Resection of Primary Tumor at Diagnosis in Stage IV-S Neuroblastoma: Does It Affect the Clinical Course?

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Purpose: **To determine whether resection of primary tumor has a favorable influence on outcome of infants (age 0 to 11 months) with stage IV-S neuroblastoma.**

Patients and Methods: **Between March 1976 and December 1993, 97 infants with previously untreated neuroblastoma diagnosed in 21 Italian institutions were classified as having stage IV-S disease. Seventy percent were younger than 4 months. Adrenal was the primary tumor site in 64 of 85 patients with a recognizable primary tumor. Liver was the organ most often infiltrated by the tumor (82 patients), followed by bone marrow and skin.**

Results: **The overall survival (OS) rate at 5 years is 80% and event-free survival (EFS) rate 68%. In 24 infants, the effect of resection of primary tumor could not be evaluated because of rapidly fatal disease progression (n = 8), absence of a primary tumor (n = 12), or partial resection (n = 4). Of 73 assessable patients, 26 underwent primary tumor resection at diagnosis: one died of surgical complications, one relapsed locally and died, and two others relapsed (one of these two locally) and survived, for a 5-year OS rate of 92% and EFS rate of 84%. Of the remaining 47 patients who did not undergo primary tumor resection at diagnosis 11 suffered unfavorable events, of whom five died, for an OS rate of 89% and EFS rate of 75% (no significant difference from previous group). Disease recurred at the primary tumor site in only one of five who died, and in only one of six survivors of progression or relapse; in these patients, the primary tumor, located in the mediastinum, was successfully resected.**

Conclusion: **Infants who underwent resection of the primary tumor at diagnosis had no better outcome than those in whom the decision was made not to operate.**

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APPROXIMATELY HALF of children with newly diagnosed neuroblastoma present with widespread disease.[1] The prognosis for most of these patients is poor, with the exception of those diagnosed under 1 year of life,[2] in part because this age range consists of almost all cases of stage IV-S,[3] which is often characterized by spontaneous regression of all tumor lesions.[4] Definition of stage IV-S disease implies a primary tumor that does not infiltrate across the midline, and tumor foci in the liver, skin, and bone marrow (in any combination).[3] The degree of liver infiltration is of crucial importance, since 20% to 50% of such cases develop hepatomegaly that progressively impairs respiratory function and eventually causes the patient's death.[5-16]

The effects of chemotherapy and radiotherapy on the evolution of stage IV-S disease, and in particular their capacity to accelerate regression or halt disease progression, remain unclear. Most pediatric oncologists therefore avoid using these treatments in the absence of life-threatening disease progression.[11,13-14,16]

The role of surgical resection of the primary tumor is also poorly defined. This is in part because of the possibly multifocal rather than metastatic nature of stage IV-S disease.[17] For this reason, even the use of the term primary tumor may be questionable, given the lack of clear evidence of its potential to give rise to relapse or dissemination. So far, it has been common practice to resect the primary tumor at some time during the clinical course, for fear that it may grow or metastasize despite regression of distant disease,[13] although no firm data exist to indicate that resection of primary tumor prevents disease relapse.

Since only a few series that have evaluated primary resection in stage IV-S disease have been reported, we retrospectively reviewed the history of infants with stage IV-S neuroblastoma diagnosed at institutions participating in the Italian Cooperative Group for Neuroblastoma (ICGNB). A description of other clinical features and outcome of some of these patients has been published previously.[15]

PATIENTS AND METHODS

Of 1,084 children aged 0 to 15 years with previously untreated neuroblastoma diagnosed between March 1976 and December 1993 in 21 institutions participating in ICGNB, 97 (8.9%) infants (age 0 to 11 months), had stage IV-S characteristics. All patients were

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registered at diagnosis. The ICGNB policy since 1976 has been to register at diagnosis stage III, IV, and IV-S and, since 1979, all stages; hence, the period chosen for the study.

The diagnosis was made either histologically or on the basis of clinical, laboratory, and imaging data. Staging work-up included abdominal ultrasonography followed in most cases by computed tomography or magnetic resonance imaging, chest roentgenogram, radiographic skeletal survey, and at least one bone marrow aspiration. Technetium 99m methylene diphosphonate bone scan was not usually performed, since in infants it may show so much activity that it is difficult to detect small lesions.[18] Iodine 131 or iodine 125 metaiodobenzylguanidine (MIBG) scintigraphy was performed in some patients from 1987 onward.[19]

Definitions of Stage IV-S Disease

According to both Evans' and the Italian staging systems,[3,20] patients were included in stage IV-S if they had an intracavitary mass that did not infiltrate across the midline and tumor lesions that were confined to liver, bone marrow, and skin (in any combination).

Surgery of the Primary Tumor

Complete resection was defined as an excision described either as radical or with minimal residue. Partial resection was defined as an excision greater than 50%, but less than complete, and biopsy was an excision that varied from a fragment suitable for histologic examination to 50% of the primary tumor mass.

Therapy

Age 0 to 5 months. Between 1976 and 1984, the majority of these patients were treated with 1 month of chemotherapy, which usually consisted of two cycles of peptichemio (Istituto Sieroterapico Milanese, Milano, Italy), a mixture of oligopeptides of m-L-phenylalanine mustard.[21,22] Radiotherapy was not part of the planned treatment for these patients and was administered to only eight patients. Since 1985, recommendations were given to avoid any therapy, except in case of life-threatening tumor progression.

Age 6 to 11 months. These patients received the same treatment as patients of the same age who had stage IV disease.[23] In no case was radiotherapy administered.

Surgical guidelines were flexible. Resection of the primary tumor at the time of diagnosis was encouraged when feasible without endangering the patient's life. From 1985 onwards, this procedure was recommended on the grounds that histologic and biologic characteristics of the tumor might provide valuable prognostic information.[24] In patients who did not undergo surgery at diagnosis, surgery was delayed until the patient's status would permit safe laparotomy. However, in cases of marked reduction of tumor mass (either spontaneously or following some kind of therapy), the decision to operate or not was left to the individual physician.

Definition of Disease Progression and Relapse

Progression referred to the clear increase of any tumor lesion or the appearance of new lesion(s) before regression of all preexisting lesions. Progression to stage IV implied involvement of sites beyond liver, bone marrow, and skin, ie, bone, distant nodes, and orbit. Relapse referred to the appearance of any tumor lesion after the achievement of complete regression, except for residual ganglioneuromatous skin lesions or an irregular ultrasonographic pattern of the liver.

Statistical Analysis

The probabilities of overall survival (OS) and event-free survival (EFS) projected at 5 years were calculated from the time of diagnosis according to the Kaplan-Meier product-limit method.[25] In the OS analysis, deaths for any reason were considered as events. In the EFS analysis, disease progression, relapse, and death for any reason were considered as events. OS and EFS survival curves were compared by log-rank test. All P values were two-tailed.[26]

RESULTS

The distribution for age at diagnosis of the 97 patients with stage IV-S disease is shown diagrammatically in Fig 1. Sixty-eight patients (70%) were aged ≤ 3 months; only 15 patients (15%) were diagnosed after age 5 months. The main clinical characteristics are listed in Table 1. Males predominated, with an approximately 2:1 ratio. The primary tumor was located in the adrenal in 64 patients, in the mediastinum in 10, in the retroperitoneal ganglia in seven, and in the neck in four. In 12 patients, the primary tumor was not identified. The liver was the distant organ most often infiltrated by the tumor, either alone (n = 44) or combined with bone marrow (n = 20), skin (n = 14), or both (n = 4). Bone marrow and skin were the only sites of infiltration in eight and five cases, respectively.

Urinary excretion of the catecholamine metabolite vanillylmandelic acid (VMA) was measured in 79 patients and found to be 2.5 SD above the mean in 67. Homovanillic acid (HVA) was assayed in 42 patients and 33 had values 2.5 SD above the mean.

Among serum markers, lactate dehydrogenase (LDH) serum concentration was greater than 1,000 IU/L in 11 of 65 patients tested. Ferritin was measured in 56 patients and found to be abnormal (> 150 ng/mL) in 22. Neuron-specific enolase (NSE) was assayed in 30 patients and was increased to greater than 100 ng/mL in five. A search for N-*myc* gene amplification was performed in 33 patients, of whom three had more than 10 copies.

Clinical Course

Seventy-seven of 97 patients (79%) were alive in December 1994, with a median follow-up time of 75 months (range, 0 to 183). Twenty patients died between 1 day from birth and 70 months from diagnosis (median, 1.5 months). One died of surgical complications, one of sepsis related to chemotherapy, and 18 of disease. The projected OS rate at 5 years is 80% (confidence limits [CI], 72 to 88) for the entire series of 97 patients. OS was significantly better for patients aged ≥ 2 months at diagnosis (91% *v* 60%; P = .0004) (Table 2). The EFS rate at 5 years is 68% (CI, 58 to 77) for the entire series. As for OS, the EFS of patients aged ≥ 2 months was significantly better (73% *v* 60%; P = .05). However, no differences in either OS or EFS were observed in relation

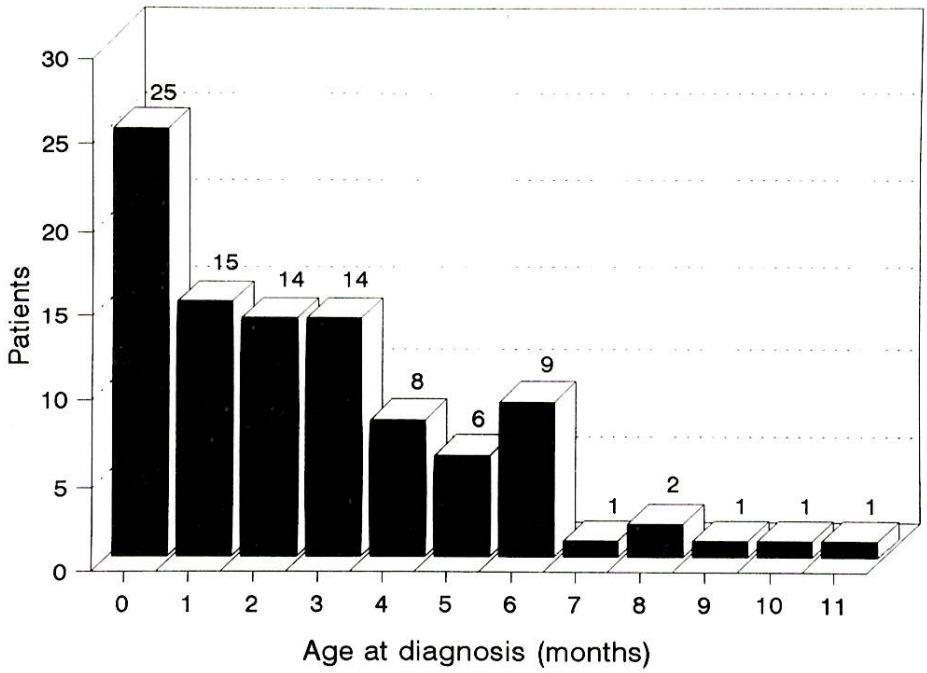

Fig 1. Age distribution at diagnosis.

to sex, primary tumor site, organs infiltrated by tumor, and period of diagnosis (before and after 1985), or for levels of VMA and HVA, LDH, ferritin, and NSE, or N-*myc* copy number (Table 1). All three patients with amplified N-*myc* survived without progression or relapse.

Resection of the Primary Tumor and Clinical Course

The effect of primary tumor resection on outcome could not be evaluated in 24 of 97 patients. Eight with detectable primary tumors had massive progressive liver infiltration that proved fatal (usually as a result of respiratory failure) over a period that ranged from the day of birth to 4 months from diagnosis (Table 3). Twelve had no identifiable primary tumor; of these, two died of progressive hepatomegaly, one died of chemotherapy-related sepsis, and one who relapsed twice was alive in remission 5 months from second relapse, for a 5-year OS rate of 75% (CI, 51 to 100) and EFS rate of 66% (CI, 38 to 93). Four patients underwent only partial resection of the primary tumor at diagnosis; of these, one died of progressive hepatomegaly, one died after multiple bone marrow (and then bone) relapses, and one is alive without disease after successful resection of a progressive mediastinal primary tumor, for a 5-year OS rate of 75% (CI, 33 to 100) and EFS rate of 25% (CI, 0 to 67) (Table 3).

Twenty-six of the 73 remaining patients underwent complete resection of the primary tumor at diagnosis; one died on the day of surgery of abdominal bleeding. Three of these 26 patients suffered disease progression or relapse, which proved fatal in one, for a 5-year OS rate of 92% (CI, 82 to 100) and EFS rate of 84% (CI, 70 to 98) (Tables 2 and 3).

In the remaining 47 assessable patients, no attempt was made to remove the primary tumor at the time of diagnosis, although 34 underwent biopsy of the primary tumor itself (n = 10), or of a metastasis (n = 23), or of both (n = 1). In 14, complete resection was subsequently performed following partial disease regression that had occurred either spontaneously (n = 1), or following administration of chemotherapy (n = 12), or following chemotherapy plus radiotherapy (n = 1). Eleven of these 47 patients suffered disease progression or relapse, which proved fatal in five, for a 5-year OS rate of 89% (CI, 79 to 98) and EFS rate of 75% (CI, 63 to 88) (Tables 2 and 3). None of 14 patients in whom complete resection was performed at 1 to 12 months (median, 3) from diagnosis following partial disease regression experienced relapse, and all are alive without disease.

Sites of Progression and Relapse and Outcome

The liver was the single site of progression in 11 patients and of relapse in one. All 12 patients died. An additional patient who relapsed in the liver, skin, and bone marrow also died. One who relapsed in liver and bone marrow is alive. One patient who relapsed in bone marrow died. Two of three patients who either relapsed or progressed in bone and bone marrow died. One patient who progressed in bone, bone marrow, distant lymph

Table 1. Characteristics of 97 Infants With Stage IV-S Neuroblastoma

Characteristic	No.	%
Sex		
Male	66	68
Female	31	32
Age (months)	2	
Median		
0-5	82	84
6-11	15	16
Primary tumor site		
Adrenal	64	66
Mediastinum	10	10
Retroperitoneal ganglia	7	7
Neck	4	4
Not detected	12	12
Organs infiltrated by tumor		
Liver only	44	45
Liver + bone marrow	20	20
Liver + skin	14	15
Liver + bone marrow + skin	4	4
Bone marrow only	8	9
Skin only	5	5
Others	2	2
VMA (79 tested)		
< 2.5 SD	12	15
≥ 2.5 SD	67	85
HVA (42 tested)		
< 2.5 SD	9	21
≥ 2.5 SD	33	79
LDH (65 tested)		
< 1,000 IU/L	54	83
≥ 1,000 IU/L	11	17
Ferritin (56 tested)		
< 150 ng/mL	34	61
≥ 150 ng/mL	22	39
NSE (30 tested)		
< 100 ng/mL	25	83
≥ 100 ng/mL	5	17
N-*myc* (33 tested)		
< 10 copies	30	91
≥ 10 copies	3	9

nodes, and orbit survives. One patient who progressed in distant nodes, one who progressed in the brain, and one who relapsed in bone marrow and nodes underwent successful rescue therapy. One patient without identifiable primary tumor relapsed in the abdominal sympathetic ganglia and survives.

The primary tumor was the only site of relapse in one patient who had undergone total resection at diagnosis, and the only site of progression in two patients, one of whom had undergone a partial resection of the primary tumor and one who had no surgery. The first patient died, while the other two were successfully treated by surgery. Two other patients relapsed in the primary tumor site in combination with another site: one in distant lymph nodes and one in the bone marrow. The first, who had previously had total resection at diagnosis, is alive; the other patient died.

In summary, the primary tumor site was involved in two episodes of progression and in three of relapse. Both patients whose primary tumor located in the mediastinum progressed underwent successful surgery. Of the three relapses, two occurred in patients who had undergone total resection at diagnosis, of whom one died. The third patient who relapsed at the primary tumor site also had bone marrow relapse, and subsequently died. Thus, only two deaths were associated with disease relapse or progression at the site of the primary tumor, one of which occurred in a patient who had undergone complete resection of the primary tumor at diagnosis.

DISCUSSION

The good outcome (80% OS, at 5 years) for the 97 stage IV-S neuroblastoma patients described here is in agreement with previous data from the literature.[8-17] As in other reports,[10,12,13,16] patients diagnosed in the first 2 months of life had a significantly worse prognosis than older patients (OS, 64% *v* 91%). This may be because the disease diagnosed in very young infants continues to grow for some time (weeks to months) before initiation of regression. There is no convincing evidence that any therapy halts the progression of the disease in such patients.

Patient deaths were evenly distributed through the 16 years of the study, despite the better supportive care developed in more recent years. This suggests that stage IV-S disease includes a subset of patients who continu to do poorly despite best medical efforts.

In this study, we examined the influence that resectio of the primary tumor at diagnosis may have on diseas course. The question is important, since a clear answ would result in clear guidance for clinical managemer The literature regarding this issue provides conflicti information. Some investigators state that the removal the primary tumor does not correlate with an increas survival rate,[7,12] while others say that the primary tum should be resected to prevent late local recurrence ev if the remainder of the disease has regressed.[9,13] Only t reports support a positive role of surgery based on th own experience. Berthold et al,[27] who reported on stage IV-S patients, stated that both initial and delay resection together with general condition are import for outcome. More recently, in a series of 37 patie Martinez et al[28] advocated either complete or partial section of the primary tumor based on a better outco for the patients in whom either were performed, parti larly for infants aged less than 2 months.

Our analysis, performed on 97 patients, does not s port the conclusions of these two groups. Certainly, tients who underwent radical surgery fared well, only two deaths occurring among 26 patients. Howe

Table 2. Five-Year OS and EFS Rates in Relation to Primary Tumor Resection and Characteristics at Diagnosis of 73 Eligible Patients

Characteristic	Resection					No Resection				
	No.	Deaths	OS (%)	Any Event	EFS (%)	No.	Deaths	OS (%)	Any Event	EFS (%)
All patients	26	2	92	4	84	47	5	89	11	75
Sex										
Male	17	2	88	3	82	32	3	89	7	77
Female	9	0	100	1	88	15	2	87	4	22
Age (months)										
0-5	21	1	95	3	85	39	4	89	8	78
6-11	5	1	80	1	80	8	1	88	3	63
0-1	10	1	90	1	90	17	3	81	3	82
2-11	16	1	94	3	80	30	2	93	8	72
Primary site										
Adrenal	23	2	91	4	82	33	4	87	8	74
Other sites	3	0	100	0	100	14	1	93	3	78
Organs infiltrated by tumor										
Liver only	10	1	90	1	90	17	1	94	3	82
Liver + others	9	1	89	2	74	26	4	84	7	71
Others	7	0	100	1	86	4	0	100	1	75
Year of diagnosis										
1976-1984	3	0	100	0	100	17	3	82	4	76
1985-1994	23	2	91	4	82	30	2	92	7	74
VMA										
< 2.5 SD	4	1	75	1	75	1	0	100	0	100
≥ 2.5 SD	17	1	94	3	82	41	5	87	10	75
HVA										
< 2.5 SD	1	0	100	0	100	1	0	100	0	100
≥ 2.5 SD	12	1	92	3	74	19	4	77	6	68
LDH										
< 1,000 IU/L	19	1	95	3	84	24	2	90	3	87
≥ 1,000 IU/L	2	1	50	1	50	8	1	88	4	38
Ferritin										
< 150 ng/mL	8	0	100	1	83	19	2	89	5	73
≥ 150 ng/mL	9	2	78	3	67	10	1	86	1	88
NSE										
< 100 ng/mL	10	1	90	3	69	8	2	64	21	73
≥ 100 ng/mL	0	—	—	—	—	5	0	100	2	60
N-*myc*										
< 10 copies	12	0	100	2	81	14	2	83	6	55
≥ 10 copies	2	0	100	0	100	0	—	—	—	—

two experienced relapses at the primary tumor site, which indicates that macroscopic resection did not preclude local tumor regrowth, and a third died as a result of surgery, which makes the value of removal of the primary tumor at diagnosis questionable.

Of four patients who had partial resection of primary tumor, the two who, respectively, relapsed in the bone marrow and progressed in the liver died. A third patient who had progression in the primary tumor site underwent successful salvage surgery. The small size of this group does not allow us to draw any conclusions on the role of partial resection of the tumor.

In comparison with the excellent survival of patients whose primary tumor was radically resected, the 67 patients who did not undergo resection had a high mortality rate (16 of 67). This would, at first sight, support the hypothesis that resection of primary tumor may increase the chance of cure and thus should be included in the overall therapeutic strategy of stage IV-S neuroblastoma. However, this patient group included three distinct subsets. One subset was that of 12 patients who had no detectable primary tumor. Three of these patients died. The second subgroup included eight patients (mostly diagnosed before 2 months of age) in whom the disease progressed and led to death before an attempt at removing the primary tumor could be considered. Progressive hepatomegaly was the main cause of death in these patients. The third subgroup, which consisted of 47 patients, was made up of patients in whom an elective decision was made not to perform surgery at diagnosis. Five of these 47 patients died; two died after progression, in bone and bone marrow in one case and

Table 3. Unfavorable Events (fatal and nonfatal)

Patient No.	Age at Diagnosis (months)	Clinical Course	Outcome	Time From Diagnosis (months)
Progressive disease (n = 8)				
1	0	Progressive hepatomegaly and respiratory failure	Dead	0
2	0	same	Dead	0
3	0	same	Dead	0
4	0	same	Dead	1
5	0	same	Dead	1
6	0	same	Dead	4
7	1	same	Dead	0
8	1	same	Dead	0
Unidentified primary tumor (n = 12)				
9	0	Progressive hepatomegaly	Dead	0
10	2	Progressive hepatomegaly following transient improvement	Dead	10
11	3	Chemotherapy related sepsis	Dead	1
12	3	Relapse in retroperitoneum at 19 months and liver at 44 months	NED	49
Partial excision of primary tumor at diagnosis (n = 4)				
13	0	Bone marrow relapse at 6 months	Dead	70
14	1	Progressive hepatomegaly	Dead	1
15	2	Progression of primary tumor in the mediastinum at 2 months. Resection	NED	31
Total excision of primary tumor at diagnosis (n = 26)				
16	0	Local relapse at 6 months	Dead	7
17	5	Post-surgical abdominal bleeding	Dead	Day of surgery
18	2	Local plus distant lymph node relapse at 4 months	NED	48
19	5	Progression in bone marrow, bone, orbit and distant lymph node at 3 months	NED	35
No surgery at diagnosis (n = 47)				
20	1	Progression in bone and bone marrow at 3 months	Dead	5
21	1	Progression in bone marrow, liver and skin at 11 months	Dead	11
22	1	Local and bone marrow relapse at 17 months	Dead	26
23	4	Relapse in the liver at 21 months	Dead	25
24	6	Relapse in bone and bone marrow at 11 months	Dead	19
25	3	Progression in distant lymph node (groin) at 4 months	NED	51
26	3	Relapse in distant lymph node and bone marrow at 29 months	NED	76
27	4	Local progression in mediastinum at 7 months	NED	32
28	4	Relapse in the brain at 3 months	NED	40
29	6	Bone and bone marrow relapse at 8 months	NED	93
30	6	Relapse in liver and bone marrow at 25 months	NED	46

Abbreviation: NED, no evidence of disease

in bone marrow, liver, and skin in the other, and three died after late relapse, involving the liver in one case, bone marrow and primary tumor in another case, and bone and bone marrow in the third case. It is noteworthy that only one of these patients suffered relapse at the site of the primary tumor. The OS of these patients was comparable to that of patients who underwent total resection at diagnosis (89% *v* 92%).

We have also analyzed the contribution of the primary tumor to the episodes of unfavorable events that occurred after partial or complete disease regression. Of 10 such events, seven developed in sites other than the primary tumor. Of the three events that involved the primary tumor site, one was a relapse that occurred following radical excision of the primary tumor, whereas the two remaining consisted of life-threatening progression of the primary tumor at the level of the upper mediastinum. In both of these patients, the surgeon succeeded in removing the

tumor and this was followed by spontaneous regression of residual lesions.

Due to its limited size, our study had adequate power (eg, 80%) to detect only large differences (> 30%) in OS and EFS among the 26 patients who underwent resection at diagnosis and the 47 eligible for resection in whom surgery was not performed. As a consequence, from the statistical viewpoint, we cannot rule out the possibility that resection of primary tumor is associated with a moderate improvement in prognosis.

However, our data, overall, support the hypothesis that the clinical course of stage IV-S neuroblastoma is mainly determined by age and entity of liver involvement at the time of diagnosis. In patients who experienced fatal disease progression or late relapse, the primary tumor was rarely involved in such events. Furthermore, even when the primary tumor was among the sites of progression or relapse, it was not the main cause of death.

In our series of 97 patients, only one patient of 47 in whom elective resection of the primary tumor was not performed died in association with a relapse at the primary tumor site. This suggests that progression or relapse following regression of the primary tumor was a rare event in patients who did not undergo resection. In contrast, two local relapses (one death) were observed also in the group of patients resected at diagnosis. The proportion and pattern of the deaths from progression in sites other than the primary tumor were also similar in the two groups.

The numbers in this series are too small to reach any conclusions about whether the primary tumor (or its organ of origin) should be removed following disease regression. It could be argued that the relapse that occurred in one patient in whom tumor resection was not performed at diagnosis and died after relapse at the primary tumor site and in the bone marrow might have been prevented by late resection. However, this would imply that stage IV-S disease represents metastatic disease from a primary tumor, rather than a widespread tissue developmental abnormality; in any case, our experience of total resection at diagnosis suggests that resection does not infallibly prevent relapse.

Therefore, we conclude that resection of primary tumor in stage IV-S neuroblastoma has little impact on outcome. In our experience, the primary tumor appeared to be one of the many lesions of a multifocal disease and does not appear to be responsible for dissemination or relapse. As stage IV-S neuroblastoma can be diagnosed from clinical findings, imaging, biochemical information, and often bone marrow cytology, surgery on the primary tumor for diagnostic purposes is usually unnecessary, or could be limited to a biopsy, if diagnosis can not be confirmed in any other way. Any requirement for tumor tissue for biologic studies can be satisfied with a minimal amount of tumor tissue,[29] although, to date, results of biologic studies have not proved predictive of outcome in this group of patients in our experience.

Follow-up data will then indicate what, if any, surgical intervention is required. A primary tumor that progressively decreases in size together with other lesions could reasonably be left in site, while the long-lasting persistence of a measurable mass would be an indication for late resection. Should a primary tumor increase in size, either independently or together with other lesions, the surgeon could be requested to operate, especially when the tumor growth is such to compromise vital functions. Two such examples that occurred in our series underwent successful emergency operations, and this was followed by spontaneous regression of the local residual tumor.

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APPENDIX

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