Late morbidity and mortality among survivors of neuroblastoma treated with contemporary therapy: A report from the Childhood Cancer Survivor Study (CCSS)

Background: Survival rates for neuroblastoma vary widely based on risk group. Therapies have evolved over the past four decades to de-intensify therapy for individuals with low/intermediate risk disease and intensify therapy for those with high risk disease. Risk stratification is predicted to result in differential outcomes in late morbidity and mortality; the magnitude of these differences has not been well studied.

Methods: We evaluated late mortality, subsequent malignant neoplasms (SMN) and chronic health conditions (CHCs) graded according to CTCAE v4.03 among 491 5-year CCSS survivors of neuroblastoma diagnosed 1987-1999 at ≥1 year of age. Using age, stage at diagnosis, and treatment, survivors were classified into risk groups (low [n=182]; intermediate [n=70]; high [n=239]). Standardized mortality ratios (SMR) and standardized incidence ratios (SIR) of SMNs were calculated using rates from NCHS and SEER, respectively. Cox regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) for CHC compared to 1,029 CCSS siblings.

Results: Among survivors (48% male; median age 22 years, range 7-42; median follow-up 19 years, range 5-29), 80.4% with low risk disease were treated with surgery alone, while 77.8% with high risk disease received surgery, radiation, chemotherapy ± transplant. The 15-year cumulative incidence of all-cause mortality was 9.2% (CI: 7.1-11.4), with a recurrence-related mortality of 7.3% (CI: 5.3-9.3) and SMN-related mortality 0.3% (CI: 0-0.7). All-cause mortality was significantly higher in all risk groups: (low, SMR=5.8 [CI: 2.6-13.0]; intermediate, SMR=5.7 [CI: 1.4-23.5]; high, SMR=38.6 [CI: 27.9-53.5]). The risk of SMN was elevated among high risk survivors (SIR=25.1, CI: 16.7-37.6), but did not differ from the US population for survivors of low or intermediate risk disease. **Table 1** describes the HR of CHCs (grades 1-5 and 3-5) in survivors, by risk group, as compared with siblings, as well as categories of CHCs for which survivors were at increased risk.

Conclusions: Long-term survivors of neuroblastoma have a high risk of late morbidity and mortality; risk is especially pronounced among survivors of high risk disease. Vigilant lifelong medical surveillance will be required for this relatively young population as they age.

Table. CHCs in neuroblastoma survivors, by risk group, compared to siblings

	HR (95% CI)		
	Low	*Intermediate*	*High*
Any grade 1-5 CHC	2.0 (1.5-2.6)	2.9 (2.0-4.3)	6.9 (5.7-8.2)
Endocrine	3.9 (2.1-7.2)	5.9 (2.9-12.1)	27.7 (17.6-43.5)
Hearing	4.0 (1.7-9.0)	11.3 (4.8-26.3)	17.9 (9.7-32.9)
Gastrointestinal	-	-	21.3 (8.0-56.8)
Cardiac	2.5 (1.3-4.6)	4.7 (1.9-11.7)	10.9 (6.7-17.7)
Renal	-	4.1 (1.8-9.4)	10.8 (6.2-19.0)
Neurologic	2.4 (1.4-4.1)	4.5 (2.3-8.8)	6.1 (4.0-9.2)
Any grade 3-5 CHC	3.0 (1.5-6.3)	10.5 (3.6-30.9)	21.3 (13.5-33.6)
Cardiac	4.1 (1.2-13.5)	12.6 (3.3-47.9)	12.7 (4.6-35.0)