Neuroblastoma Metastatic to the Central Nervous System: Survival Analyses from the German Childhood Cancer Registry and the Literature

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Abstract

Background: Therapeutic innovation has resulted in an overall decline in childhood mortality from neuroblastoma (NB); however, metastatic NB to the central nervous system (CNS NB), which has emerged as a sanctuary site for NB metastases, remains difficult to treat and is typically fatal. The objective of this study was to describe the natural course of CNS NB.

Methods: Data were sourced from a custom query of the German Childhood Cancer Registry (GCCR) and from relevant published studies. Survival statistics were prepared from a diverse, thus generalizable, pool of CNS NB patients. Data are presented as secondary event-free and overall survival (EFS and OS) after diagnosis of first CNS recurrence from initial high-risk NB.

Results: The GCCR query identified 85 patients with CNS NB diagnosed from 1990–2010, including 57 with isolated CNS disease. The median (95% confidence) EFS and OS times were 2.6 (1.5–3.8) and 4.7 (2.1–7.2) months, respectively, for all CNS NB patients, and 2.8 (1.4–4.1) and 6.8 (2.1–11.5) months, respectively, for isolated CNS NB patients. Secondary OS at 12, 18, and 36 months was 29.4%, 18.8%, and 8.2%, respectively, for all CNS NB patients, and 35.1%, 22.8%, and 12.3%, respectively, for isolated CNS NB patients. Thirteen publications were selected with 83 patients treated from 1979–2013. In addition to an inclusive analysis, a restricted analysis was performed, excluding patients who did not receive therapy with curative intent, to assess survival after therapeutic intervention. Median OS (95% confidence) was 5.6 (3.0–8.0) and 8.7 (5.8–11.0) months in the inclusive and restricted analyses, respectively. The proportion of patients surviving 12, 18, and 36 months at reporting were 24%, 12%, and 3.6%, respectively, for the inclusive population, and 33%, 17%, and 5%, respectively, for the restricted population.

Conclusions: An assessment of the natural course of CNS NB from two sources arrived at similar conclusions with respect to overall and long-term survival. In general, median secondary OS is <6 months and <10% of patients survive 36 months. The findings were consistent across geographic regions and have not changed appreciably in 4 decades.

Background

Primary Neuroblastoma: Treatment Strategies and Trends in Overall Survival

- Innovative therapies to treat primary NB has resulted in improved clinical outlook.
  - Low-risk NB treated with surgery plus observation or chemotherapy with or without surgery; high-risk NB calls for aggressive multimodal approaches, including surgery, chemotherapy, radiotherapy, myeloablative therapy and SCT, and immunotherapy.
  - Over 4 decades, NB-related deaths decreased from 0.35 deaths per 100,000 in 1975-1978 to 0.20 deaths per 100,000 in 2007-2010 (43% reduction).
  - Corresponding 5-year survival rates increased during same time period – in children 1-14 years of age, survival increased from 34% in 1975-1978 to 68% in 2003-2007.

Metastatic Neuroblastoma with Central Nervous System Involvement

- The CNS has emerged as a sanctuary site for metastatic NB in ~6-8% of patients.
- Historically, secondary overall survival after diagnosis of CNS NB, a nearly uniformly fatal disease, is estimated in months.
- Few therapies have demonstrated consistent efficacy in the treatment of CNS NB.
- The objective of the current analysis was to provide a robust evaluation of the natural course of CNS NB within the context of the therapeutic options available at the time of treatment.

Methods

Query of the German Neuroblastoma Trials Office

Patients were treated for primary NB on nationwide induction protocols NB90, NB97, and NB2004.

The inclusion criteria for the query were as follows:

- Diagnosis between 01 January 1990 and 31 December 2010
- International Neuroblastoma Staging System (INSS) Stage 4
- ≥18 months and <21 years of age at initial diagnosis of neuroblastoma
- First diagnosis or first recurrence

Diagnosis of CNS NB was based on one of the following:

- Intracerebral tumorous lesions by MRI or computed tomography
- Neuroblastoma cells in the cerebrospinal fluid
- Nodular and limited thickening of meninges with unequivocal contrast medium uptake

Treatments provided after CNS NB diagnosis are summarized in **Table 1**.

Table 1. German Neuroblastoma Trials: Summary of Treatment Provided

Category	Agent(s)	Number of Patients
Chemotherapy	High-dose chemotherapy	7
	Temozolomide	5
	Temozolomide + irinotecan	3 of 5
	Temozolomide + topotecan	1 of 5
	Topotecan + etoposide	NA
	Other chemotherapy	NA
Radiotherapy	Focal or whole brain	32
	Skull (including intracranial tumor extension)	6
	MIBG radiotherapy + whole brain radiotherapy	4
	MIBG radiotherapy	2

Literature Review

A literature search identified the references listed in **Table 2**. Individual patient information was extracted from the selected publications to generate the following CNS NB analysis populations:

- **Inclusive population:** Included all patients with survival data reported in the selected studies.
- **Restricted population:** Included only those remaining after removing patients who either (1) died before receiving therapy for CNS NB, (2) received only palliative treatment, or (3) presented with rapidly progressing systemic disease at CNS diagnosis.

Table 2. Literature Analysis: References for Included Studies

Study No.	Reference
1	Kellie et al., Cancer 1991;68:1999-2006
2	Shaw and Eden. Med Pediatr Oncol 1992;20(2):144-155
3	Watts RG. Cancer 1992;69:3012-3014
4	Sakata et al., Pediatr Hematol Oncol 1993;10:201-204
5	Astigarraga et al., Med Pediatr Oncol 1996;27:529-533
6	Kramer et al., Cancer 2001;91:1510-1519
7	Matthay et al., Cancer 2003;98:155-165
8	Jaing et al., Med Pediatr Oncol 2003;41(6):570-1
9	Choi et al., Pediatr Blood Cancer 2005;45:68-71
10	Sirachainan et al., Pediatr Blood Cancer 2008
11	Rowland et al., Case Reports in Neurological Medicine 2012
12	Wiens and Hattab. J Neurosurg Pediatr 2014;14:129-135
13	Zhu et al., Chin J Cancer 2015;34:49

Results

Figure 1. German Neuroblastoma Trials: Event-Free and Overall Survival

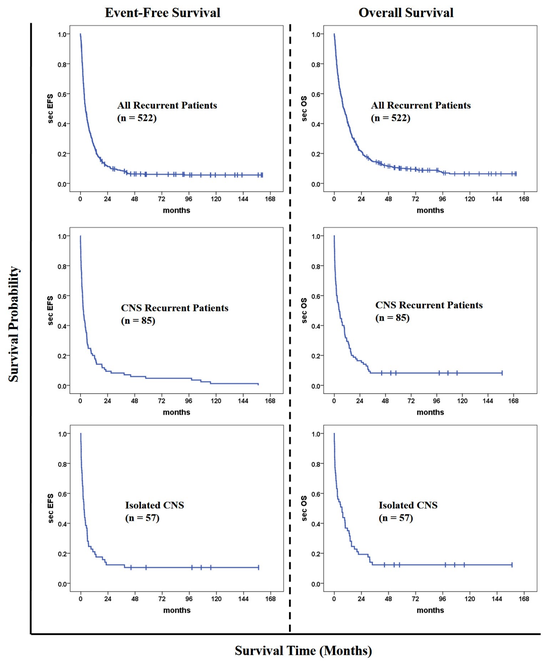


Table 3. German Neuroblastoma Trials: Summary of Survival

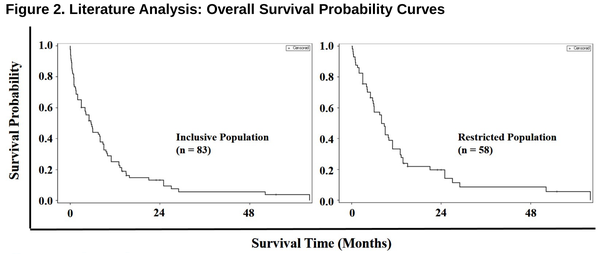
Parameter	All Recurrent (n = 522)	All CNS Recurrent (n = 85)	Isolated CNS Recurrent (n = 57)	CNS + Systemic Recurrent (n = 28)
Age at recurrence: median years (range)	5.3 (1.7–23.3)	4.7 (2.4–19.6)	4.5 (2.8–16.5)	
Secondary EFS: median months (95% CI)	4.4 (3.7–5.2)	2.6 (1.5–3.8)	2.8 (1.4–4.1)	2.2 (1.3–3.1)
Secondary OS: median months (95% CI)	8.3 (6.8–9.8)	4.7 (2.1–7.2)	6.8 (2.1–11.5)	3.8 (0.8–6.8)
12-month survival	40.2 ±2.2%	29.4 ±4.9%	35.1 ±6.3%	
18-month survival	28.3 ±2.0%	18.8 ±4.2%	22.8 ±5.6%	
36-month survival		8.2 ±3.0%	12.3 ±4.3%	

Table 4. Literature Analysis: Summary of Survival, Presented by Study

Study No.	Study Site	Year(s)†	Inclusive Analysis		Restricted Analysis	
			n	Survival range (median)	n	Survival range (median)
1	St. Jude Children's Research Hospital	1979–1988	10	0-64 m (5 m)	6	5-64 m (9 m)
2	Royal Hospital, Endinburgh	1982–1989	6	1-15 m (5 m)	4	1-15 m (8 m)
3	Pediatric Oncology Unit Children's of Alabama	Published 1992	1	14 m	1	14 m
4	Nat Kyushu Cancer Center, Japan	1984–1989	1	24 m	1	24 m
5	Hospital de Cruces, Baracaldo, Spain	Published 1996	4	0.3-3 m (0.4 m)	2	0.3-3 m
6	Memorial Sloan Kettering Cancer Center, New York	1980–1999	11	0.5-25 m (4.2 m)	6	3-25 m (4.2 m)
7	Institute Curie and Gustave-Roussy	1985–2000	23	0.1-52 m (1.6 m)	16	0.2-52 m (5.7 m)
8	Chang Gung Children's Hospital, Taiwan	1995–2002	5	5-23 m (11 m)	5	5-23 m (11 m)
9	Seoul National University Hospital, Korea	2000–2003	4	2-9 m (6 m)	4	2-9 m (6 m)
10	Mahidol University, Bangkok, Thailand	Published 2008	1	13 m	1	13 m
11	Children's Healthcare of Atlanta	Published 2012	2	7.5-15 m	2	7.5-15 m
12	Indiana University Indianapolis	1981–2011	4	4-15.8 m (13.8 m)	2	13.8-15.8 m
13	Sun Yat-sen University Cancer Center	2004–2013	11	0-55 m (4 m)	8	3-55 m (10 m)
TOTAL	**Median (95% confidence interval)**		**83**	**5.6 m (3.0-8.0 m)**	**58**	**8.0 m (5.8-11.0 m)**

† Years in which patients were diagnosed or treated if provided, or year of publication.

Figure 2. Literature Analysis: Overall Survival Probability Curves



Conclusions

Even with advancements in therapeutic strategies, the estimated survival time after CNS NB diagnosis remains unacceptably low; findings were consistent across multiple study sites and treatment modalities.

- Median survival after CNS metastasis ranged from 4.7 to 8.0 months.
- <10% survive at least 36 months.
- Survival times were not appreciably different between CNS NB patients treated in the 1970-1980s and patients treated in the 2000-2010s.