VOLUME 30 · NUMBER 15 · MAY 20 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Outcome After Surgery Alone or With Restricted Use of Chemotherapy for Patients With Low-Risk Neuroblastoma: Results of Children's Oncology Group Study P9641

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Submitted July 19, 2011; accepted February 13, 2012; published online ahead of print at www.jco.org on April 23, 2012.

Supported by National Institutes of Health Grants No. U10-CA98543, U10-CA29139, and U10 CA98413 to the Children's Oncology Group.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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0732-183X/12/3015-1842/$20.00

DOI: 10.1200/JCO.2011.37.9990

ABSTRACT

Purpose

The primary objective of Children's Oncology Group study P9641 was to demonstrate that surgery alone would achieve 3-year overall survival (OS) ≥ 95% for patients with asymptomatic International Neuroblastoma Staging System stages 2a and 2b neuroblastoma (NBL). Secondary objectives focused on other low-risk patients with NBL and on those who required chemotherapy according to protocol-defined criteria.

Patients and Methods

Patients underwent maximally safe resection of tumor. Chemotherapy was reserved for patients with, or at risk for, symptomatic disease, with less than 50% tumor resection at diagnosis, or with unresectable progressive disease after surgery alone.

Results

For all 915 eligible patients, 5-year event-free survival (EFS) and OS were 89% ± 1% and 97% ± 1%, respectively. For patients with asymptomatic stage 2a or 2b disease, 5-year EFS and OS were 87% ± 2% and 96% ± 1%, respectively. Among patients with stage 2b disease, EFS and OS were significantly lower for those with unfavorable histology or diploid tumors, and OS was significantly lower for those ≥ 18 months old. For patients with stage 1 and 4s NBL, 5-year OS rates were 99% ± 1% and 91% ± 1%, respectively. Patients who required chemotherapy at diagnosis achieved 5-year OS of 98% ± 1%. Of all patients observed after surgery, 11.1% experienced recurrence or progression of disease.

Conclusion

Excellent survival rates can be achieved in asymptomatic low-risk patients with stages 2a and 2b NBL after surgery alone. Immediate use of chemotherapy may be restricted to a minority of patients with low-risk NBL. Patients with stage 2b disease who are older or have diploid or unfavorable histology tumors fare less well. Future studies will seek to refine risk classification.

J Clin Oncol 30:1842-1848. © 2012 by American Society of Clinical Oncology

INTRODUCTION

The Children's Oncology Group (COG) established a neuroblastoma (NBL) risk classification system to define low-risk (LR), intermediate-risk, and high-risk groups based on clinical and biologic prognostic factors. Modern treatment for NBL is tailored to patient risk, and for patients with LR and intermediate-risk disease, this approach has led to decreased therapy-related toxicities and improved outcome. LR-NBL is defined as International Neuroblastoma Staging System (INSS) stage 1 disease in patients of any age; stage 2a and 2b disease with any *MYCN* status and any histology in infants ≤ 365 days of age; stage 2a and 2b *MYCN* nonamplified (*MYCN*-NA) and *MYCN* amplified (*MYCN*-A), favorable histology (FH) disease in children ≥ 365 days of age; and stage 4s, *MYCN*-NA, FH, hyperdiploid disease in infants (Table 1). In previous Pediatric Oncology Group (POG) and Children's Cancer Group (CCG) trials, overall survival (OS) rates of ≥ 95% were achieved with surgery alone or with surgery and chemotherapy in patients with low-stage, favorable biology disease.[1-3] The primary purpose of this study was to demonstrate that 3-year OS of 95% for patients with asymptomatic, LR, INSS stage 2a or 2b disease could be achieved after surgery alone. Secondary objectives included demonstration that 95% OS after surgery alone could be achieved for other patients with

Table 1. Children's Oncology Group Low-Risk Neuroblastoma

INSS Stage	Age	*MYCN* Status	Histopathology	DNA Ploidy
1	0-21 years	Any	Any	Any
2a/2b	< 365 days	Any	Any	Any
	≥ 365 days to 21 years	Nonamplified	Any	—
	≥ 365 days to 21 years	Amplified	Favorable	—
4s	< 365 days	Nonamplified	Favorable	≥ 1

Abbreviation: INSS, International Neuroblastoma Staging System.

asymptomatic LR-NBL and estimation of 3-year EFS and OS for patients who required chemotherapy at diagnosis.

PATIENTS AND METHODS

Eligibility for this study required that patients be < 22 years old and have biopsy-proven LR-NBL, as described in Table 1. Staging of disease and categorization of patients' responses to treatment, institutionally judged, followed INSS criteria.[4] Histopathology (FH or unfavorable histology [UH]), *MYCN* status (*MYCN*-A *v* *MYCN*-NA), DNA index (hyperdiploid *v* not), and risk assignment were performed centrally, as described previously.[5-7] Before the start of therapy, institutional review board approval at participating sites was obtained. Informed consent was obtained before enrollment onto both the treatment and companion biology studies according to institution guidelines.

Treatment

Patients underwent initial operation to obtain tissue for diagnosis and biology studies and for maximal safe primary tumor resection. For children with abdominal tumors, regional lymph nodes were sampled, and for those with presumed stage 4s disease, the liver was biopsied if metastases were suspected. On the basis of an earlier CCG study, all asymptomatic LR patients who underwent at least partial (> 50%) resection of tumor were eligible for observation without chemotherapy.[8] Immediate chemotherapy was offered to the following patients: patients with protocol-defined symptoms of disease that compromised organ function or were life threatening and could not be relieved by surgery; patients with less than partial resection of tumor; and, at the investigator's discretion, patients with, or at risk for developing, symptomatic spinal cord compression either before or after surgery. Two to four cycles of chemotherapy were to be given at 21-day intervals. The chemotherapy consisted of the following: cycle 1, carboplatin 560 mg/m^2 (18 mg/kg for patients < 365 days of age or weighing ≤ 12 kg) on day 1 and etoposide 120 mg/m^2 (4 mg/kg) on days 1, 2, and 3; cycle 2, carboplatin as in cycle 1 plus cyclophosphamide 1,000 mg/m^2 (33 mg/kg) and doxorubicin 30 mg/m^2 (1 mg/kg) on day 1; cycle 3, etoposide as in cycle 1 and cyclophosphamide as in cycle 2; and cycle 4, carboplatin and etoposide as in cycle 1 plus doxorubicin as in cycle 2 (Appendix Table A1, online only). Infants younger than 60 days of age, who are considered at highest risk for infectious complications, received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor after each cycle of chemotherapy. Regardless of initial therapy, all patients were observed with regularly scheduled examinations, urinary catecholamines, and imaging studies.

If NBL progressed or recurred during observation (progressive disease [PD]), treatment was based on age at progression, tumor biology, and pattern of progression. Surgery was again used as primary salvage therapy, and patients whose tumors were ≥ 90% resected were again observed. Patients having less than 90% resection were offered four or eight cycles of chemotherapy, depending on the biology of their PD. LR favorable biology NBL was treated with four cycles; UH disease or FH diploid disease was treated with eight cycles. Patients ≥ 365 days old with metastatic PD or local or regional *MYCN*-A or UH PD were removed from protocol therapy. Patients who experienced PD after protocol-directed chemotherapy were removed from protocol therapy. Protocol treatment failure was declared for patients whose disease could not be treated with surgery, protocol-defined chemotherapy, or both.

Statistical Considerations

P9641 was a phase III nonrandomized prospective study. The primary analysis was an intent-to-treat estimation of 3-year OS within the subset of patients with asymptomatic INSS stage 2a and 2b disease. The primary objective was a reduction of therapy in this cohort, while maintaining a 3-year OS of 95%.

Although OS was the primary end point, the study was conservatively powered based on monitoring of EFS. The protocol planned for 320 patients with asymptomatic INSS stages 2a and 2b disease to provide 96% power to detect a 90% 2-year EFS as inadequate or 71% power to detect a 92% 2-year EFS as inadequate, under the null hypothesis that the 2-year EFS was 95%. This monitoring was performed using a one-sample O'Brien-Fleming technique and assuming a constant hazard of 2.5 failures per hundred person-years during the first 2 years, which equated to 95% 2-year EFS (ie, comparing the

Table 2. P9641 Patient Characteristics

Stage and Age	Biologic Category (No. of Patients)					Total Patients		Postsurgical Therapy (No. of Patients)	
	NA/FH	NA/UH	A/FH	A/UH	Unknown	No.	%	Observe	Immediate Chemotherapy
Stage 1						453	50		
< 1 year	182	5	4	0	3	194		194	0
≥ 1 year	174	73	3	3	6	259		259	0
Stage 2a						145	16		
< 1 year	58	4	0	0	0	62		49	13
≥ 1 year	56	26	1	NE	0	83		75	8
Stage 2b						237	26		
< 1 year	106	14	0	0	2	122		93	29
≥ 1 year	64	50	0	NE	1	115		89	26
Stage 4s, < 1 year	80*	NE	NE	NE	0	80	9	41	39
Total	720	172	8	3	12	915		800	115
%	80	19	1	< 1					

NOTE. Of all patients, 459 (50%) were female and 456 (50%) were male, and patient age was as follows: < 12 months, 458 patients (50%); ≥ 12 months, 457 patients (50%); < 18 months, 567 patients (62%); and ≥ 18 months, 348 months (38%).

Abbreviations: A, *MYCN* amplified; FH, favorable histology; NA, *MYCN* nonamplified; NE, not eligible for this low-risk study; UH, unfavorable histology.

*All patients with stage 4s low-risk disease had hyperdiploid tumors.

Table 3. Outcome of 915 Eligible Patients Enrolled Onto Children's Oncology Group Study P9641 by Treatment and Risk Factors

Characteristic	No. of Patients	%*	EFS			OS		
			5-Year EFS (%)	± SE (%)	*P*	5-Year OS (%)	± SE (%)	*P*
Overall	915		89	1	NA	97	1	NA
Asymptomatic stage 2a/2b	306		87	2	NA	96	1	NA
Initial treatment					.5317			.6667
Surgery and observation	800	87	89	1		97	1	
Surgery and chemotherapy	115	13	91	3		98	1	
Age, months					.8889			.0092
< 18	567	62	89	2		98	1	
≥ 18	348	38	90	2		95	1	
INSS stage								
1	453	50	93	2	.0021†	99	1	.0190†
2a	145	16	92	3	.0321‡	98	2	.2867‡
2b	237	26	85	3		96	2	
4s	80	9	77	6		91	4	
Unknown	0							
MYCN status					.0686			.0054
Not amplified	897	99	89	1		97	1	
Amplified	11	1	73	15		82	13	
Unknown	7							
Histology					< .001			< .001
Favorable	730	81	91	1		98	1	
Unfavorable	175	19	83	4		91	3	
Unknown	10							
Ploidy					.3433			.0252
Hyperdiploid	646	75	90	2		98	1	
Diploid	215	25	89	3		94	2	
Unknown	54							
INSS stage 1								
MYCN not amplified	437	98	93	2	.0042	99	1	< .001
MYCN amplified	10	2	70	17		80	15	
Favorable histology	365	82	94	2	.0060	100		< .001
Unfavorable histology	81	18	86	5		93	3	
Hyperdiploid	292	70	93	2	.8363	99	1	.4343
Diploid	128	30	94	3		98	2	
INSS stage 2a/2b								
MYCN not amplified	380	99.7	88	2	.7126	96	1	.8481
MYCN amplified	1	0.3	0 events			0 deaths		
Favorable histology	285	75	90	2	.0023	99	1	< .001
Unfavorable histology	94	25	80	5		89	4	
Hyperdiploid	274	76	90	2	.0129	99	1	< .001
Diploid	87	24	82	5		89	4	
INSS stage 4s								
MYCN not amplified	80	100	77	6	NA	91	4	NA
MYCN amplified	0							
Favorable histology	80	100	77	6	NA	91	4	NA
Unfavorable histology	0							
Hyperdiploid	80	100	77	6	NA	91	4	NA
Diploid	0							
Surgery and observation	41	51	63	10	.0016	84	7	.1302
Surgery and chemotherapy	39	49	92	5		97	3	

Abbreviations: EFS, event-free survival; INSS, International Neuroblastoma Staging System; NA, not applicable to this low-risk study; OS, overall survival.
*The calculation of the percentages and the log-rank *P* value for each category (ie, ploidy) is based only on the known number of patients of each type (ie, hyperdiploid *v* diploid) and excludes patients for whom the value is unknown.
†INSS stage 1 *v* stages 2 and 4s.
‡INSS stage 2a *v* stage 2b.

number of events observed to that expected under the null hypothesis). Monitored events were counted only if they occurred after the patient received P9641 chemotherapy or if P9641 chemotherapy was not appropriate for the patient, according to explicit provisions of the protocol. This permitted a comparison of comparably treated patients to historic data for EFS because the historic patients would have received chemotherapy.

For EFS, the time to event was the time from study enrollment until the first occurrence of relapse, PD, secondary malignancy, or death from any

cause, or until last contact with the patient if no event occurred. For OS, the time to event was the time from study enrollment until death from any cause or until last contact with the patient. Kaplan-Meier survival curves were generated overall and by subgroup.[9] Survival is reported as the 5-year estimate ± SE, except when addressing study objectives (3-year estimates) or monitoring (2-year estimates), per protocol.[10] Survival curves were compared using a two-sided log-rank test. Unplanned comparisons were performed within subsets, the results of which must be prospectively validated. $P < .05$ was considered statistically significant.

RESULTS

Between April 6, 1998, and November 16, 2004, the study enrolled 968 patients, of whom 915 were eligible (Table 2). Patients were ineligible because of incorrect staging or risk assignment (n = 48) or because of insufficient data to assign risk (n = 5). Treating surgeons recorded the degree of initial tumor resection as complete in 82% of patients (n = 638), more than 90% in 15% (n = 118), more than 50% and less than 90% in 2% (n = 15), and less than 5% in 1% of patients (n = 7); for 137 patients, the degree of initial tumor resection was unknown. Patients alive without an event were observed for a median of 5.8 years (range, < 1 to 10.9 years). Overall, 5-year EFS and OS estimates were 89% ± 1% and 97% ± 1%, respectively (Table 3; Fig 1A). Asymptomatic patients with stage 2a and 2b disease (n = 306) who were observed after initial operation had 5-year EFS and OS rates of 87% ± 2% and 96% ± 1%, respectively (Table 3; Fig 1B). EFS was significantly better for patients with stage 2a than 2b NBL (92% ± 3% and 85% ± 3%, respectively; $P = .0321$), but OS did not differ (98% ± 2% and 96% ± 2%, respectively; $P = .2867$). At the final protocol-specified EFS monitoring time point, 16 of the 306 symptomatic patients with stage 2a or 2b NBL had a monitored event ($z = 0.92$). Per O'Brien-Fleming monitoring, the stopping rule for inferior EFS was not met because the stopping boundary was 21 events ($z = 2.2$). The 2-year EFS of 95% was achieved. Furthermore, the 95% CI on the 3-year OS was 96% to 100%, which excluded 95%. Therefore, the primary objective of the study to achieve 3-year OS of 95% within asymptomatic patients with stage 2a and 2b disease was met.

Patients with stage 1 disease achieved 5-year EFS of 93% ± 2%, significantly higher than the combined cohort of patients with stages 2a (92% ± 3%), 2b (85% ± 3%), and 4s (77% ± 6%) disease ($P = .0021$). Five-year OS for stage 1 patients was 99% ± 1%, significantly higher than the other patients combined ($P = .019$). For the 80 patients with stage 4s disease, 5-year EFS and OS were 77% ± 6% and 91% ± 4%, respectively. Five-year EFS was 63% ± 10% for the 41 patients with asymptomatic stage 4s NBL treated with surgery alone and 92% ± 5% for the 39 patients treated with surgery and chemotherapy ($P = .0016$); their 5-year OS rates were 84% ± 7% and 97% ± 3%, respectively ($P = .1302$). Our secondary objectives to maintain 3-year OS of 95% for patients with asymptomatic LR-NBL were met within both stage 1 and stage 4s disease (95% CI on 3-year OS, 99% to 100% and 77% to 98%, respectively).

Of the initial 915 patients, 800 were asymptomatic at diagnosis and observed after their initial operations. Within this group, 89 patients (11.1%) experienced recurrence or PD; 47 remained on protocol-directed therapy, and 42 received unknown off-protocol therapy. At diagnosis, 115 patients received immediate chemotherapy (median, four cycles; range, one to eight cycles). At the end of scheduled chemotherapy, 81% of patients had a very good partial response or better. After chemotherapy, 11 (10%) of the 115 patients had disease recurrence or PD. Five-year EFS rates for patients treated with surgery alone and for patients treated with surgery and immediate chemotherapy were 89% ± 1% and 91% ± 3%, respectively; 5-year OS estimates were 97% ± 1% and 98% ± 1%, respectively (Table 3).

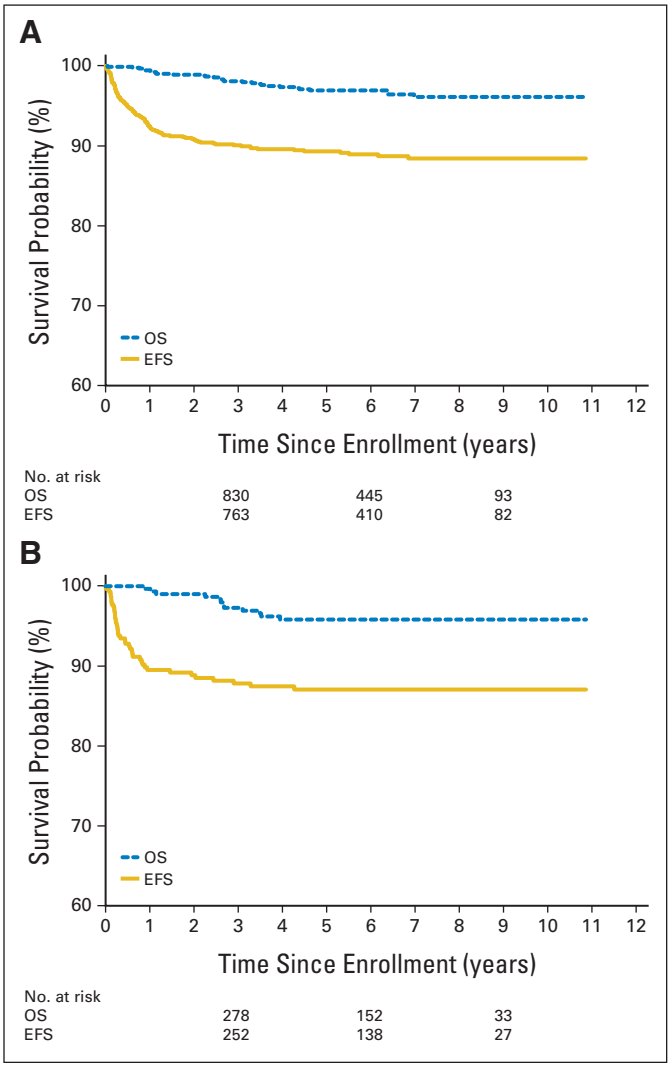

Fig 1. (A) Event-free survival (EFS) and overall survival (OS) curves for patients with low-risk neuroblastoma (n = 915; *y*-axis begins at 60%, not 0%). The numbers of patients at risk for an event or death are shown in the table below the figure at years 3, 6, and 9. (B) EFS and OS curves for asymptomatic patients with International Neuroblastoma Staging System stage 2a or 2b low-risk neuroblastoma (n = 306; *y*-axis begins at 60%, not 0%). The numbers of patients at risk for an event or death are shown in the table below the figure at years 3, 6, and 9.

Risk Factors

Risk categorization was based on an age cutoff of 1 year (Table 1), but we analyzed an age cutoff of 18 months[11] and found OS to be significantly different, but clinically similar, between patients less than 18 months of age and those ≥ 18 months (98% ± 1% and 95% ± 1%, respectively; $P = .0092$; Table 3).

Only 1% (n = 11, 10 with stage 1 and one with stage 2a disease) of study patients had *MYCN*-A tumors. The impact of *MYCN* status was analyzed only in patients with stage 1 disease; for patients with *MYCN*-NA and *MYCN*-A tumors 5-year EFS was 93% ± 2% and

Table 4. EFS and OS of Patients With INSS Stage 2a and 2b Disease

Characteristic	No. of Patients		EFS					OS				
			Stage 2a		Stage 2b			Stage 2a		Stage 2b		
	Stage 2a	Stage 2b	5-Year EFS (%)	± SE (%)	5-Year EFS (%)	± SE (%)	*P*	5-Year OS (%)	± SE (%)	5-Year OS (%)	± SE (%)	
Age, months							.2837					.0037
< 18	83	155	92	4	88	3		99	2	99	1	
≥ 18	62	82	94	4	80	5		97	3	90	4	
MYCN status												
Not amplified	144	236	92	3	85	3		98	2	96	2	
Amplified	1	0	No event		NA			No death		NA		
Unknown	0	1										
Histology							.0023					< .001
Favorable	115	170	91	3	90	3		98	2	99	1	
Unfavorable	30	64	97	4	72	7		96	4	86	5	
Unknown	0	3										
Ploidy							.0129					< .001
Hyperdiploid	103	171	92	3	89	3		98	2	99	1	
Diploid	34	53	91	6	75	8		97	4	84	6	
Unknown	8	13										

Abbreviation: EFS, event-free survival; NA, not applicable to this low-risk study; OS, overall survival.

70% ± 17% ($P = .0042$), respectively, and 5-year OS was 99% ± 1% and 80% ± 15% ($P < .001$), respectively.

FH disease was seen in 730 patients (81%) and was associated with higher EFS (91% ± 1%) than that achieved for the 175 patients with UH tumors (83% ± 4%; $P < .001$); OS differed significantly as well (98% ± 1% for FH and 91% ± 3% for UH; $P < .001$). Histology had a significant impact on outcome for patients with stage 1 NBL (EFS: 94% ± 2% for FH *v* 86% ± 5% for UH, $P = .0060$; OS: 100% for FH *v* 93% ± 3% for UH, $P < .001$) and for patients with stage 2b disease (EFS: 90% ± 3% for FH *v* 72% ± 7% for UH, $P = .0023$; OS: 99% ± 1% for FH *v* 86% ± 5% for UH, $P < .001$; Table 4).

Three-quarters of patients with LR-NBL had hyperdiploid tumors. In the overall LR-NBL cohort, ploidy only affected OS (98% ± 1% for hyperdiploid *v* 94% ± 2% for diploid, respectively; $P = .0252$; Table 3). As with histology, the effect of ploidy on EFS was driven by the stage 2b subset (EFS: 89% ± 3% for hyperdiploid *v* 75% ± 8% for diploid, $P = .0129$; OS: 99% ± 1% for hyperdiploid *v* 84% ± 6% for diploid, $P < .001$; Table 4).

Twenty-nine patients died; 27 died from disease progression, one died from treatment toxicity for secondary acute myeloid leukemia, and one had an accidental death (Appendix Table A2, online only). Of patients with PD, two had been given chemotherapy at diagnosis, six had received chemotherapy on study after PD, and 18 had received therapy off protocol.

Patients were evaluated for response to chemotherapy after the last planned cycle of treatment. Responses for the 115 patients who received chemotherapy were as follows: 21 complete responses (21%), 31 very good partial responses (31%), 29 partial responses (29%), five mixed responses (5%), 13 no responses (13%), and one early death (1%); in 15 patients, response was not reported.

The incidence and severity of toxicities reported during this study were as expected (Appendix Table A3, online only). The most frequently reported grade 3 or 4 toxicities were for bone marrow (81.4%) and infections (36%; wherein 49 of 58 patients were < 1 year old). There were no fatal chemotherapy toxicities. Two patients, neither of whom received chemotherapy, experienced a second malignancy.

DISCUSSION

Before their merger, the CCG and POG used different NBL staging systems and different biologic factors to determine therapy. The POG relied on tumor ploidy and the CCG on histology; both groups recognized *MYCN* amplification as a predictor of poor prognosis. Despite similar therapy approaches, meaningful comparison of results across stages was not possible.[12] P9641 and the contemporary study for intermediate-risk NBL[13] were the first NBL studies in COG to test risk stratification based on consensus-derived factors. For former POG member institutions, the study represented a reduction in therapy for patients with stage 2a, 2b, and 4s disease.

In P9641, asymptomatic patients with INSS stage 2a and 2b disease achieved 5-year EFS and OS rates of 87% ± 2% and 96% ± 1%, respectively. These are similar to the OS rates reported in previous POG studies in which these patients received multiagent chemotherapy for up to 8 months.[2,14,15] The EFS and OS rates achieved for patients with stage 1 disease were similar to those achieved with primary surgical approaches in previous POG and CCG studies.[1,3] For patients with LR stage 4s disease, the EFS and OS rates were higher than those on earlier POG studies when different factors were used to assign therapy,[14,16] but similar to the OS of 92% reported by the CCG.[17] Patients on P9641 who received chemotherapy also experienced fewer and less severe toxicities than patients in these earlier studies. Together with recently published International Society of Pediatric Oncology Europe Neuroblastoma Study Group results using a similar approach for the treatment of LR-NBL (LNESG1),[18] the results of P9641 demonstrate that surgery alone, even less than complete resection, can cure nearly all patients with stage 1 NBL and the

vast majority of patients with asymptomatic, favorable biology, INSS stage 2a and 2b disease.

The difference in OS of patients with stage 4s NBL who were initially observed versus patients who were treated immediately with chemotherapy (5-year OS: 84% ± 7% *v* 97% ± 3%, respectively) was not significant but was surprising nonetheless. All of these patients had favorable biology tumors. Because earlier work of the POG and CCG suggested that chemotherapy toxicity may have contributed to lower survival of patients with stage 4s disease, we restricted the use of chemotherapy to specific situations and suggested that the number of cycles of chemotherapy be limited if there was clinical improvement. The reason for the potential difference in our patient cohorts is not yet evident. Further analyses are planned for these patients combined with patients with intermediate-risk stage 4s NBL for whom chemotherapy treatment was nearly identical.[13]

Using the risk classification of P9641, not all LR patients fared equally well. The survival rates for patients with stage 2b NBL with UH or diploid tumors were possibly not high enough to warrant a designation of low risk. These patients seem to have similar survival to that of patients on a POG study (where histology was not examined) who were more than 1 year old with *MYCN*-NA diploid stage B tumors and received chemotherapy similar to that given to intermediate-risk patients.[15] In an earlier CCG study, UH was a significant prognostic factor in Evans stage II disease, but results were not reported using INSS criteria.[3] In the LNESG1 study, ploidy was not prognostic of the survival of patients with INSS stage 2 disease, a cohort that included many patients analogous to those with POG stage B disease; however, UH was associated with a 5-year OS of only 75.9%, worse than what was observed on P9641 (5-year OS: 89% ± 4% for patients with stage 2a and 2b NBL).[18] In P9641, *MYCN*-A was associated with significantly lower EFS and OS rates in patients with stage 1 disease; the occurrence of *MYCN*-A with FH stage 2 disease was quite rare. However, the majority of patients with *MYCN*-A tumors did not have an event after surgical resection. De Bernardi et al[18] observed similar findings in the LNESG1 study. Taken together, these data suggest that ploidy, histology, and *MYCN* status affect patients with LR-NBL differently, particularly with regard to *MYCN* in stage 1 NBL and UH and ploidy in stage 2b disease. Further refinements in risk classification to define LR-NBL will need to be tested prospectively.

Results of the companion biology study onto which patients were enrolled revealed that patients whose tumors harbored 1p36 loss of heterozygosity (LOH), unbalanced 11qLOH, or both had a significantly worse outcomes than patients whose tumors lacked these characteristics.[19] Furthermore, because unbalanced 11qLOH was not associated with *MYCN*-A, these factors may independently reflect more aggressive clinical behavior in what otherwise appears to be LR disease. In the COG NBL intermediate-risk trial ongoing at the time of this report, 1pLOH and unbalanced 11qLOH are used in addition to the factors of P9641 to assign risk and therapy. Whether these alone will improve prognostication remains to be seen. Microarray profiling has also shown promise in identifying patients with LR-NBL at greater risk for recurrence,[20-23] and results of these studies might be evaluated for future risk stratification.

The chemotherapy regimen used in this study had not been used in earlier trials. At the end of scheduled chemotherapy, 81% of patients had a partial response or better. In earlier POG trials, patients with less than complete response to chemotherapy would have proceeded to surgery to remove residual disease or to additional chemotherapy. In P9641, in which 79% of patients had less than complete response after chemotherapy, delayed resection was optional. Given the survival rates achieved on P9641, delayed resection of residual disease may not be necessary for cure of patients with LR-NBL.

In conclusion, our data demonstrate that the use of surgery alone is curative therapy for most patients with LR-NBL and that the use of chemotherapy may be restricted to specific situations. Patients need not undergo complete resection of disease to be cured by surgery alone. Children with *MYCN*-A stage 1 NBL and those with *MYCN*-NA stage 2b NBL who are ≥ 18 months of age or who have UH or diploid disease have a less favorable outcome than other low-risk patients. Further refinements of risk classification schema are needed for these patients. These refinements, further restriction of chemotherapy, and questions about the extent of surgical resection necessary for cure will be the goals of future studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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