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Original Paper

Event-free Survival of Children with Biologically Favourable Neuroblastoma Based on the Degree of Initial Tumour Resection: Results From The Pediatric Oncology Group

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We analysed the 2-year event-free survival (EFS) of 49 patients 1 year of age and older, with stage 2B or 3 neuroblastoma, treated on Pediatric Oncology Group protocols 8742 and 9244, with respect to the degree of tumour resection at diagnosis. The 2-year EFS rate for 21 children whose tumours were completely resected at diagnosis was 85% (SE = 10%) compared with an EFS rate of 70% (SE = 9%) for the 28 children whose tumours were incompletely resected at diagnosis. Despite the observed trend in favour of complete resection, these EFS curves were not statistically significantly different ($P = 0.259$). Patients with favourable Shimada histology tumours had an EFS rate of 92% (SE = 7%) compared with a rate of 58% (SE = 15%) for patients with unfavourable histology tumours. EFS curves for the two histologic groups were significantly different ($P = 0.009$). The impact of aggressive surgery and adjuvant chemotherapy on the outcome of patients with biologically favourable regional neuroblastoma is still unclear. © **1997 Elsevier Science Ltd.**

Key words: stage 2B/3 neuroblastoma, chemotherapy, surgery, Shimada, histology
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INTRODUCTION

THE TREATMENT of regional neuroblastoma has historically consisted of surgery and some combination of chemotherapy and radiation therapy. The degree of tumour resection may have a significant impact on survival. This was observed in the Pediatric Oncology Group (POG) protocol 8742 for children with POG stage C neuroblastoma (data not shown). The POG staging system, used prior to the development of international staging criteria, defined stage C disease as that in which metastatic disease from a completely or incompletely excised primary tumour was confined to non-adherent regional lymph nodes, generally within the same cavity as the primary tumour. The results of protocol 8742 indicated that the patients whose tumours were completely resected at diagnosis had a significantly better rate of continuous complete response and event-free survival (EFS) than those patients whose tumours were incompletely resected at diagnosis ($P < 0.05$) (data not shown). To determine if the extent of initial tumour resection significantly influenced the ultimate outcome of therapy in a larger group of patients, the results of two consecutive POG protocols were analysed for children 1 year of age and older with biologically favourable regional neuroblastoma, i.e. *MYCN* non-amplified International Neuroblastoma Staging System (INSS) stages 2B and 3 disease.

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PATIENTS AND METHODS

Patients were eligible for this retrospective analysis if the following criteria were met: stage 2B or 3 *MYCN* non-amplified neuroblastoma was identified at diagnosis, the patient was treated on protocol 8742 or 9244, and treatment and

follow-up data were available. Disease stages were reassigned prior to data analysis to conform with the revised international criteria [1].

A similar approach to therapy was used in the two studies. Maximum safe tumour resection was performed initially. If possible, regional lymph node biopsies were obtained during this procedure, particularly in patients with unilateral tumours. However, if the primary tumour was too large to safely access lymph nodes, the tumour was biopsied and patients were assigned to POG stage C (protocol 8742) or to INSS stage 3 (protocol 9244) without pathological confirmation of lymph node involvement. To be included in the data analysis for this paper, cases without pathological confirmation of lymph node involvement were assigned to stage 2B or 3 only if there were surgical observations or diagnostic images which clearly indicated bilateral extension of tumour or non-adherent regional lymph node enlargement.

The first tumour resection was followed by five courses of induction chemotherapy. The chemotherapy on protocol 8742 consisted of intravenous high-dose cisplatin (40 mg/m^2/day) on days 1–5 with etoposide (200 mg/m^2/day) on days 2–4, alternated every 3 weeks with oral cyclophosphamide (150 mg/m^2/day) for 7 days followed on day 8 by intravenous doxorubicin (35 mg/m^2). The chemotherapy on protocol 9244 consisted of alternating courses, every 3 weeks, of OPEC (vincristine 1.5 mg/m^2, cisplatin 80 mg/m^2, etoposide 200 mg/m^2, cyclophosphamide 600 mg/m^2) and OJEC (vincristine 1.5 mg/m^2, carboplatin 500 mg/m^2, etoposide 200 mg/m^2, cyclophosphamide 600 mg/m^2). The induction chemotherapy was followed by a second surgical procedure to confirm disease status or to remove or debulk residual tumour. This was followed by maintenance chemotherapy with the same drugs as those in use during induction. External beam radiation therapy (RT) was given concurrently with maintenance chemotherapy to patients who had residual gross or microscopic disease after their second operation. For children aged 12 to 24 months on day one of RT, 24 Gy in 1.5 Gy/fraction was given. Children older than 24 months received 30 Gy in 1.5 Gy/fraction.

The median length of follow-up on study 8742 was 54 months; on study 9244 it was 23 months. The median length of follow-up was 30 months for the combined protocols. For analysis of event-free survival (EFS), events were defined as the following: relapse, progression of disease, second malignancy or death. Since chemotherapy used in the two protocols might have independently contributed to differences in EFS, and because of unequal length of follow-up of the two protocols, analyses were conducted separately for each protocol as well as for both protocols combined. EFS curves were estimated using the method of Kaplan and Meier. Log-rank tests were used for comparing the survival curves and Fisher's exact tests were used for testing association in 2×2 tables.

Table 1. *Estimated two-year EFS rates following complete and incomplete resection of disease at diagnosis*

Patient group	Extent of resection	*N*	EFS % (SE %)		*P**
All	Complete	21	85	(10)	0.259
	Incomplete	28	70	(9)	
Stage 2B	Complete	15	86	(13)	0.475
	Incomplete	5	80	(18)	
Stage 3	Complete	6	83	(17)	0.636
	Incomplete	23	78	(9)	
8742	Complete	8	88	(12)	0.448
	Incomplete	15	73	(11)	
9244	Complete	13	83	(20)	0.410
		13	65	(16)	

*Log-rank *P* value for comparing the complete and incomplete EFS curves.

RESULTS

Of the 62 patients enrolled on these protocols whose tumours lacked amplification of *MYCN*, 1 patient with stage 1 disease and 10 patients with stage 2A disease were excluded from analysis. Two other patients were excluded for lack of treatment data. In total, there were 49 evaluable patients from both protocols, 23 from protocol 8742 and 26 from protocol 9244. Twenty patients had stage 2B disease and 29 had stage 3. Of the 21 patients who had complete resection of their disease at diagnosis, 15 had stage 2B disease compared with 6 with stage 3 disease. An incomplete resection of the tumours in the remaining 28 patients most commonly consisted of a biopsy.

Table 1 summarises the estimated 2-year EFS rates achieved with therapy following complete and incomplete resection of disease at diagnosis. The number of patients on each protocol was small, but when the protocols were combined, a 2-year EFS rate of 85% (SE = 10%) was estimated for patients who underwent complete tumour resection at diagnosis. The corresponding estimate was 70% (SE = 9%) for patients who had incomplete resection of tumour at diagnosis. There was no statistically significant difference in EFS curves for these two groups of patients ($P = 0.259$, Figure 1), despite the trend we observed for higher rates of EFS following complete resection of disease.

Two of the events in the group of patients with incomplete initial resection were early deaths during therapy, one from infection and the other from intratumoral haemorrhage. 7 patients relapsed. On protocol 8742, relapse was ultimately associated with death. After treatment on protocol 9244, however, 3 of 4 patients who relapsed remain alive and disease free after other therapy. Four patients from both protocols are alive with biopsy-proven stable disease and no further neuroblastoma therapy; 1 of these patients developed leukaemia as a second malignancy.

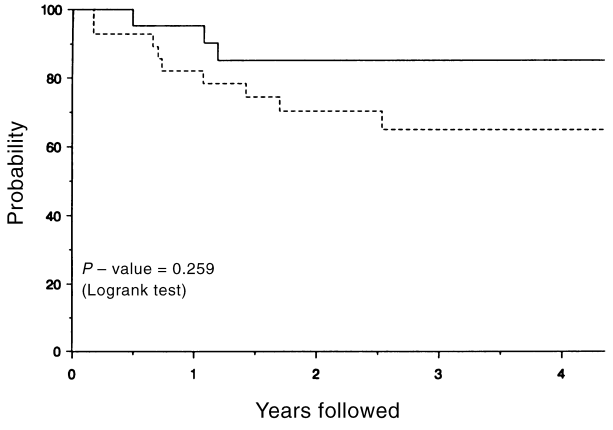

Figure 1. EFS of patients following complete (——) and incomplete (- - - -) resection of disease at diagnosis.

The effect of histology on degree of initial tumour resection and ultimate patient outcome was examined. On protocol 8742, 11 patients had favourable histology and 6 had unfavourable histology by Shimada criteria. On protocol 9244, favourable and unfavorable histology was seen in 13 and 9 patients, respectively. Histology was not determined for 4 patients on protocol 8742 and on 6 patients on protocol 9244. The difference between the proportions of favourable histology patients in the two groups was not statistically significant ($P = 0.75$). Thirteen of the 24 (54%) patients with favourable histology tumours had a complete tumour resection at diagnosis compared with 6 of 15 (40%) with unfavourable histology tumours. Thus, histology of tumours did not have a significant association with the surgeon's ability to resect disease at diagnosis ($P = 0.51$). The EFS curves for the favourable and unfavourable histology groups did not differ significantly on protocol 8742 ($P = 0.272$), but on protocol 9244 and for the protocols combined, there were significant differences ($P = 0.016$ for protocol 9244 and 0.009 for the combined protocols).

When the data were analysed by the histological classification of Joshi, similar results were obtained for the combined group of 37 patients for whom Joshi histological grades were available. In these analyses, grades 2 and 3 tumours, associated with a poorer prognosis in older children, were combined for comparison of EFS rates of patients with grade 1 tumours. The results are summarised in Table 2.

EFS and overall survival rates achieved on each protocol are shown in Table 3. For the combined protocols, the rate of two-year EFS was 76% (37/49 patients). Of the 37 patients who survived event-free, 11 (30%) received RT. On protocol 8742, the 2-year EFS rate was 70%; on protocol 9244, the corresponding rate was 81%. The overall survival rate for the combined studies was 84%. Because RT was not randomised to patients on either of the two protocols, its impact on EFS and ultimate overall survival could not be determined.

Table 2. Estimated EFS by histology

Histology	Group	*N*	EFS %	(SE %)	*P**
Shimada	Favourable	24	92	(7)	0.009
	Unfavourable	15	58	(15)	
Joshi	Grade 1	16	93	(7)	0.035
	Grade 2 or 3	21	71	(13)	

*Log-rank *P* value for comparing the EFS curves for histology groups.

Table 3. EFS (two-year) and overall survival(s) rates achieved for all patients on each protocol and for the protocols combined

		EFS		S	
Study		*n*	%	*n*	%
8742	(*n*=23)	16	70	17	74
9244	(*n*=26)	21	81	24	92
Combined	(*n*=49)	37	76	41	84

DISCUSSION

The impact of initial tumour resection on the ultimate outcome of patients with regional neuroblastoma defined by INSS staging criteria (stages 2B and 3), who are treated with chemotherapy or radiation therapy in addition to surgery, has not been analysed before. However, the role of surgery in multimodality therapy has been reported within the context of the Evans' staging system by several investigators [2–6]. Of these reports, one by Haase and associates is most comparable to this analysis. In 58 patients 1 year of age and older with Evans stage III neuroblastoma, comparable to INSS stage 3 disease, the degree of initial tumour resection did not significantly correlate with event-free survival [2]. There was, however, a clear trend towards higher EFS rates following complete resection at diagnosis, similar to the findings in this analysis. The influence of Shimada histology on surgical resectability and EFS rates was also comparable.

In smaller series which combined patients with Evans' stage III and IV disease, complete resection of disease has been associated with significantly higher survival rates, but the effect on patients with stage III disease is difficult to assess [3, 4]. In other reports, no difference in survival was seen between patients having complete or incomplete resection of stage III disease [5, 6]. In fact early complete resection of disease was associated with a higher rate of surgical complications [5].

It might be argued that the lack of difference in outcome between patients with completely and incompletely resected tumours is attributable to the use of chemotherapy or RT. However, in the subset of patients 1 year of age and older with stages 2B and 3 neuroblastoma, the use of any adjuvant therapy at all is challenged by the experiences reported by Matthay [7] and by Kushner [8]. Using surgery only, achieving complete or partial resection of disease, 80% of patients with Evans' stage II disease [7] and 88% of patients with INSS stages 2B and 3 disease [8] survived without progression of disease and without the use of adjuvant chemotherapy or radiation therapy. The survival rates in both series were 100%. This treatment approach needs to be studied in a much larger group of patients, but the results suggest that, for patients with biologically favourable tumours, that is, those lacking amplification of the *MYC*N oncogene, the use of chemotherapy might be safely restricted to a relatively few specific conditions.

For patients with biologically favourable regional neuroblastoma, we will need to determine if the use of adjuvant chemotherapy has any impact at all on survival. What role aggressive surgery plays in the outcome for these patients, beyond the establishment of diagnosis and biological characteristics, also remains to be defined, since even partial resection may be associated with apparent cure in a subset of patients. These questions will be answered in future cooperative group studies wherein adjuvant chemotherapy and RT will be reduced in an increasing proportion of patients with biologically favourable tumours in an effort to avoid their associated acute and long-term complications.

For patients with biologically unfavourable tumours, survival rates remain intermediate to those for infants with all stages of neuroblastoma and those for children with widely disseminated disease. For these patients, randomised trials are needed to determine the optimal use of chemotherapy and RT. Continued identification of prognostic biological factors will further aid in the development of risk-based treatment regimens.

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APPENDIX

Institution	Grant no.
Alberta Pediatric Oncology Consortium, Edmonton, Canada	
All Children's Hospital, St. Petersburgh, Florida	
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Ochsner Clinic, New Orleans, Los Angeles	
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POG Operations Office, Chicago, Illinois	CA-30969

contd.

APPENDIX *contd.*

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