

Long-term complications in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study

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ABSTRACT

Background

Neuroblastoma (NB) survivors can develop many complications from their treatment. We evaluated long-term morbidity and mortality in a large cohort of NB survivors.

Procedures

Late effects data from 5-year NB survivors diagnosed between 1970-86 enrolled in the Childhood Cancer Survivor Study (CCSS) were collected from self-administered questionnaires. 832 survivors and 3899 siblings were included. Treatment data were abstracted from the medical records of all survivors. Late mortality, second malignant neoplasm (SMN), and chronic health conditions were analyzed in relation to treatment factors.

Results

46 survivors (6%) died more than 5 years after their diagnosis (standardized mortality ratio [SMR]=4.8; 95% CI 3.5-6.5). Causes of death included: disease recurrence (n=23), SMN (n=6) (SMR: 8.5; 95% CI 3.1-18.4), cardiac (n=1) (SMR 2.9; 95% CI 0.04-16.0), pulmonary (n=1) (SMR 4.8; 95% CI 0.1-26.5), external causes (n=4), other and unknown (n=1). 33 developed a SMN (standardized incidence ratio [SIR] 8.6; 95% CI 5.9-12.1); thyroid (n=7), renal (n=6), soft tissue sarcomas (n=3), acute myeloid leukemia (n=2), breast cancer (n=2) and other (n=13). Exposure to radiation therapy (RT) (p<0.003) and to VP-16 (p=0.04) were significant risk factors for SMN. Compared to siblings, survivors were more likely to report any chronic health condition (risk ratio [RR] 14.7; 95% CI, 12.4-17.6). The most prevalent conditions included: musculoskeletal (RR 49.8; 95% CI, 27.9-88.8), endocrine (RR 36.2; 95% CI 24.1-54.5), sensory (RR 21.5; 95% CI, 14.6-31.7) and neurological (RR 13.1; 95% CI 10.8-16). Specific risk-factor associations include: laminectomy (RR 8.6; 95% CI 3.5-21) and chest RT (RR 2.8; 95% CI 1.3-6.5) as risk factors for scoliosis; age < 1 year at diagnosis (RR 1.9; 95% CI 1.4-2.6) and laminectomy (RR 3.5; 95% CI 2.4-5.3) for neurological complications and neck RT (RR 6.6; 95% CI 2.4-18) for hypothyroidism.

Conclusions

NB survivors are at risk of developing chronic health conditions. Long-term surveillance is required for early detection of these complications.

INTRODUCTION

- Increased Overall Survival for Neuroblastoma (NB) patients:
 - 50% (1975-1984)
 - 65% (1985-2002) (SEER data)
- Therapy for low and intermediate risk NB has become less intensive
- High-risk patients continue to fare poorly despite the use of multimodal intensive therapy

OBJECTIVES

- Compare the risk for NB survivors of developing any medical complications relative to siblings
- Evaluate the impact of the type of therapy among survivors
- Assess the role of potential risk factors on the development of a specific medical complication

METHODS

- CCSS cohort of 5-year NB survivors diagnosed between 1970-1986 (n = 832)
- Baseline questionnaire and follow-up surveys
- Medical information abstracted from medical record : chemotherapeutic agents and cumulative doses, surgical procedures, quantitative radiation therapy data
- Comparison group of siblings of cancer survivors (n = 3899)

RESULTS

- Chronic health conditions attributable to treatment

- Musculoskeletal (RR 49.8; 95% CI, 27.9-88.8)
- Endocrine (RR 36.2; 95% CI, 24.1-54.5)
- Sensory (RR 21.5; 95% CI, 14.6-31.7)
- Neurological (RR 13.1; 95% CI, 10.8-16)

- Secondary malignant neoplasm (n = 33)

- Types
 - thyroid (7) - renal (6)
 - soft tissue sarcoma (3) - breast (2)
 - AML (2) - other (13)

- Standardized incidence ratio:
 - 8.6 (95% CI, 5.9-12.1)

- Risk factors:

- Exposure to Radiation Therapy (p=0.003)
- Exposure to Etoposide (p=0.04)

Demographics and health status of study subjects (age adjusted)

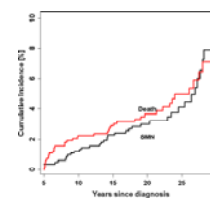
Characteristics	Survivors (%)	Siblings (%)	P-Value
Highest level of schooling*			
Not High School Grad	3.0	2.7	0.86
High School Grad	47.6	45.4	
College Grad	49.4	51.9	
Ever employed*			
No	1.5	0.2	0.02
Total household income (\$)*			
< 19,999	14	10.2	0.004
20,000 - 39,999	31.9	24.0	
40,000 - 59,999	22.6	23.3	
> 60,000	31.5	42.5	
Total home income (\$)*			
< 19,999	41.3	31.9	0.007
20,000 - 39,999	34.9	36.8	
40,000 - 59,999	17.1	18.4	
> 60,000	6.7	12.9	
Health insurance*			
Yes	79.3	79.5	0.44
No	13.8	11.7	
Canadian	6.9	8.8	
Ever married*			
Yes	53.5	47.9	<0.001
General health status†			
No adverse	91.3	95.4	0.01
Adverse	8.7	4.6	
Mental health status‡			
No adverse	93.2	95.6	0.19
Adverse	6.8	4.4	

* NB survivors and siblings, > 25 years old at last follow-up
 † Health status is defined for baseline only, age > 18 years old at baseline questionnaire

Characteristics of NB survivors and sibling cohorts

Characteristics	Survivors (n=832) (%)	Siblings (n=3899) (%)	P-value
Gender			
Male	397 (46)	1975 (48)	0.41
Female	445 (54)	2024 (52)	
Vital status at baseline questionnaire			
Alive	804 (97)		
Dead	28 (3)		
Age at interview (y) at baseline			
< 10	32 (4)	76 (2)	< 0.001
10-19	543 (65)	1010 (26)	
20-29	236 (28)	1381 (35)	
30-39	29 (2)	1116 (29)	
40-49	1 (1)	316 (8)	
Age at interview (y) at latest follow-up			
< 10	9 (1)	12 (1)	< 0.001
10-19	222 (27)	379 (10)	
20-29	409 (49)	1353 (35)	
30-39	137 (17)	1332 (34)	
40-49	5 (1)	823 (21)	
Age at diagnosis (y)			
< 1	458 (55)		
1-4	239 (29)		
5-9	37 (7)		
10-14	12 (1)		
15-21	6 (1)		
Year of diagnosis (y)			
1970-1978	337 (41)		
1979-1984	367 (44)		
1985-1986	128 (15)		
Survival time (y) at baseline			
5-9	97 (12)		
10-14	296 (35)		
15-19	249 (30)		
20-24	163 (20)		
> 25	37 (5)		
Survival time (y) at latest follow-up			
5-9	28 (4)		
10-14	44 (5)		
15-19	236 (28)		
20-24	265 (32)		
> 25	259 (31)		
Treatment groups			
Surgery only	200 (24)		
Surgery + chemotherapy (CT)	217 (26)		
Surgery + radiation therapy (RT)	131 (16)		
Surgery + CT + RT	267 (32)		
Others	17 (2)		

Cumulative incidence of death and SMN in NB survivors



Age-Adjusted ratios of chronic health conditions in NB survivors compared to siblings

Conditions	RR	95% CI	P-Value
Endocrine complications			
Medication needed to initiate puberty	6.2	1.7-24.0	<0.001
Growth hormone deficiency	29.3	10.6-80.9	<0.001
Growth hormone injections	29.3	9.9-88.8	<0.001
Hypothyroidism	6.1	1.7-20.9	<0.001
Musculoskeletal complications			
Scoliosis surgery	20.0	9.6-41.7	<0.001
Osteoporosis	10.7	1.9-29.5	<0.001
Neurological complications			
Weakness in arm or leg	12.1	7.8-18.9	<0.001
Decreased sense of touch, feelings in hands, fingers, arms or legs	5.4	3.7-8.0	<0.001
Prolonged pain or abnormal sensations in arm, leg or back	5.2	3.8-7.2	<0.001
Problems with balance	3.9	2.4-6.5	<0.001
Seizures	3.9	2.3-6.5	<0.001
Tremor or movement problems	3.8	1.8-8.1	<0.001
Paresthesia	3.6	1.8-7.4	<0.001
Sensory complications			
Cataract	6.4	2.3-18.0	<0.001
Hearing loss / deafness	4.1	1.8-9.2	<0.001
Blindness	3.2	1.5-7.5	0.004

CONCLUSIONS

- Mortality and risk of chronic health conditions are significantly higher for NB survivors than for siblings
- High risk of musculoskeletal, SMN, hearing loss, endocrine and neurological complications among NB survivors
- Long-term medical follow-up is required for early detection of medical complications in NB survivors