

# Favorable Biology and Outcome of Stage IV-S Neuroblastoma With Supportive Care or Minimal Therapy: A Children's Cancer Group Study

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**Purpose:** Stage IV-S neuroblastoma is a metastatic disease associated with spontaneous regression and good survival, but 10% to 20% of infants die from early complications. The purpose of this study was to evaluate outcome and prognostic factors in infants with stage IV-S neuroblastoma treated prospectively with supportive care only or, in symptomatic patients, with low-dose cytotoxic therapy.

**Patients and Methods:** Eighty eligible infants were studied for response and survival with supportive care or, for symptomatic patients, cyclophosphamide 5 mg/kg/d for 5 days with or without hepatic radiation of 4.5 Gy over 3 days. Staging was reviewed centrally, and MYCN gene copy number, Shimada histopathologic classification, serum ferritin levels, and bone marrow immunocytology were determined.

**Results:** Stage IV-S and International Neuroblastoma Staging System stage 4S were 98% concordant. MYCN was not amplified in any of the tumors tested (n = 58), and Shimada histopathologic classification was favorable in 96% (n = 68/71). The 5-year event-free survival (EFS) rate for all infants was 86% and the survival rate was 92%. Supportive care was the only

treatment provided for 44 (55%) of 80 infants, and their 5-year survival rate was 100%, compared with 81% survival for those requiring cytotoxic therapy for symptoms (P = .005). Five of six deaths were in infants younger than 2 months of age at diagnosis and were due to complications of extensive abdominal involvement with respiratory compromise or disseminated intravascular coagulation. Although age  $\leq$  3 months at diagnosis was significant for EFS (P = .043), it was less significant for survival (P = .077). The only other significant factor predictive for improved survival was favorable Shimada histopathologic classification. Sites of metastatic involvement (liver, skin, or bone marrow) and surgical resection of the primary tumor were not significant for survival.

**Conclusion:** This study confirms the favorable biologic features and excellent survival of infants with stage IV-S neuroblastoma with minimal therapy. Infants younger than 2 months old at diagnosis with rapidly progressive abdominal disease may benefit from earlier and more intensive treatment.

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STAGE IV-S NEUROBLASTOMA describes a specific metastatic pattern of a tumor of the peripheral nervous system. This pattern is seen almost exclusively in infants and is associated with a high survival rate and spontaneous maturation and regression, often without the necessity for cytotoxic therapy. Originally defined as a unique group by D'Angio, Evans, and Koop in 1971,<sup>1</sup> the definition for this stage has been clarified by the recently adopted International Neuroblastoma Staging System (INSS). INSS 4S is defined as tumor in an infant less than 1 year of age with metastases restricted to the liver, skin, and bone marrow (< 10% tumor) in whom the primary tumor is localized (INSS 1 or 2), that is, there is no infiltration across the midline or contralateral lymph node involvement.<sup>2</sup> Retrospective studies indicate that the disease-free survival for children with stage IV-S ranges from 70% to 97%.<sup>3-14</sup> Although many infants seem to require little or no therapy, the role of radiation therapy, surgery, and chemotherapy for those infants with progressive or symptomatic disease remains controversial.<sup>5,15,16</sup> Some studies have indicated that MYCN oncogene amplification and other biologic factors may be associated with poor survival, even in stage IV-S.<sup>17-19</sup> We report a prospective study of stage IV-S

neuroblastoma in infants less than 1 year of age conducted to evaluate the outcome with supportive care only or, for symptomatic infants, with low-dose cytotoxic therapy and to determine tumor biologic and clinical prognostic features.

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## PATIENTS AND METHODS

Children's Cancer Group (CCG) protocol 3881 (open from June 1989 to August 1995) registered patients with good-, intermediate-, and selected poor-risk neuroblastoma. Eighty infants were eligible with stage IV-S neuroblastoma after central staging review of all 507 infants entered onto the CCG-3881 study. Three of these patients, who were initially registered as stage IV, received combination chemotherapy intended for stage IV disease and these three are excluded from the analysis of effect of therapy on survival. Institutional human research committee approval and appropriate informed consent were obtained for all patients.

Evans staging for stage IV-S disease was used, as previously described, to include infants with small primary tumors that did not cross the midline and were associated with metastases limited to skin, liver, and bone marrow.<sup>3</sup> INSS 4S criteria differ from those for stage IV-S in that the age at diagnosis is explicitly limited to infants less than 1 year and bone marrow involvement is limited to less than 10% malignant cells on biopsy or aspirate. Patients who did not have the surgical exploration required for rigorous INSS staging were classified on the basis of radiologic and clinical evaluations. Minimum staging studies included appropriate radiologic imaging of the primary tumor with ultrasound, computed tomography, or magnetic resonance imaging; bilateral bone marrow aspirate and biopsy; urine catecholamines; and either skeletal survey or bone scan. Surgical staging was encouraged for infants who were not severely compromised. Central review of staging was performed by three experienced surgeons and two oncologists and included review of data forms, operative and pathology reports, and, in some cases, radiology reports. Infants less than 2 months of age with massive liver enlargement were considered poor surgical candidates, and diagnostic material was obtained by percutaneous needle biopsy of the liver or by biopsy of skin lesions when present.

Shimada histopathology of tumor specimens was centrally reviewed and reported as favorable or unfavorable, as previously described.<sup>20</sup> Bone marrow immunocytology (sensitivity of one tumor cell per 10<sup>5</sup> nucleated bone marrow cells) was performed in the CCG Neuroblastoma Reference Laboratory.<sup>21</sup> Local institutions obtained serum at diagnosis for ferritin determination by radioimmunoassay.<sup>22</sup> The *MYCN* gene copy number was determined by the Neuroblastoma Reference Laboratory by using either Southern analysis of DNA<sup>23</sup> or, after 1993, analysis of *MYCN* protein expression by semiquantitative polymerase chain reaction<sup>24</sup> and immunoperoxidase stain.<sup>25</sup>

All infants were treated with supportive care alone, unless there was respiratory or renal compromise caused by massive liver enlargement or evidence of disease progression. Rapid tumor growth and impending compromise of vital organ functions were indications for chemotherapy with or without radiation therapy, after consultation with the study chair. When chemotherapy was given, a 5-day course of cyclophosphamide at 5 mg/kg/d, either orally or intravenously, was used. This treatment could be repeated at 2-week intervals if the absolute neutrophil count was greater than 1,000/ $\mu$ L. Cyclophosphamide was to be discontinued at the first indication of tumor regression or resolution of symptoms. Radiation therapy was administered as cross-table hepatic radiation daily for 3 days (total of 4.5 Gy).

Life table methods were used to estimate the event-free survival (EFS) from time of diagnosis.<sup>26</sup> The Fisher exact test from the permutation distribution of the log-rank statistic was used to compare the EFS probabilities between subgroups of patients.<sup>27</sup> For all analyses of outcome by treatment, three patients who were originally mistakenly

Table 1. Tumor Distribution for 80 Stage IV-S Infants

Primary Tumor Site	No. of Infants	Additional Sites of Disease			
		Liver	Bone Marrow	Skin	Lymph Nodes
Adrenal*	59	52	17	10	4
Chest	7	5	3	0	2
Abdominal-thoracic	4	1	4	0	0
Celiac	1	1	0	0	0
Neck	4	2	2	0	0
Unknown	4	3	0	1	1
Other	1	1	1	0	0
Total	80	65	27	11	7

NOTE. Each infant may have one, two, three, or four additional sites of disease. Bone marrow tumor was detected by bone marrow aspiration or biopsy using light microscopy at the primary institution.

\*Includes five infants with bilateral adrenal primary tumors.

classified as having stage IV disease and treated more intensively were excluded.

## RESULTS

*Patient Characteristics and Staging*

Eighty eligible infants met central criteria for stage IV-S neuroblastoma. Only one of the infants classified as having Evans stage IV-S disease did not meet the INSS 4S criteria because of 45% tumor cells in the bone marrow. Sites of primary and metastatic tumor distribution are shown in Table 1. The majority (74%) of patients had an adrenal primary site, and the liver was the most common metastatic site (81%), with bone marrow metastases in only 34% of infants and skin metastases in 14%. Regional lymph node involvement was rare, as one would expect with primary type limited to stage I or II tumors.

*Surgical Resection*

Open surgical procedures were performed in 49 infants, including 42 procedures at diagnosis, five delayed explorations, and five second explorations. Complete primary tumor resection was achieved in 31 patients, with 25 resections at diagnosis, five at delayed surgery, and one at second surgery. Of the other 18 patients, there were six whose best resection left microscopic residual, two with partial resection (< 50% tumor remaining), and 10 with biopsies only (> 50% tumor remaining). Thirty-one infants had no open surgical procedures but were staged by magnetic resonance imaging or computed tomography. Diagnosis was verified in these cases by needle biopsy of the primary tumor or liver, skin, or bone marrow and urinary catecholamines. Two infants required silastic abdominal pouches for rapidly expanding abdominal disease and both died.

**Table 2. Treatment of 77 Infants With Stage IV-S Neuroblastoma**

Treatment	Age	
	0-2 Months	> 2 Months
Supportive only	12	32
Radiation and chemotherapy	17	5
Chemotherapy alone	6	4
Radiation alone	0	1
Total no. of patients	35	42

NOTE. Three additional patients initially categorized as having stage IV disease were treated with combination chemotherapy.

Five infants had bilateral adrenal primary tumors, and one of the five had both primary tumors resected. The other four had only partial resection ( $n = 1$ ) or biopsy only ( $n = 3$ ). One of these patients had bilateral adrenal disease detected at autopsy, and in one patient the adrenal disease was in situ. Except for bilateral adrenal disease, these patients met the criteria for stage IV-S and were similar to other cases reported.<sup>28,29</sup>

#### Cytotoxic Therapy

Supportive observation after surgical or clinical staging was the only therapy in 44 infants (55%), whereas cytotoxic therapy as prescribed by protocol was given to 33 patients. Thirteen asymptomatic patients did not have surgical resection of their primary tumor and had no further antitumor treatment, and all are surviving free of disease. An additional three patients were excluded from the therapy analysis because they received combined-modality therapy as prescribed on CCG-3881 for infants with stage III and IV disease.<sup>30</sup> Cytotoxic therapy included radiation only in one patient, chemotherapy only in 10 patients, and both modalities in 22 patients. Of the patients treated with chemother-

apy who survived, 24 had only a single course of cyclophosphamide, two patients received two courses, and one additional patient initially treated with two courses of cyclophosphamide went on to receive additional treatment with cisplatin, etoposide, and doxorubicin. Treatment of the patients who died included multiagent chemotherapy in two patients, cyclophosphamide in three patients, and radiation only in one patient. Supportive care alone was used in 32 (76%) of 42 infants older than 2 months at diagnosis, compared with only 12 (34%) of 35 infants  $\leq 2$  months of age (Table 2).

Radiation therapy to the liver and/or abdomen was given to 23 patients. Eighteen patients received 4.5 Gy over 3 days. Two additional patients received 6 and 2.4 Gy at the discretion of their investigators, and data were not available on the remaining three. Twenty-two of the 23 patients who received radiation therapy were given intravenous or oral cyclophosphamide; one patient received radiation alone.

#### Outcome

The overall 5-year EFS rate was 86% and the survival rate was 92%, with a median follow-up of 43 months (range, 0.6 to 88 months). Progressive disease, defined as an increase in tumor size or development of new tumors, developed as the first event in eight infants. Three of them died of their disease, while the remaining five improved with further therapy and are now surviving at 4 to 6 years from the time of disease progression. The sites of progression in these eight patients were the liver (five patients), the adrenals (four patients), the lymph nodes (three patients), the bone marrow (two patients), and the lung, neck, chest, and bone (one patient each). Three of the patients with disease progression met criteria for stage IV disease at the time of progression. Two other infants developed progres-

**Table 3. Deaths**

Age at Diagnosis (days)	Disease Sites		Biology		Protocol Therapy	Survival (days)	Cause of Death, Additional Therapy
	Primary	Metastatic	MYCN	Shimada			
1	Adrenal	Liver	NA	U	RT, Cy	43	Progression with respiratory failure from enlarging liver despite a silastic graft, doxorubicin, cisplatin, etoposide
4	Adrenal	Liver, BM	NA	ND	RT, Cy	136	Liver failure from unresponsive disease, ventilator-dependent, unresponsive to two cycles of cyclophosphamide, etoposide, cisplatin
18	Neck	Adrenal	ND	F	RT, Cy	100	Aspiration into tracheotomy, initial good response from two courses of cyclophosphamide
20	Unknown	Liver	NA	F	RT, Cy	23	Progression with liver enlargement, ventilator-dependent, no improvement with initial therapy
54	Adrenal	Liver, BM	ND	ND	RT, Cy	42	Hemorrhage after abdominal silastic graft for progressive disease in rapidly enlarging abdominal mass; bone marrow had 45% tumor cells
72	Adrenal	Liver	NA	U	RT	2	Progressive liver enlargement with disseminated intravascular coagulation; at autopsy had liver and bilateral adrenal disease

Abbreviations: BM, bone marrow; NA, nonamplified MYCN; U, unfavorable Shimada; F, favorable Shimada; ND, not done; RT, radiation therapy to liver; Cy, cyclophosphamide.

**Table 4. Prognostic Factors, EFS, and Overall Survival for 80 Infants With Stage IV-S Neuroblastoma**

Risk Factor	Comparison		5-Year EFS (%)		P*	5-Year OS (%)		P*
	A	B	A	B		A	B	
Age	> 2 mo v ≤ 2 mo		93	77	.051	98	86	.081
Age	> 3 mo v ≤ 3 mo		97	79	.043	100	88	.077
Liver metastases	No v yes		87	86	.99	100	91	.59
Bone marrow metastases by light microscopy	No v yes		91	77	.17	92	92	.99
Skin metastases	No v yes		85	91	.99	91	100	.59
MYCN gene copy†	NA v A		86	—	—	93	—	—
Histopathology‡	F v U		93	33	.024	97	33	.007
Ferritin	< 143 v ≥ 143 ng/mL		93	79	.227	96	88	.32
BMI§	Negative v positive		100	80	.083	100	87	.20
Surgical resection	CR/MR v PR/Bx		92	82	.584	100	91	.25
Cytotoxic therapy	No v yes		93	75	.047	100	81	.005

Abbreviations: BMI, bone marrow immunocytology; NA, not amplified; A, amplified; F, favorable; U, unfavorable; CR/MR, complete resection or microscopic residual; PR/Bx, partial resection or biopsy; OS, overall survival.

\*All P values were determined using Fisher's exact test.

†There were no tumors with MYCN amplification.

‡Only three patients had tumors with unfavorable histopathologic characteristics. Two of these developed progressive disease and died within 2 months of study entry.

§A negative BMI indicates that there was less than one tumor cell per 10<sup>5</sup> nucleated cells.

||The three patients treated with the combination therapy for stage IV infants because of initial staging were excluded from this analysis.

sive disease and died, with death as the first event (Table 3). In all, six infants with stage IV-S died. These infants were 1 to 72 days of age at diagnosis and four of six survived 43 days or less. Four of the deaths were due directly to complications of progressive or unresponsive abdominal disease, and all were in infants diagnosed before 2 months of age. The fifth infant had bilateral adrenal disease and liver involvement and died of widespread disseminated intravascular coagulation as a terminal event. The sixth infant died from aspiration after an initial response to cyclophosphamide.

#### Biologic and Clinical Prognostic Features

The MYCN oncogene was not amplified in any of the tumors tested (n = 58). Fewer samples were assessable for the MYCN determination than for the Shimada classification because of the requirement for supplemental frozen tissue. Since 31 patients had only a biopsy at diagnosis, rather than a complete surgical excision, adequate samples were not always available. The Shimada histopathologic classification was favorable in 68 (96%) of 71 infants. Two of the three children whose tumors showed unfavorable histopathology died. Their ages were 1 and 72 days at diagnosis. Initial serum ferritin levels were elevated above 143 ng/mL in 24 of 52 infants. Seventeen of these 24 were 2 months (60 days) of age or younger at diagnosis and only three of the infants with elevated ferritin levels died. Bone marrow immunocytology was positive in 15 (47%) of 32 infants. Only four of 32 infants had greater than 100 tumor cells per

10<sup>5</sup> nucleated bone marrow cells present by immunocytology, indicating that there was more than 0.1% tumor. Bone marrow by light microscopy was positive in 27 (34%) of 80 infants. Thirty-five (44%) of 80 patients had bone marrow involvement as detected by either light microscopy or bone marrow immunocytology. Although the 5-year EFS and survival rates were greater for those patients with negative bone marrow immunocytology than for those with positive immunocytology, these differences were not significant (Table 4). Bone marrow by simple light microscopy, available in the majority of patients, also did not significantly predict for either EFS or survival.

Clinical and biologic prognostic factors for EFS and survival are shown and compared in Table 4. Unfavorable histopathology and the use of cytotoxic therapy, given to symptomatic infants, were significant unfavorable risk factors for both EFS and for survival. Despite the fact that five of six deaths occurred in infants less than 2 months of age at diagnosis and in all six at less than 3 months, the difference in survival for both the 2-month and 3-month age cut-off was not significant using Fisher's exact test. However, younger infants ≤ 2 months of age at diagnosis presented with symptoms requiring cytotoxic therapy twice as frequently as older infants. The 5-year survival rate for those requiring treatment was 78% for infants ≤ 2 months at diagnosis (n = 23), compared with 90% for those older than 2 months at diagnosis (n = 10; P = .64). There was equally excellent survival of 92% and 100% for asymptomatic infants age ≤ 2 months or more than 2 months,

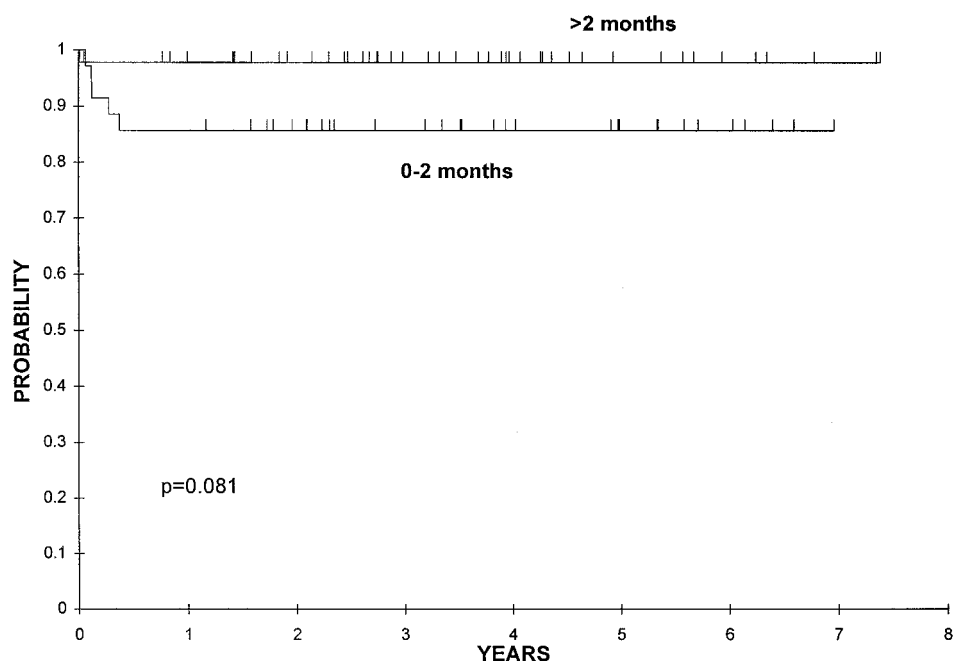


Fig 1. Survival of 80 infants with stage IV-S neuroblastoma who are 0 to 2 months old ( $n = 35$ ) versus older than 2 months ( $n = 45$ ) at diagnosis.

respectively ( $P = .99$ ). The 5-year survival rate for all infants older than 2 months of age at diagnosis was 98%, compared with 86% for those 0 to 2 months of age (Fig 1). The 5-year survival rate for infants requiring cytotoxic therapy was 81%, compared with 100% survival for those who did not require treatment (Fig 2). Sites of metastases, including bone marrow by light microscopy, skin, and liver, were not significant for EFS. Complete gross resection of the primary tumor did not confer an advantage for EFS ( $P = .58$ ) or survival ( $P = .25$ ).

#### DISCUSSION

The current study demonstrates that the majority of children with accurately classified stage IV-S neuroblastoma have biologically and clinically favorable tumors and require minimal therapy. CCG stage IV-S in this study was completely concordant with the newer, agreed upon international staging system, except in one infant with 45% bone marrow tumor.<sup>2</sup> We included five infants with bilateral adrenal primary tumors that otherwise conformed to INSS 4S criteria. Bilateral synchronous tumors have not previously been included in the definitions, but in INSS stage 4S, multifocal tumors have been included.<sup>2</sup> Other reports have confirmed the high probability of survival with bilateral adrenal neuroblastoma.<sup>31,32</sup>

Surgical staging was possible in 61% of the infants studied. The smaller infants with large abdominal masses or extensive liver replacement at diagnosis were not good candidates for surgical staging and were therefore staged by

needle biopsies and imaging studies. In many of these infants, it was not possible to obtain adequate specimens for biologic studies or to remove the primary tumor. This problem has been previously described in other critically ill infants with stage IV-S disease and is associated with decreased EFS.<sup>31</sup> It is theoretically possible that the biologic features of tumors that could not be safely sampled were actually less favorable than those of the group as a whole. This is unlikely, however, since infants in the symptomatic group who did have tumor samples had no genomic amplification of *MYCN* and, except in two cases, favorable histologic characteristics.

Complete gross surgical removal of the primary tumor was performed in 37 of the 49 infants who underwent an open surgical procedure. The EFS and survival rates for the group with gross resection, although higher, were not significantly different from those of infants with partial resection or biopsy (Table 4). We did not test the hypothesis of whether any surgery was necessary, although the fact that 13 infants had neither surgical resection nor any cytotoxic therapy and are surviving free of disease is further evidence against the need for complete surgical resection. This result is similar to results in previous studies, including an Italian report of a retrospective 15-year follow-up of 73 stage IV-S infants, in which the EFS rate was 92% with resection compared with 89% without removal of the primary tumor,<sup>32</sup> and the recent Pediatric Oncology Group (POG) report of 110 stage IV-S (POG stage Ds) infants on two consecutive protocols in which survival was 90% for those

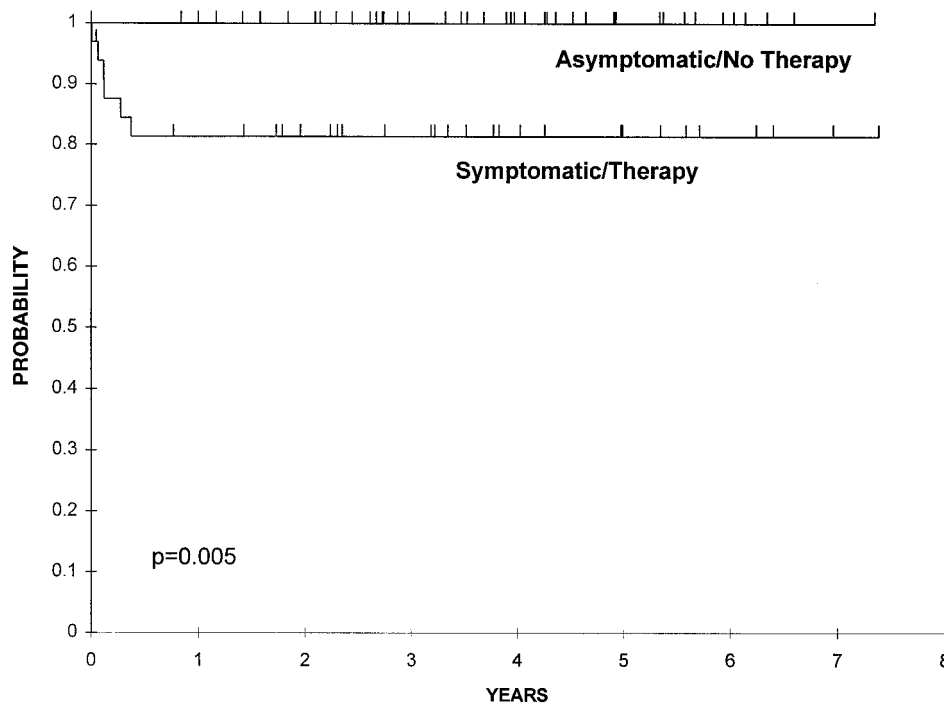


Fig 2. Survival for asymptomatic infants requiring no cytotoxic therapy (n = 44) compared with that of symptomatic infants receiving therapy (n = 33).

with resection compared with 78% for those without ( $P = .083$ ).<sup>18</sup>

In stage IV-S disease, the *MYCN* oncogene is rarely amplified.<sup>33</sup> None of the 58 infants tested in the study reported here had *MYCN* gene amplification. One possible reason is statistical chance, since *MYCN* amplification is found in less than 10% of infants with stage IV-S disease. A second explanation may be that the incidence of *MYCN* amplification is even lower than previously reported in children with verified stage IV-S neuroblastoma. All infants in this study were subjected to careful central review of their staging by three surgeons and two oncologists. As a result, four infants who were originally registered, including the only three with *MYCN* amplification, were reclassified as having stage IV disease (one bone metastasis and three primary tumors that invaded across the midline or had extensive bilateral nodal involvement). A third possibility is that *MYCN* is more frequently amplified in symptomatic patients, in whom one might postulate that it is more difficult to obtain the sample for testing. The proportion of children with symptomatology who did not have measurement of *MYCN* (14 of 38) was higher than the proportion without symptoms who did not have measurement of *MYCN* (eight of 44). The more recent change in methodology to fluorescent in situ hybridization for detection of *MYCN* amplification will allow measurement from touch preparations in future studies. In cases of prenatally diagnosed stage

IV-S disease, 16 of 16 infants tested also had tumors without *MYCN* amplification.<sup>34</sup> Seventeen other reported stage IV-S infants have shown a lack of *MYCN* amplification, and all of them survived.<sup>35-38</sup> However, in a recent series of 110 stage DS infants, nine of 94 tested had *MYCN*-amplified tumors, ie, more than three copies, and the survival of these infants was significantly lower than that for infants without tumor *MYCN* gene amplification ( $P < .001$ ).<sup>18</sup> In a smaller series of 25 stage DS infants, none of 11 tumors showed *MYCN* amplification.<sup>39</sup> Hyperdiploidy, also a favorable prognostic factor in infants with stage IV-S disease,<sup>18,37,39</sup> was not assessed in the current study. Although a few infants with stage IV-S neuroblastoma and *MYCN* gene amplification have been reported with a good outcome,<sup>38</sup> 11 of 13 reported children with *MYCN*-amplified tumors and stage IV-S have died.<sup>40-42</sup>

Favorable Shimada histopathology was present in 96% of the stage IV-S infants in our study, but those three infants with unfavorable pathology had a significantly lower survival rate. The Shimada histopathologic classification also separately reported one stage IV-S infant whose tumor had unfavorable histologic characteristics and *MYCN* amplification who died. In the same report, two other stage IV-S infants with unfavorable histologic characteristics and no amplification of *MYCN* developed progressive disease.<sup>43</sup> In a recent review, 43 of 45 stage IV-S infants had a favorable

Shimada histologic classification. The remaining two had unfavorable classifications and died.<sup>41</sup>

Moss et al<sup>21</sup> reported that bone marrow immunocytology can define risk groups in both advanced and localized neuroblastoma, although not in 11 stage IV-S patients. In our study, one infant who died had 45,000 tumor cells per 10<sup>5</sup> nucleated bone marrow cells according to immunocytology. However, by the INSS definition, such a patient would be classified as stage 4. The presence of neuroblastoma cells by immunocytology was a more significant factor for EFS ( $P = .049$ ) than was light microscopic examination of bone marrow, which suggests that infants with bone marrow involvement by the more sensitive detection method may have a worse outcome. However, neither light microscopic or immunocytologic detection of tumor in bone marrow was predictive of overall survival.

Elevated serum ferritin levels were not an indicator of poor prognosis in stage IV-S infants on this study. This may be related in part to the high serum levels normally present in the first few months of life.<sup>44,45</sup> This is in contrast with stage III and IV neuroblastoma, where ferritin levels are frequently elevated and correlate with poor prognosis.<sup>22,30,46</sup>

Other biologic factors, including tumor suppressor genes, expression of nerve growth factor and its high-affinity receptor, TrkA, and low telomerase activity, have been associated with tumor maturation and regression and may account for the behavior of tumors in stage IV-S disease.<sup>47</sup> Further investigation of these factors and other genetic features of stage IV-S tumors are planned as part of an intergroup CCG-POG study (P9641). Eventually, elucidation of the biochemical and genetic mechanisms that lead to spontaneous maturation and regression of neuroblastoma may obviate the need for precise anatomic staging.

Our study substantiates the use of supportive care alone as the best treatment approach in asymptomatic infants with stage IV-S disease. Supportive care alone was possible in 57% of the infants in our study, with 100% survival in this group. This approach was recommended initially by Evans.<sup>4</sup> However, in five retrospective studies reported up to 1992, the number of patients surviving after observation only was quite low at 17% (26 of 155).<sup>3,5,10,14,16</sup> By 1998, three more retrospective studies reported survival rates of 88% to 100% with no cytotoxic treatment.<sup>7,18,48</sup> The spontaneous resolution of metastatic disease in the 44 infants in our study who did not receive cytotoxic therapy confirms and extends in a prospective study previous observations made of stage IV-S neuroblastoma. The intrinsically biologically favorable na-

ture of this disease is further supported by the lack of effect of primary tumor resection on EFS or survival (Table 4).

Radiation therapy alone in doses of 6 Gy or more has been used in other studies, compared with the 4.5 Gy used in our study.<sup>5</sup> However, when doses of 6 and up to 30 Gy were used, multiple late effects, such as rib osteochondromas, chest and pelvic wall hypoplasia, scoliosis, and radiation nephritis or hepatic fibrosis, were seen.<sup>4,49,50</sup> More intensive chemotherapy may obviate the need for radiation, as was used in a POG study of stage D(S) infants, where only 6% needed radiation in addition to chemotherapy.<sup>18</sup>

Once intra-abdominal disease progression caused clinically significant organ dysfunction, low-dose cytotoxic therapy was used in 43% of our infants. The chemotherapy and radiation therapy used in our study were not always effective, since all the deaths occurred in symptomatic patients, who usually received both therapeutic modalities. Unfortunately, it is not possible by present staging procedures to determine in advance all infants who will need therapy.<sup>8,15</sup> However, the use of both radiation and chemotherapy was required nearly three times as frequently in infants  $\leq 2$  months of age, compared with those older than 2 months. Four of the six children who died in our study were younger than 4 weeks old at diagnosis, and five were younger than 8 weeks old. Our results showed an EFS rate of 77% for infants  $\leq 2$  months of age compared with 93% for older infants ( $P = .051$ ) but less difference in overall survival, at 86% and 98%, respectively ( $P = .081$ ). The survival for symptomatic infants who were  $\leq 2$  months of age was lower than that for symptomatic infants older than 2 months of age (78% v 90%), suggesting again that very young infants who are symptomatic are at the highest risk for death. The literature has previously suggested that the majority of infants with stage IV-S neuroblastoma who die are those who present in the first 2 months of life.<sup>11,16,18,51</sup> Such infants with rapidly expanding liver disease may need earlier and more aggressive chemotherapy to decrease the risk of abdominal distention causing mechanical respiratory failure.<sup>8,9</sup>

In conclusion, our study of 80 infants with stage IV-S neuroblastoma confirms this as a biologically favorable group. The asymptomatic patients had 100% survival with supportive care only, and the symptomatic patients had an 81% survival rate with low-dose cytotoxic therapy. The survival of the infants younger than 2 to 3 months of age with symptomatic disease may be improved further by prompt initiation of more intensive combination therapy.

APPENDIX  
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## REFERENCES

1. D'Angio G, Evans A, Koop C: Special pattern of widespread neuroblastoma with a favourable prognosis. *Lancet* 1:1046-1049, 1971
2. Brodeur GM, Pritchard J, Berthold F, et al: Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment [see comments]. *J Clin Oncol* 11:1466-1477, 1993
3. Evans AE, D'Angio GJ, Randolph J: A proposed staging for children with neuroblastoma: Children's Cancer Study Group A. *Cancer* 27:374-378, 1971
4. Evans AE, Chatten J, D'Angio GJ, et al: A review of 17 IV-S neuroblastoma patients at the Children's Hospital of Philadelphia. *Cancer* 45:833-839, 1980
5. Evans AE, Baum E, Chard R: Do infants with stage IV-S neuroblastoma need treatment? *Arch Dis Child* 56:271-274, 1981
6. Grosfeld JL, Rescorla FJ, West KW, et al: Neuroblastoma in the first year of life: Clinical and biologic factors influencing outcome. *Semin Pediatr Surg* 2:37-46, 1993
7. Kushner BH, Cheung NK, LaQuaglia MP, et al: Survival from locally invasive or widespread neuroblastoma without cytotoxic therapy. *J Clin Oncol* 14:373-381, 1996
8. Mancini AF, Rosito P, Vitelli A, et al: IV-S neuroblastoma: A cooperative study of 30 children. *Med Pediatr Oncol* 12:155-161, 1984
9. De Bernardi B, Pianca C, Boni L, et al: Disseminated neuroblastoma (stage IV and IV-S) in the first year of life: Outcome related to age and stage—Italian Cooperative Group on Neuroblastoma. *Cancer* 70:1625-1633, 1992
10. Martinez DA, King DR, Ginn-Pease ME, et al: Resection of the primary tumor is appropriate for children with stage IV-S neuroblastoma: An analysis of 37 patients. *J Pediatr Surg* 27:1016-1020, discussion 1020-1021, 1992
11. Stephenson SR, Cook BA, Mease AD, et al: The prognostic significance of age and pattern of metastases in stage IV-S neuroblastoma. *Cancer* 58:372-375, 1986
12. Suarez A, Hartmann O, Vassal G, et al: Treatment of stage IV-S neuroblastoma: A study of 34 cases treated between 1982 and 1987. *Med Pediatr Oncol* 19:473-477, 1991
13. Strother D, Shuster JJ, McWilliams N, et al: Results of Pediatric Oncology Group protocol 8104 for infants with stages D and DS neuroblastoma. *J Pediatr Hematol Oncol* 17:254-259, 1995
14. Wilson PC, Coppes MJ, Solh H, et al: Neuroblastoma stage IV-S: A heterogeneous disease. *Med Pediatr Oncol* 19:467-472, 1991
15. McWilliams NB: IV-S neuroblastoma: Treatment controversy revisited. *Med Pediatr Oncol* 14:41-44, 1986
16. Nickerson HJ, Nesbit ME, Grosfeld JL, et al: Comparison of stage IV and IV-S neuroblastoma in the first year of life. *Med Pediatr Oncol* 13:261-268, 1985
17. Brodeur GM, Seeger RC, Sather H, et al: Clinical implications of oncogene activation in human neuroblastomas. *Cancer* 58:541-545, 1986
18. Katzenstein HM, Bowman LC, Brodeur GM, et al: Prognostic significance of age, MYCN oncogene amplification, tumor cell ploidy, and histology in 110 infants with stage D S neuroblastoma: The Pediatric Oncology Group experience—A Pediatric Oncology Group study. *J Clin Oncol* 16:2007-2017, 1998
19. Seeger RC, Brodeur GM, Sather H, et al: Association of multiple copies of the N-myc oncogene with rapid progression of neuroblastomas. *N Engl J Med* 313:1111-1116, 1985
20. Shimada H, Chatten J, Newton WA Jr, et al: Histopathologic prognostic factors in neuroblastic tumors: Definition of subtypes of ganglioneuroblastoma and an age-linked classification of neuroblastomas. *J Natl Cancer Inst* 73:405-416, 1984
21. Moss TJ, Reynolds CP, Sather HN, et al: Prognostic value of immunocytologic detection of bone marrow metastases in neuroblastoma. *N Engl J Med* 324:219-226, 1991
22. Hann HW, Evans AE, Siegel SE, et al: Prognostic importance of serum ferritin in patients with stages III and IV neuroblastoma: The Children's Cancer Study Group experience. *Cancer Res* 45:2843-2848, 1985
23. Schwab M, Varmus HE, Bishop JM: Human N-myc gene contributes to neoplastic transformation of mammalian cells in culture. *Nature* 316:160-162, 1985
24. Crabbe DC, Peters J, Seeger RC: Rapid detection of MYCN gene amplification in neuroblastomas using the polymerase chain reaction. *Diagn Mol Pathol* 1:229-234, 1992
25. Seeger RC, Wada R, Brodeur GM, et al: Expression of N-myc by neuroblastomas with one or multiple copies of the oncogene. *Prog Clin Biol Res* 271:41-49, 1988
26. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
27. Kalbfleisch JD, Prentice RL: *The Statistical Analysis of Failure Time Data*. New York, NY, John Wiley and Sons, Inc, 1980
28. Shaw A, Sabio H: Bilateral adrenal neuroblastoma. *Am J Pediatr Hematol Oncol* 6:41-43, 1984
29. Ishiguro Y, Iio K, Seo T, et al: Bilateral adrenal neuroblastoma. *Eur J Pediatr Surg* 4:37-39, 1994
30. Matthay KK, Perez C, Seeger RC, et al: Successful treatment of stage III neuroblastoma based on prospective biologic staging: A Children's Cancer Group study. *J Clin Oncol* 16:1256-1264, 1998
31. Berthold F, Harms D, Lampert F, et al: Risk factors in neuroblastoma of infants. *Contrib Oncol* 41:101-117, 1990
32. Guglielmi M, De Bernardi B, Rizzo A, et al: Resection of primary tumor at diagnosis in stage IV-S neuroblastoma: Does it affect the clinical course? *J Clin Oncol* 14:1537-1544, 1996
33. Brodeur GM, Maris JM, Yamashiro DJ, et al: Biology and genetics of human neuroblastomas. *J Pediatr Hematol Oncol* 19:93-101, 1997
34. Acharya S, Jayabose S, Kogan SJ, et al: Prenatally diagnosed neuroblastoma. *Cancer* 80:304-310, 1997
35. Haas D, Ablin AR, Miller C, et al: Complete pathologic maturation and regression of stage IVS neuroblastoma without treatment. *Cancer* 62:818-825, 1988
36. Hayashi Y, Inaba T, Hanada R, et al: Similar chromosomal patterns and lack of N-myc gene amplification in localized and IV-S stage neuroblastomas in infants. *Med Pediatr Oncol* 17:111-115, 1989
37. Look AT, Hayes FA, Shuster JJ, et al: Clinical relevance of tumor cell ploidy and N-myc gene amplification in childhood neuroblastoma: A Pediatric Oncology Group study. *J Clin Oncol* 9:581-591, 1991
38. Tonini GP, Boni L, Pession A, et al: MYCN oncogene amplification in neuroblastoma is associated with worse prognosis, except in stage 4s: The Italian experience with 295 children. *J Clin Oncol* 15:85-93, 1997
39. Bowman LC, Castleberry RP, Cantor A, et al: Genetic staging of unresectable or metastatic neuroblastoma in infants: A Pediatric Oncology Group study. *J Natl Cancer Inst* 89:373-380, 1997
40. Garvin J, Bendit I, Nisen PD: N-myc oncogene expression and amplification in metastatic lesions of stage IV-S neuroblastoma. *Cancer* 65:2572-2575, 1990
41. Hachitanda Y, Hata J: Stage IVS neuroblastoma: A clinical, histological, and biological analysis of 45 cases. *Hum Pathol* 27:1135-1138, 1996

42. van Noesel MM, Heahlen K, Hakvoort-Cammel FG, et al: Neuroblastoma 4S: A heterogeneous disease with variable risk factors and treatment strategies. *Cancer* 80:834-843, 1997
43. Shimada H, Stram DO, Chatten J, et al: Identification of subsets of neuroblastomas by combined histopathologic and N-myc analysis. *J Natl Cancer Inst* 87:1470-1476, 1995
44. Siimes MA, Addiego JEJ, Dallman PR: Ferritin in serum: Diagnosis of iron deficiency and iron overload in infants and children. *Blood* 43:581-590, 1974
45. Segall ML, Heese HV, Dempster WS, et al: Serum ferritin: An evaluation of maternal and infant iron stores, in Stern L, Friis-Hansen B, Kildeberg P (eds): *Intensive Care in the Newborn, I-IV*. New York, NY, Masson, 1976-1983, pp 159-170
46. Silber JH, Evans AE, Fridman M: Models to predict outcome from childhood neuroblastoma: The role of serum ferritin and tumor histology. *Cancer Res* 51:1426-1433, 1991
47. Matthay KK: Stage 4S neuroblastoma: What makes it special? *J Clin Oncol* 16:2003-2006, 1998 (editorial)
48. Evans AE, Silber JH, Shpilsky A, et al: Successful management of low-stage neuroblastoma without adjuvant therapies: A comparison of two decades, 1972 through 1981 and 1982 through 1992, in a single institution. *J Clin Oncol* 14:2504-2510, 1996
49. Blatt J, Deutsch M, Wollman MR: Results of therapy in stage IV-S neuroblastoma with massive hepatomegaly. *Int J Radiat Oncol Biol Phys* 13:1467-1471, 1987
50. Halperin EC, Cox EB: Radiation therapy in the management of neuroblastoma: The Duke University Medical Center experience 1967-1984. *Int J Radiat Oncol Biol Phys* 12:1829-1837, 1986
51. Hsu LL, Evans AE, D'Angio GJ: Hepatomegaly in neuroblastoma stage 4s: Criteria for treatment of the vulnerable neonate. *Med Pediatr Oncol* 27:521-528, 1996