ORIGINAL ARTICLE

# Outcome after Reduced Chemotherapy for Intermediate-Risk Neuroblastoma

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## ABSTRACT

### BACKGROUND

The survival rate among patients with intermediate-risk neuroblastoma who receive dose-intensive chemotherapy is excellent, but the survival rate among patients who receive reduced doses of chemotherapy for shorter periods of time is not known.

### METHODS

We conducted a prospective, phase 3, nonrandomized trial to determine whether a 3-year estimated overall survival of more than 90% could be maintained with reductions in the duration of therapy and drug doses, using a tumor biology–based therapy assignment. Eligible patients had newly diagnosed, intermediate-risk neuroblastoma without *MYCN* amplification; these patients included infants (<365 days of age) who had stage 3 or 4 disease, children (≥365 days of age) who had stage 3 tumors with favorable histopathological features, and infants who had stage 4S disease with a diploid DNA index or unfavorable histopathological features. Patients who had disease with favorable histopathological features and hyperdiploidy were assigned to four cycles of chemotherapy, and those with an incomplete response or either unfavorable feature were assigned to eight cycles.

### RESULTS

Between 1997 and 2005, a total of 479 eligible patients were enrolled in this trial (270 patients with stage 3 disease, 178 with stage 4 disease, and 31 with stage 4S disease). A total of 323 patients had tumors with favorable biologic features, and 141 had tumors with unfavorable biologic features. Ploidy, but not histopathological features, was significantly predictive of the outcome. Severe adverse events without disease progression occurred in 10 patients (2.1%), including secondary leukemia (in 3 patients), death from infection (in 3 patients), and death at surgery (in 4 patients). The 3-year estimate (±SE) of overall survival for the entire group was 96±1%, with an overall survival rate of 98±1% among patients who had tumors with favorable biologic features and 93±2% among patients who had tumors with unfavorable biologic features.

### CONCLUSIONS

A very high rate of survival among patients with intermediate-risk neuroblastoma was achieved with a biologically based treatment assignment involving a substantially reduced duration of chemotherapy and reduced doses of chemotherapeutic agents as compared with the regimens used in earlier trials. These data provide support for further reduction in chemotherapy with more refined risk stratification. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00003093.)

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Neuroblastoma is the most common extracranial solid tumor in childhood, accounting for 50% of neoplasms diagnosed in the first year of life.[1] This disease has a heterogeneous course, ranging from spontaneous regression to inexorable progression and death, depending on the biologic features of the tumor.[2-6] Identification of risk groups on the basis of clinical and molecular prognostic variables has allowed tailoring of therapy to improve outcomes and minimize the risk of deleterious consequences of therapy.[7-14]

In 1998, the Children's Oncology Group (COG) established a system of risk stratification for neuroblastoma that was based on clinical data (the patient's age at diagnosis and the tumor stage) and tumor-derived biologic data (histopathological classification, *MYCN* oncogene amplification status, and ploidy).[15,16] Intermediate-risk neuroblastoma was defined as stage 3 or 4 disease without *MYCN* amplification in an infant (<365 days of age), stage 3 disease and favorable histopathological features in a child (≥365 days of age),[5,6] and stage 4S disease with a diploid tumor-cell DNA index, unfavorable histopathological features, or both.[5,6] Stage 4S denotes a special metastatic stage of neuroblastoma in infants with a primary tumor that is restricted to one side of the midline and with metastatic sites limited to the liver, skin, bone marrow, or a combination of these sites (with <10% of marrow cells replaced by tumor). The rate of overall survival among patients with intermediate-risk disease exceeded 80% with the use of moderately aggressive chemotherapy in cooperative-group trials.[7-10] The purpose of the phase 3 study Treatment for Infants and Children with Intermediate-Risk Neuroblastoma (A3961) was to achieve a 3-year estimate of overall survival of more than 90% with the use of reduced outpatient-based chemotherapy in children with intermediate-risk neuroblastoma; this level was selected on the basis of preceding trials involving similar patients.

## METHODS

### STUDY DESIGN AND OVERSIGHT

The study was a prospective, uncontrolled, nonrandomized, phase 3 clinical trial in which we evaluated survival associated with reduced therapy for intermediate-risk neuroblastoma, as compared with a standard rate, which was associated with a 3-year estimate of overall survival of 90%; this rate was selected on the basis of a subjective review of the previous phase 3 COG study of intermediate-risk neuroblastoma. The length of therapy was stratified according to the biologic features of the tumor.

All authors contributed to the study design, data collection, analysis, and manuscript preparation. All data were collected and entered electronically at COG treating institutions, which undergo routine COG audits. All data were subjected to quality assurance, maintained by the COG Statistics and Data Center, and reviewed by the COG data and safety monitoring committee. All authors vouch for the accuracy and completeness of the reported data and for the conformance of this report to the protocol. The National Cancer Institute sponsored the trial and imposed no impediments, direct or indirect, on the publication of the study's full results. The protocol is available with the full text of this article at NEJM.org. All chemotherapy drugs were purchased.

### PATIENTS AND TUMOR ASSESSMENTS

Infants (<365 days old) and children (≥365 days old) who had newly diagnosed, intermediate-risk neuroblastoma without tumor *MYCN* amplification were eligible for the study. The DNA index was used for risk stratification in infants only. Patients included infants with International Neuroblastoma Staging System (INSS) stage 3 or 4 disease, children with stage 3 disease (favorable histopathological features),[6] and infants with stage 4S disease (unfavorable biologic features). Staging and response evaluation were performed according to INSS recommendations (Tables 1 and 2 in the Supplementary Appendix, available at NEJM.org), with metaiodobenzylguanidine (MIBG) scans available for 262 patients (58%).[17] Parents or guardians provided written informed consent, and the study was approved by local institutional review boards. Enrollment began in March 1998 and ended in May 2005.

*MYCN* copy-number determination with the use of fluorescence in situ hybridization[18] and DNA index assays with the use of flow cytometry were performed by COG reference laboratories.[19] One investigator reviewed all tumors and classified histopathological findings as favorable or unfavorable according to the method described by Shimada et al.[6] Favorable biologic features were defined as favorable histologic characteristics[5] and

a DNA index of more than 1; unfavorable biologic features were defined as unfavorable histologic characteristics, a DNA index of 1 or less, or both (Table 3 in the Supplementary Appendix).

### TREATMENT

Intermediate-risk patients were assigned to one of two strata according to biologic features of the tumor (Fig. 1 and Table 3 in the Supplementary Appendix). Patients who had tumors with favorable biologic features received four cycles and those who had tumors with unfavorable biologic features received eight cycles of chemotherapy with carboplatin, etoposide, cyclophosphamide, and doxorubicin, administered at 3-week intervals (Table 1), followed by surgical excision of the primary tumor to achieve a complete response or a very good partial response according to the International Neuroblastoma Response Criteria (Table 2 in the Supplementary Appendix).[17] Eligible patients with disease that could not be classified as favorable or unfavorable were included in the overall outcome analyses. All infants younger than 60 days of age received granulocyte colony-stimulating factor after each chemotherapy cycle (after 1999), whereas it was optional in all other patients. Patients with tumors with favorable biologic features who did not have a complete response or a very good partial response after four cycles of chemotherapy received four additional cycles, for a total of eight.

### TOXICITY MONITORING

All patients underwent evaluations of renal, hepatic, and hematologic function at 3-week intervals; cardiac function at diagnosis, after cycle 4, and at the end of therapy; and auditory function at diagnosis and at the end of therapy. Toxic effects were defined according to the National Cancer Institute's Common Toxicity Criteria, version 2.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcv20_4-30-992.pdf), and all grade 3 and 4 toxic effects were documented.

**Table 1. Chemotherapy Regimen for Intermediate-Risk Neuroblastoma.***

| Cycle and Day | Treatment | Dose | |
|---|---|---|---|
| | | *mg/m²/day* | *mg/kg/day in children <12 kg* |
| Cycle 1 | | | |
| Day 1 | Carboplatin | 560 | 18 |
| Days 1–3 | Etoposide | 120 | 4 |
| Cycle 2 | | | |
| Day 1 | Carboplatin | 560 | 18 |
| Day 1 | Cyclophosphamide | 1000 | 33 |
| Day 1 | Doxorubicin | 30 | 1 |
| Cycle 3 | | | |
| Day 1 | Cyclophosphamide | 1000 | 3 |
| Days 1–3 | Etoposide | 120 | 4 |
| Cycle 4 | | | |
| Day 1 | Carboplatin | 560 | 18 |
| Days 1–3 | Etoposide | 120 | 4 |
| Day 1 | Doxorubicin | 30 | 1 |
| Cycle 5 | | | |
| Day 1 | Cyclophosphamide | 1000 | 33 |
| Days 1–3 | Etoposide | 120 | 4 |
| Cycle 6 | | | |
| Day 1 | Carboplatin | 560 | 18 |
| Day 1 | Cyclophosphamide | 1000 | 3 |
| Day 1 | Doxorubicin | 30 | 1 |
| Cycle 7 | | | |
| Day 1 | Carboplatin | 560 | 18 |
| Days 1–3 | Etoposide | 120 | 4 |
| Cycle 8 | | | |
| Day 1 | Cyclophosphamide | 1000 | 3 |
| Day 1 | Doxorubicin | 30 | 1 |

* Patients who had tumors with favorable biologic features (defined as tumors that did not have *MYCN* amplification and that had a DNA index greater than 1 and favorable histopathological features) received cycles 1 through 4 and only proceeded to cycles 5 through 8 if a complete response was not attained. After four cycles, the response was assessed, and surgery was performed if feasible. After eight cycles, the response was assessed, and surgery was performed if residual primary tumor was detected. Patients who had tumors with unfavorable biologic characteristics (patients with tumors that did not have *MYCN* amplification but that had a DNA index of 1, unfavorable histopathological features, or both) were assigned to receive all eight cycles.

### STATISTICAL ANALYSIS

Intention-to-treat analyses of event-free survival and overall survival were performed. The primary end point was overall survival at 3 years. The time to an event was calculated from enrollment to the first occurrence of relapse, progression, death from any cause, or secondary cancer, or the time to the last contact if no event was observed. For overall survival, the event was death. Survival estimates based on the Kaplan–Meier method were reported at the 3-year time point, with standard errors calculated according to the method of Greenwood.[20] With the exception of P values for maintenance of the rate of event-free survival (with adjustment for multiple testing), P values of less than 0.05

were considered to indicate statistical significance. Reported P values during the monitoring for maintenance of event-free survival and overall survival are one-sided; all other reported P values are two-sided.

We tested for maintenance of a 3-year overall survival estimate of 90%, assuming the cumulative hazard function (null hypothesis)

$$\Lambda(t_i) = -\log_e [0.9 + 0.1e^{(-t_i)}],\ i = 1,\ \ldots,\ n.$$

Under the null hypothesis, an expected overall survival of 90% at 3 years was specified for patients who were considered to be cured, with the assumption that treatment failed in an exponential manner in the other 10% of patients within the first 3 years; this closely resembles the overall survival curve in the previous COG study of intermediate-risk neuroblastoma (which involved more intensive therapy than that used in this study). Using a chi-square test, we compared the number of deaths expected under the null hypothesis with the number of deaths observed. Similarly, we monitored for maintenance of the rate of event-free survival (90% at 3 years) (alpha level for analysis of cumulative data, 0.05; alpha level for analysis of data at last evaluation, 0.035) with the use of O'Brien–Fleming methods.[21] A copy of the COG database as it existed on November 4, 2008, was used for the final analysis.

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

A total of 479 eligible patients were enrolled between 1997 and 2005; of these, 270 had stage 3 disease (102 children and 168 infants), 178 infants had stage 4 disease, and 31 infants had stage 4S disease (Table 4 in the Supplementary Appendix). Of the 464 patients with fully known biologic features, 323 patients had tumors with favorable biologic features (69.6%) and 141 had tumors with unfavorable biologic features (30.4%). Fifteen had incomplete assessment with favorable known factors (13 received four cycles and 2 received eight cycles of chemotherapy). A total of 138 patients (36 children and 41 infants with stage 3 disease and 61 infants with stage 4 disease) who had tumors with favorable biologic features and who did not have a complete response or a very good partial response after cycle 4 received four more cycles, for a total of eight.

### SURGERY AND LOCAL TUMOR CONTROL

At the time of this analysis, complete surgical data were available for 235 of the 479 eligible patients. Baseline characteristics of the surgical cohort with respect to disease stage, age, histopathological features of the tumor, and ploidy status did not differ significantly from the characteristics of the overall cohort; therefore, the patients with surgical review were considered to be representative of the entire study cohort. Definitive surgical resection of the primary tumor was attempted in 234 patients (99.6%). Eighty-nine patients underwent gross total resection, 51 underwent near total resection (>90% of the tumor), 26 underwent major resection (>50% of the tumor), and 54 underwent limited resection (≤50% of the tumor); the degree of resection was unknown in 14 patients. No significant difference was noted in overall survival according to the degree of resection (complete vs. incomplete, P=0.37). Twenty-eight percent of patients had one or more complications: major hemorrhage (14%), loss of a normal organ during surgery (6%), renal injury (4%), vascular injury (4%), pulmonary injury (3%), nerve resection (2%), wound complications (2%), nephrectomy (1%), and other complications (7%).

Only 12 of 479 patients (2.5%) received local radiotherapy (21 Gy); of these patients, 1 patient had stage 4S disease, 5 patients had stage 3 disease, and 6 patients had stage 4 disease. Radiotherapy was administered for clinical deterioration despite initial therapy (in 8 patients), residual macroscopic disease and unfavorable biologic features (in 3 patients), or relapse after therapy (in 1 patient).

### TREATMENT-RELATED TOXICITY

Reversible myelosuppression was the most common grade 3 or 4 toxic effect, occurring in 68% of patients during cycles 1 through 4 and in 67% during cycles 5 through 8 (P=0.68) (Table 5 in the Supplementary Appendix). Nonhematologic organ toxicity was minimal. In cycles 1 through 4, grade 3 or 4 toxic effects on the kidneys (in 2% of patients), heart (in 4%), and hearing (in <1%) were each reversible. From cycles 1 through 4 to cycles 5 through 8, the proportion of patients with gastrointestinal toxicity decreased (from 8% to 3%, P=0.004), as did the proportion of patients with liver toxicity (from 6% to 2%, P=0.01).

The rate of grade 3 or 4 infections was 13% in cycles 1 through 4 and 11% in cycles 5 through 8

(P=0.48) (Table 5 in the Supplementary Appendix), with infection the sole cause of death in three patients (<1%). Secondary leukemia with chromosome 11q aberrations was diagnosed in three patients (acute myeloid leukemia in two and acute lymphoblastic leukemia in one) at 16, 17, and 27 months after the diagnosis of neuroblastoma; all three patients received eight cycles of chemotherapy and no radiation. In one patient, secondary leukemia developed after additional therapy for persistent disease, including myeloablative chemotherapy with autologous stem-cell rescue. The cumulative incidence of secondary cancer was 0.7% (95% confidence interval [CI], 0.2 to 1.8).

### EVENT-FREE SURVIVAL, OVERALL SURVIVAL, AND PROGNOSTIC FACTORS

Among all 476 eligible patients for whom follow-up data were available, the 3-year estimates (±SE) of event-free and overall survival were 88±2% (95% CI, 84 to 90) and 96±1% (95% CI, 94 to 97), respectively (Fig. 1). The median follow-up time for patients who survived without an event was 5.2 years (range, 9 days to 10.1 years). During the interim monitoring for maintenance of the event-free survival rate of 90% at 3 years, the monitoring boundary for insufficient event-free survival was not crossed.

The 3-year event-free survival estimate among the 269 patients with stage 3 disease was 92±2%, among the 31 patients with stage 4S disease it was 90±5%, and among the 176 patients with stage 4 disease it was 81±3% (P<0.001 for stages 3 and 4S vs. stage 4); the respective 3-year overall survival estimates were 98±1%, 97±3%, and 93±2% (P=0.002 for stages 3 and 4S vs. stage 4) (Fig. 2A and 2B). The outcome for patients with stage 4 disease was slightly inferior to that for patients with stage 3 or 4S disease, but the goal of exceeding a 90% estimate of overall survival at 3 years was maintained. The 3-year event-free and overall survival estimates among patients who had tumors with favorable biologic features as compared with patients who had tumors with unfavorable features were 90±2% versus 83±3% (P=0.04) and 98±1% versus 93±2% (P=0.02), respectively (Table 2 and Fig. 2C and 2D). Of the two prognostic factors used to stratify risk (ploidy and histopathological features), only ploidy was significantly associated with the outcome, both in infants only (Table 2) and in patients of any age (Fig. 2E through 2H). Outcomes according to INSS stage did not differ significantly between patients with tumors that had favorable biologic features and those with tumors that had unfavorable features (Table 2). A total of 308 patients had a complete response or a very good partial response to chemotherapy, with or without surgery — 37.2% after four cycles and 61.7% after eight cycles. Among patients with tumors that had favorable biologic features, the overall survival rate at 3 years (±2%) among those who received eight cycles of chemotherapy was similar to the rate among those who received four cycles (100% and 96%, respectively).

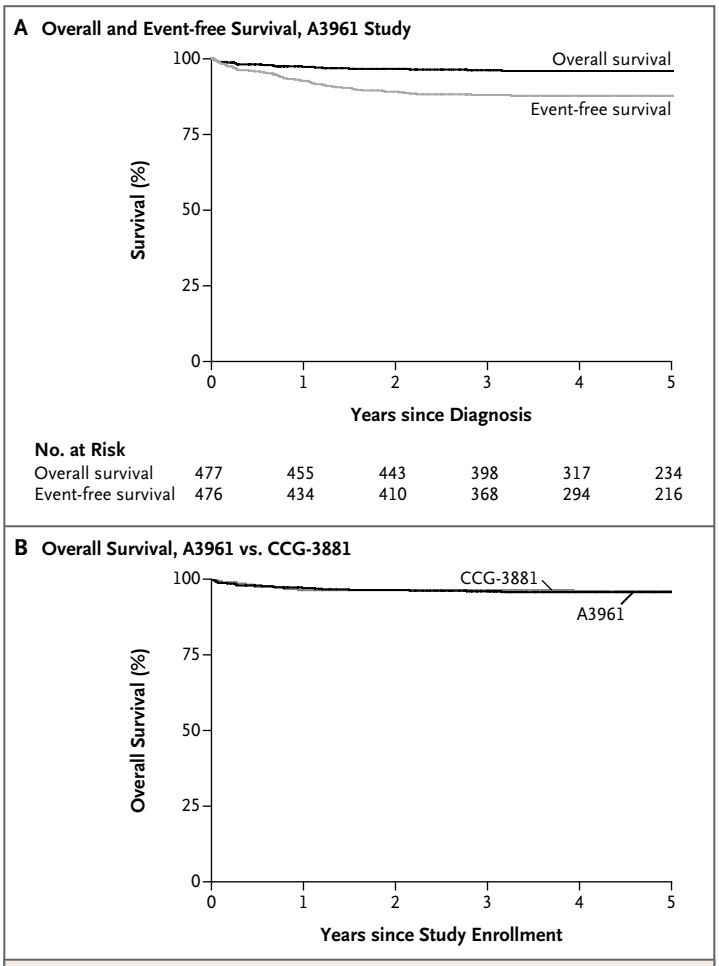


**Figure 1. Event-free and Overall Survival among Patients with Intermediate-Risk Neuroblastoma.**

Panel A shows overall and event-free survival in the Treatment for Infants and Children with Intermediate-Risk Neuroblastoma study (A3961), and Panel B shows overall survival among the 476 patients in the A3961 study as compared with overall survival among the 276 patients in the Children's Cancer Group study (CCG-3881).

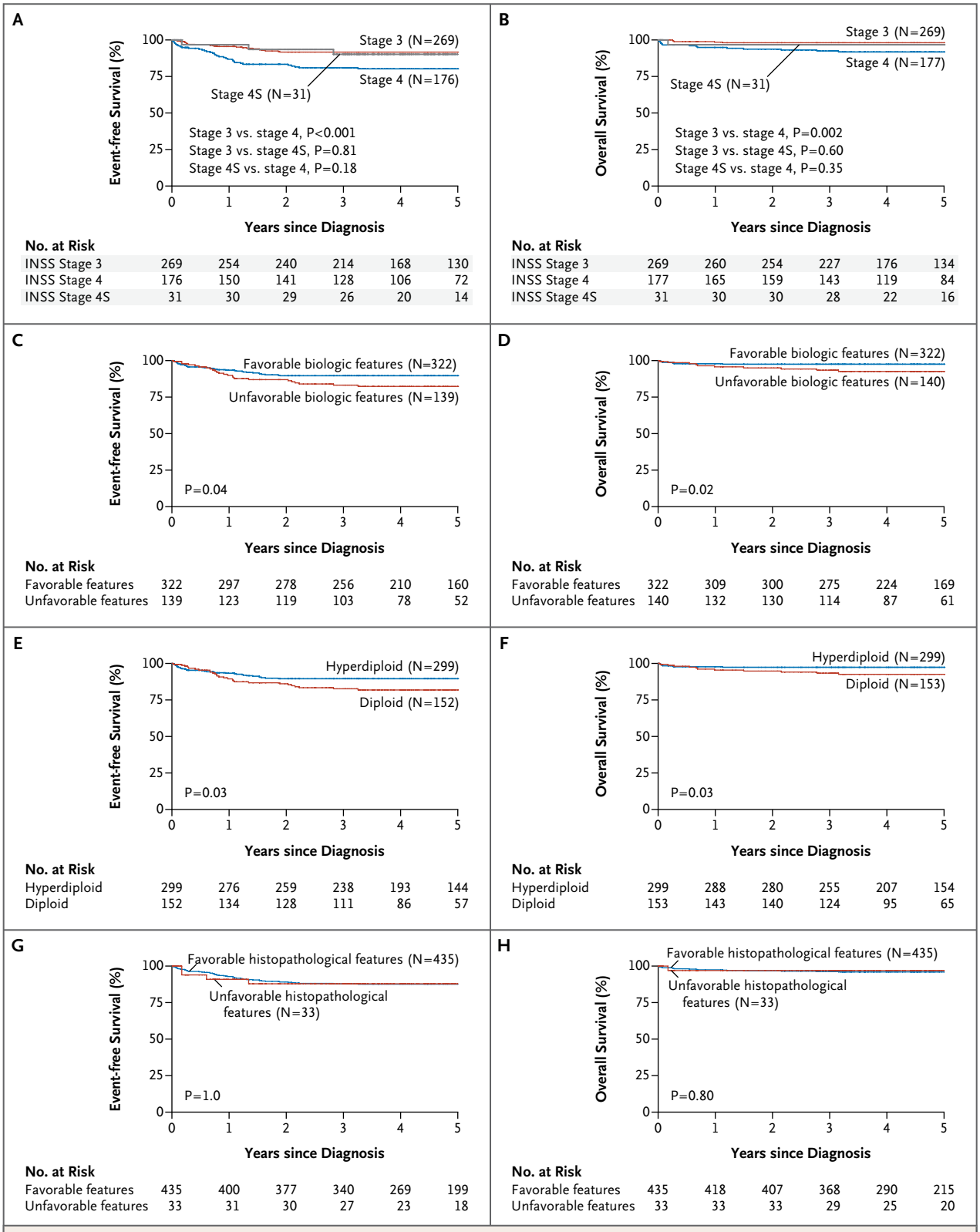


**Figure 2. A3961 Outcomes According to Risk Cohort.**

INSS denotes International Neuroblastoma Staging System.

**Table 2. Outcomes According to Characteristics of the Patients.***

| Cohort and Status | No. of Patients | 3-Yr Event-free Survival | P Value | 3-Yr Overall Survival | P Value |
|---|---|---|---|---|---|
| | | % | | % | |
| Overall | 476† | 88±2 | NA | 96+1 | NA |
| INSS stage | | | | | |
| 3 (overall) | 269 | 92±2 | <0.001‡ | 98±1 | 0.002‡ |
| Infants | 167 | 95±2 | | 98±1 | |
| Children | 102 | 87±3 | | 99±1 | |
| 4 | 176 | 81±3 | | 93±2 | |
| 4S | 31 | 90±5 | | 97±3 | |
| Biologic features | | | | | |
| Favorable | 322 | 90±2 | 0.04 | 98±1 | 0.02 |
| Unfavorable | 139 | 83±3 | | 93±2 | |
| Unknown | 15 | | | | |
| Favorable biologic features | | | | | |
| Four cycles administered | 182 | 88±2 | 0.19 | 96±2 | 0.13 |
| Eight cycles administered | 138 | 92±2 | | 100 | |
| Unknown no. of cycles | 2 | | | | |
| Stage 3 | 220 | 90±2 | 0.48 | 98±1 | 0.25 |
| Stage 4 | 102 | 88±3 | | 96±2 | |
| Unfavorable biologic features | | | | | |
| Stage 3 | 38 | 97±3 | <0.001‡ | 97±3 | 0.05‡ |
| Stage 4 | 70 | 73±5 | | 90±4 | |
| Stage 4S | 31 | 90±5 | | 97±3 | |
| Ploidy (374 infants only) | | | | | |
| Hyperdiploid | 245 | 91±2 | 0.02 | 97±1 | 0.04 |
| Diploid | 118 | 82±4 | | 92±2 | |
| Unknown | 11 | | | | |
| Hyperdiploid (infants only) | | | | | |
| Stage 3 | 129 | 94±2 | 0.05‡ | 98±1 | 0.33‡ |
| Stage 4 | 113 | 87±3 | | 96±2 | |
| Stage 4S | 3 | 100 | | 100 | |
| Diploid (infants only) | | | | | |
| Stage 3 | 30 | 97±3 | 0.014‡ | 97±3 | 0.06‡ |
| Stage 4 | 60 | 71±6 | | 88±4 | |
| Stage 4S | 28 | 89±6 | | 96±4 | |
| Histopathological features | | | | | |
| Favorable | 435 | 88±2 | 1.00 | 96±1 | 0.80 |
| Unfavorable | 33 | 88±6 | | 97±3 | |
| Unknown | 8 | | | | |

* Plus–minus values are survival estimates ±SE. INSS denotes International Neuroblastoma Staging System, and NA not applicable.
† Three infants were excluded because no follow-up data were available.
‡ The P value is for the comparison of stage 3 and 4S versus stage 4.

### DISEASE PROGRESSION AND DEATH

Among all 479 patients, 59 first events were documented: disease progression (in 42 patients), death (in 14 patients), and secondary leukemia (in 3 patients). Among the 461 patients with known biologic type and follow-up data, 57 events were noted: 33 events in the 322 patients with favorable biologic features (10%) and 24 events in the 139 patients with unfavorable biologic features (17%). Disease progression was locoregional in 30 patients, metastatic in 11, and both in 1. Six of the patients with disease progression subsequently died from the disease, complications of therapy, or both, and the 36 other patients received salvage therapy and survived. Among the 20 patients who died, the primary cause of death was the disease (in 9 patients), operative complications (in 4 patients), infection (in 3 patients), the disease and infection (in 2 patients), secondary leukemia (in 1 patient), or an unrelated cause (in 1 patient).

## DISCUSSION

In our large, prospective, multicenter trial involving patients with intermediate-risk neuroblastoma, including infants with locoregional or metastatic disease and children older than 1 year of age with stage 3 tumors, a 3-year overall survival estimate of 96±1% was achieved with a substantial reduction of cytotoxic therapy. The largest previously published study of treatment for intermediate-risk neuroblastoma (defined on the basis of *MYCN* status, age at diagnosis, histopathological features, and ferritin level) was the Children's Cancer Group trial CCG-3881. Among patients with tumors that had favorable biologic features, the overall survival estimates among the cohorts with INSS stages 4S, 4, and 3 disease were 92%, 93% and 100%, respectively. Among infants with unfavorable biologic features, the overall survival estimate was 93%.[7-9] This outcome was achieved with 9 months of chemotherapy (10 cycles) consisting of cisplatin, doxorubicin, etoposide, and cyclophosphamide, administered in total cumulative doses substantially exceeding those in the current study (Table 3).

Several trials have shown similar survival rates with reduced therapy among patients with intermediate-risk neuroblastoma, but because of differences in the staging and risk factors used and the wide variation within studies of cumulative chemotherapy doses, the results cannot be directly compared. Bagatell et al.[10] reported the outcomes for 220 patients with intermediate-risk neuroblastoma treated in the Pediatric Oncology Group (POG) trial 9243 (Table 3), including infants with all stages of disease except those with localized disease that was completely resected, with a 6-year overall survival estimate of 88%. In multiple European trials, therapy was administered to infants with stage 3, 4S, and 4 disease; treatment intensity was adjusted according to sites of metastases and tumor response. The amount and duration of therapy in these trials ranged from no chemotherapy to eight cycles, depending on the response of the patients.[23-26] The overall survival estimates in these studies were generally similar to those in our study, ranging from 87 to 95%. Some groups have successfully used observation alone in selected infants who had stage 4 disease without radiologic evidence of bone involvement or progression; in these groups the 2-year overall survival estimate was 95%.[23] In infants with localized resectable disease, whose tumors regressed without chemotherapy in half the cases, there was an overall survival estimate of 99%.[24] None of these other studies included dose reduction in children older than 1 year of age who had stage 3 disease with favorable features; in our study, a similar survival rate was achieved with reduced chemotherapy among such children.

In multiple POG studies of neuroblastoma in infants, diploid DNA status negatively affected the outcome, although this may be partly attributable to the inclusion of some infants who had tumors with *MYCN* amplification.[22,27-29] A more recent POG study showed an overall survival estimate of 86% among patients with diploid DNA status, as compared with 94% among patients with hyperdiploid DNA status.[10] In the European studies involving patients with metastatic disease, the rate of event-free survival was higher among 41 infants with hyperdiploidy than among 9 infants with diploid tumors ($P=0.005$).[23] Furthermore, the recently published International Neuroblastoma Risk Group (INRG) analysis showed that diploid DNA status, as compared with hyperdiploid DNA status, was strongly associated with reduced rates of event-free and overall survival ($P<0.001$) in infants with stage 4 disease.[30] Among the patients without *MYCN* amplification in our study, only ploidy, and not histopathological features, predicted the outcome. Although diploidy

**Table 3. Duration of Therapy and Cumulative Drug Doses in Patients Who Had Tumors without *MYCN* Amplification.***

| Variable | A3961† | | CCG-3881‡ | POG-9243§ | | | | SIOPEN 99.2/99.3¶ | | NB 95-S/NB 97‖ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Group A | | Group B | | | | | |
| | *favorable biologic features* | *unfavorable biologic features or poor response* | | *favorable biologic features* | *poor response* | *unfavorable biologic features* | *poor response* | *initial chemotherapy* | *chemotherapy for poor response* | *age <6 mo* | *age ≥6 mo* |
| Duration of therapy (days) | 84 | 168 | 267 | 106 | 190 | 147 | 210 | 42–84 | 126–168 | 42–84 | 84–126 |
| Cumulative dose (mg/m²) | | | | | | | | | | | |
| Cyclophosphamide | 2000 | 5000 | 8100 | 5250 | 7350 | 1050 | 1050 | | 3000–6000 | 4200–8400 | |
| Ifosfamide** | | | | | | 24,000 | 40,000 | | | | 15,000–22,500 |
| Doxorubicin | 60 | 120 | 170 | 175 | 245 | 35 | 35 | | 120–240 | 90–180 | |
| Vincristine | | | | | | | | | 6–12 | 4.5–9 | 6–9 |
| Etoposide | 1080 | 1800 | 2495 | | 180 | 1770 | 2950 | 900–1800 | 1800 | 800–1600 | 800–1200 |
| Cisplatin | | | 510 | | 180 | | | | | | 320–480 |
| Carboplatin** | 1680 | 2800 | | | | 1680 | 2800 | 1200–2400 | 2400 | | |
| Vindesine | | | | | | | | | | | 6–12 |
| Dacarbazine | | | | | | | | | | | 2000–3000 |

* A poor response included an incomplete response to therapy.

† The Treatment for Infants and Children with Intermediate-Risk Neuroblastoma study (A3961) included only patients who had tumors without *MYCN* amplification, including infants with stage 3, 4, or 4S disease (unfavorable histopathological features or diploid tumors) and children with stage 3 disease and favorable histopathological features. Patients who had hyperdiploid tumors with favorable histopathological features received four cycles of therapy, with an additional four cycles in patients with an incomplete response; those who had tumors with unfavorable histopathological features or diploid tumors were assigned to eight cycles.

‡ The Children's Cancer Group study (CCG-3881)[7,8] involving patients treated with chemotherapy included only infants with stage 3 disease (3 of 80 patients had *MYCN*-amplified tumors) and stage 4 disease (excluding patients with *MYCN* amplification) and children older than 1 year of age with stage 3 disease who had tumors with favorable histopathological features, a serum ferritin level of less than 143 ng per milliliter, and no tumor *MYCN* amplification. All patients received the same amount of chemotherapy.

§ The Pediatric Oncology Group (POG) 9243 trial[10,22] included all infants with neuroblastoma except those with localized, completely resectable disease without lymph-node extension; however, group B included 29 of 249 infants with tumors that had *MYCN* gene amplification. Infants who had hyperdiploid tumors without *MYCN* amplification were treated in group A; those with diploid or *MYCN*-amplified tumors were treated in group B.

¶ In the International Society of Paediatric Oncology, European Neuroblastoma Group (SIOPEN) Infant Neuroblastoma 99.2/99.3 study,[23] 125 infants with stage 4S or 4 neuroblastoma underwent observation if they were asymptomatic and did not have bone metastases. If they had symptoms from organ involvement or disease progression (68 patients) they were treated as needed to obtain a response with two to four cycles of carboplatin and etoposide plus up to four cycles of cyclophosphamide, doxorubicin, and vincristine if they did not have a response to the initial therapy. Patients with bone metastases (45 infants) were initially assigned to carboplatin and etoposide, but their treatment was switched to cyclophosphamide, doxorubicin, and vincristine if they did not have a sufficient response.

‖ In the German Pediatric Oncology Group study Treatment for Infants with Localized Neuroblastoma without *MYCN* Amplification (NB 95-S/NB 97),[24] 93 asymptomatic infants (including 21 infants with stage 3 disease) who had localized neuroblastoma that was not resected at diagnosis underwent primary observation. Patients with asymptomatic, regressing tumors underwent observation with or without surgery; infants younger than 6 months of age with disease progression or no regression received two to four cycles of cyclophosphamide, doxorubicin, and vincristine, and infants 6 months of age or older received four to six cycles of cisplatin, etoposide, and vindesine, alternating with doxorubicin, ifosfamide, vincristine, and dacarbazine every 3 weeks. Eventually, 39 of the patients assigned to observation received chemotherapy.

** Five milligrams of carboplatin is approximately equivalent to 1 mg of cisplatin, and 4.3 mg of ifosfamide is approximately equivalent to 1 mg of cyclophosphamide.







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predicted a significantly inferior outcome, the estimates of overall survival at 3 years were 92±1% among infants with diploid DNA status and 97±1% among infants with hyperdiploid DNA status were similar, suggesting that most patients who have a relapse after this moderate chemotherapy can survive with further treatment.

The current study shows that the majority of infants and some children who have advanced neuroblastoma without *MYCN* amplification can be cured with substantially reduced cytotoxic therapy as compared with the regimens used in previous pediatric cooperative-group trials.[7-10,22-29,31] As compared with the regimen used in the CCG-3881 study,[7-9] the duration of therapy has been reduced by 40% (eight cycles) and 70% (four cycles), respectively, with similar outcomes maintained (Fig. 1). In addition, as compared with previous clinical trials involving patients with intermediate-risk neuroblastoma, total cumulative doses of anthracyclines, topoisomerase II inhibitors, and platinum agents were reduced to minimize both acute and long-term toxic effects on hearing, the heart, and the kidneys (Table 3).[11-14,32-35] Recent reports from Europe suggest that some infants with intermediate-risk neuroblastoma can survive without receiving chemotherapy, but identification of these patients at diagnosis may depend on further genetic studies.[23,24] Other reports that residual disease in patients with favorable biologic features does not adversely affect survival suggest that therapy may be further reduced in such patients despite incomplete surgical resection.[9] In our study, the results achieved with four cycles of chemotherapy were similar to the results with eight cycles in patients with tumors that had favorable biologic features. The estimate of overall survival at 3 years was 96%, suggesting that therapy might even be further reduced, as long as patients who have an insufficient response receive additional cycles of therapy. With this approach, a reduction in costs, improvement in the quality of life, and a reduction in late effects of therapy are anticipated.

The extent of surgical resection of the primary tumor did not influence the outcomes in our study, a finding in keeping with the results of other studies.[36] In addition, the relatively high surgical complication rate of 28% with four deaths highlights the need for these procedures to be undertaken by experienced pediatric surgeons in specialized pediatric hospitals, using a selective surgical approach to minimize surgical morbidity in these patients. It is hoped that the determination of surgical risk factors on the basis of radiologic assessment of resectability ("image-defined risk factors") in future clinical trials, as defined by the INRG staging system, will guide the timing of primary resection and decrease surgical complications.[37-39] Radiotherapy was not necessary as a primary treatment in this study; it was successfully restricted to 12 patients (2.5%), without detriment to the outcome. These findings are consistent with the observations of others.[40]

In conclusion, using risk stratification based on clinical and genetic data, we substantially reduced both the doses and duration of therapy for intermediate-risk neuroblastoma and maintained very high survival rates. These data, along with the low rate of treatment-related deaths (1.7%) and low incidence of secondary leukemia (three cases), provide support for further dose reduction in this population, and assessment of chromosomal deletions and segmental aberrations may provide more specific criteria for determining the duration of therapy in individual patients.[41-46] Functional imaging with MIBG and fluorodeoxyglucose positron-emission tomographic scans may also improve a response-based algorithm, allowing further individualization of therapy to minimize chemotherapy exposure and late effects of treatment.[47]

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