

## Long Term Morbidity and Mortality among Survivors of Infant Neuroblastoma: A Report from the Childhood Cancer Survivor Study (CCSS)

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### BACKGROUND

Infants with neuroblastoma typically have low-risk disease with excellent survival. Therapy has been de-intensified over time to minimize late effects, however the impact on survivors' risk of late mortality, subsequent malignant neoplasms (SMN), and chronic health conditions (CHC) is unclear.

### METHODS

We evaluated late mortality, SMNs and CHCs (graded according to CTCAE v4.03), overall and by diagnosis era, among 990 5-year neuroblastoma survivors diagnosed at <1 year of age between 1970-1999. Cumulative mortality, standardized mortality ratios (SMR), and standardized incidence ratios (SIR) of SMNs were estimated using the National Death Index and SEER rates, respectively. Cox proportional hazards estimated hazard ratios (HR) and 95% confidence intervals (CI) for CHC, compared to 5,051 CCSS siblings.

### RESULTS

Among survivors (48% female; median attained age: 24 years, range 6-46), there was increased treatment with surgery alone across the 1970s, 1980s and 1990s (21.5%, 35.3%, 41.1%, respectively), decreased treatment with combination surgery + radiation (22.5%, 5.3%, 0.3%, respectively) and surgery + radiation + chemotherapy (28.7%, 14.7%, 9.3%, respectively). The 20-year cumulative mortality was 2.3% (95% CI, 1.4-3.8), primarily due to SMNs ( $SMR_{SMN}=10.0$ , 95% CI, 4.5-22.3). The 20-year cumulative incidence of SMN was 1.2% (95% CI, 0.3-3.2), 2.5% (95% CI, 1.3-4.4), and zero for those diagnosed in the 1970s, 1980s, and 1990s, respectively. SIR was highest for renal SMNs (SIR 12.5, 95% CI, 1.7-89.4). Compared to siblings, survivors were at increased risk for grade 1-5 CHC (HR 2.1, 95% CI, 1.9-2.3) with similar HR across eras ( $HR_{1970s}=1.9$ , 95% CI, 1.6-2.2;  $HR_{1980s}=2.2$ , 95% CI, 1.9-2.6;  $HR_{1990s}=2.0$ , 95% CI, 1.7-2.4). The HR of severe, disabling, life-threatening and fatal CHC (grades 3-5) decreased in more recent eras ( $HR_{1970s}=4.7$ , 95% CI, 3.4-6.6;  $HR_{1980s}=4.4$ , 95% CI, 3.2-6.2;  $HR_{1990s}=2.9$ , 95% CI, 2.0-4.3).

### CONCLUSIONS

Survivors of infant neuroblastoma remain at increased risk for late mortality, SMN, and CHCs many years after diagnosis. However, the risk of grade 3-5 CHCs has declined in more recent eras, likely reflecting de-intensification of therapy.

CHARACTERS: 1994 (max 2000)