyroid are much higher in brain tumor protocols than ALL protocols. Therefore, while no dose-response relationships between radiation and subsequent endocrine sequelae were noted by Gurney et al, they may exist at the lower doses experienced by ALL patients.

## References

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