Efficacy of Complete Resection for High-Risk Neuroblastoma: A Children's Cancer Group Study

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Background/Purpose: Previous reports indicate that complete resection of high-risk neuroblastoma improves outcome but may entail high surgical complication rates. The authors evaluated the effect of complete primary site resection on event-free survival (EFS), overall survival (OS), and complication rates in patients entered on a high-risk neuroblastoma treatment protocol.

Methods: A total of 539 eligible patients with high-risk neuroblastoma were entered on protocol CCG-3891. Patients were assigned randomly to continuation chemotherapy or autologous bone marrow transplantation. Surgical resection was performed at diagnosis or after induction chemotherapy. Surgeons assessed resection as complete (CR), minimal residual (<5%, MR), or partial (PR). Incomplete resections received secondary resection or 10 Gy of external beam radiation. Patients were evaluated for EFS, OS, and complications of surgery based on completeness of overall best resection.

Results: The proportion of patients resectable at diagnosis was 27% for CR and 14% for MR. This improved after chemotherapy to 45% and 25%. Complication rates based on completeness of resection were 29%, 38%, and 36% for CR, MR, and PR, respectively. Estimated 5-year EFS rate was 30% $\pm$ 3% for patients who achieved CR (n = 210) compared with 25% $\pm$ 3% (P = .1010) for those with less than CR (n = 258).

Conclusions: Resectability improved after neoadjuvant chemotherapy. Complete resection did not increase complications. There was a small survival benefit for complete resection. This study suggests that complete resection may still be important in the current era of intense chemotherapy and transplant.

INDEX WORDS: Neuroblastoma, high risk, surgery, complications, survival.

NEUROBLASTOMA, a neoplasm of the sympathetic nervous system, is the most common solid extracranial tumor of childhood. The clinical behavior varies widely. Some tumors may regress spontaneously, others may be cured with surgery alone, and others are resistant to aggressive combined-modality therapy. Of the approximately 650 children with neuroblastoma diagnosed in the United States annually, half fall into the resistant high-risk group.[1] Survival rate in this group has been poor, with fewer than 30% surviving 5 years.

The Children's Cancer Group study (CCG-3891) showed superior clinical outcomes for patients with high-risk neuroblastoma who were treated with surgery, myeloablative chemotherapy, total body irradiation, and transplantation of purged autologous bone marrow, followed by treatment with 13-*cis*-retinoic acid.[2] This analysis assesses the efficacy of completeness and timing of surgical resection of primary tumor in children with high-risk neuroblastoma treated on CCG protocol 3891. Resectability, complications, and survival rate were evaluated.

MATERIALS AND METHODS

Patients

CCG-3891 was a study of conventional induction chemotherapy followed by a randomized consolidation regimen for patients with high-risk neuroblastoma. The protocol was approved by the Institutional Review Board at each participating institution. The first randomization compared high-dose consolidation chemotherapy with myeloablative chemoradiotherapy supported by purged autologous bone marrow transplantation (ABMT). A second randomization after consolidation treatment evaluated 13-*cis*-retinoic acid in minimal residual disease. Surgical resection was not randomized and was performed either at diagnosis (Initial Resection-IR) or after 4 to 5 cycles of chemotherapy (Delayed Resection-DR). Second-look surgery (SL) was

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Table 1. Patient Characteristics for all 539 Eligible Patients

Characteristic	No. (%)
Age at diagnosis	
<1 yr	23 (4)
1-2 yr	134 (25)
>2 yr	382 (71)
Total	539
Evans Stage	
II	1 (0)
III	72 (13)
IV*	466 (87)
Total	539
INSS Stage	
2b	1 (0)
3	77 (15)
4	449 (85)
Total	527
Unknown	12
MYCN	
Non-amplified	239 (61)
Amplified	156 (39)
Total	395
Unknown	144
Histology	
Favorable	21 (6)
Unfavorable	352 (94)
Total	373
Unknown	166
Primary Site	
Head	2 (0)
Neck	3 (1)
Chest	27 (6)
Thoracoabdominal	14 (3)
Adrenal	327 (69)
Celiac	34 (7)
Other abdominal	46 (10)
Pelvis	11 (2)
Other	9 (2)
Total	473
Unknown	66

*Includes 13 patients who were initially in stage I or II but in whom bone metastases developed before therapy other than surgery.

often performed in cases in which local control was not achieved with the initial procedure. All surgical procedures for a given patient (IR, DR, or SL) were considered in identifying the overall best extent of resection for that patient. Enrollment began in January 1991 and ended in April 1996. Eligible patients had newly diagnosed high-risk neuroblastoma and were 1 to 18 years old. Table 1 delineates patient characteristics. Seventy-seven had INSS stage 3 disease with one or more of the following unfavorable prognostic factors: amplification of the *MYCN* oncogene,[3] unfavorable Shimada classification,[4,5] or serum ferritin ≥143 ng/mL[6] at diagnosis. The one patient who had stage 2b disease, had *MYCN* amplification. Eight percent (n = 42) of patients were not assigned to any regimen because of relapse, death, or withdrawal before the time of first randomization (8 weeks after diagnosis).

Therapy

Tumors felt to be resectable at diagnosis underwent initial resection (IR) before chemotherapy. Initially unresectable tumors were treated with induction chemotherapy and evaluated for response. Patients without disease progression underwent delayed resection (DR) of the primary tumor and bulky metastatic lesions greater than 3 cm in diameter. Induction chemotherapy consisted of cisplatin, doxorubicin, etoposide, and cyclophosphamide for 5 cycles at 28-day intervals. The operative goal was total resection of the tumors including involved adrenal glands, sympathetic ganglia, and regional lymph nodes, without removal or permanent damage to other structures.

The operating surgeon assessed extent of surgical resection as complete resection, no visible tumor (CR); minimal residual, visible tumor less than 5% (MR); partial resection, greater than 50% removal (PR); and biopsy only (BX). In situations in which local control was not achieved, second-look surgery with re-excision of the tumor or external beam radiotherapy (EBRT) to gross residual disease was administered before continuation chemotherapy (CC) or transplantation (ABMT).

After completion of induction and local control measures, patients received continuation chemotherapy or myeloablative chemoradiotherapy followed by infusion of immunomagnetically purged autologous bone marrow. Patients who were unable to be assigned randomly (n = 160) because of medical or psychosocial reasons were assigned nonrandomly to the same chemotherapy as the randomized CC group.[2] The second randomization followed ABMT or CC. Patients without disease progression were assigned randomly to receive 13-*cis*-retinoic acid or no further therapy.

Statistical Analysis

Life-table methods[7,8] were used to estimate event-free survival (EFS) and overall survival (OS). The method of Peto and Peto[9] was used to estimate standard errors. Elapsed time from study entry to an event or to end of follow-up was used to compute EFS and OS probabilities. Comparisons of EFS and OS according to overall best extent of surgical resection were made, and the log-rank statistic was used to compare EFS rates for CR versus less than CR.

RESULTS

The 5-year EFS and OS rates (n = 539) were 25% +/− 2% and 35% +/− 2%, respectively. The 5-year EFS rates by overall best extent of resection are shown in Table 2. The best resection achieved CR in 210 patients (45%), whereas 258 (55%) achieved less than CR (either MR, PR, or BX). There is a trend toward higher EFS with achieving CR as the overall best extent of resection, but this difference is not statistically significant (P = .1010 for CR [30% +/− 3%] *v.* <CR [25% +/− 3%; Fig. 1A]). When EFS was examined by tumor stage, CR did not significantly improve EFS among stage 3 tumors (P = .8175 for CR [56% +/− 10%] *v.* <CR [46% +/− 9%]) but did significantly improve EFS of stage 4 tumors (P = .0278 for CR [26% +/− 4%] *v.* <CR [19% +/− 3%; Fig 1B]). For OS, there is a trend toward better

Table 2. EFS by Extent of Resection

	For Extent of Resection at Initial Surgery, 5-yr EFS rate (n)	Overall Best Extent of Resection, 5-yr EFS rate (n)
CR	28% +/23 4% (120)	30% +/− 3% (210)
<CR	27% +/− 3% (324)	25% +/− 3% (258)
MR	26% +/− 6% (60)	27 +/− 4% (115)
PR	34% +/− 8% (51)	26% +/− 6% (74)
BX	25% +/− 3% (213)	19% +/− 5% (69)

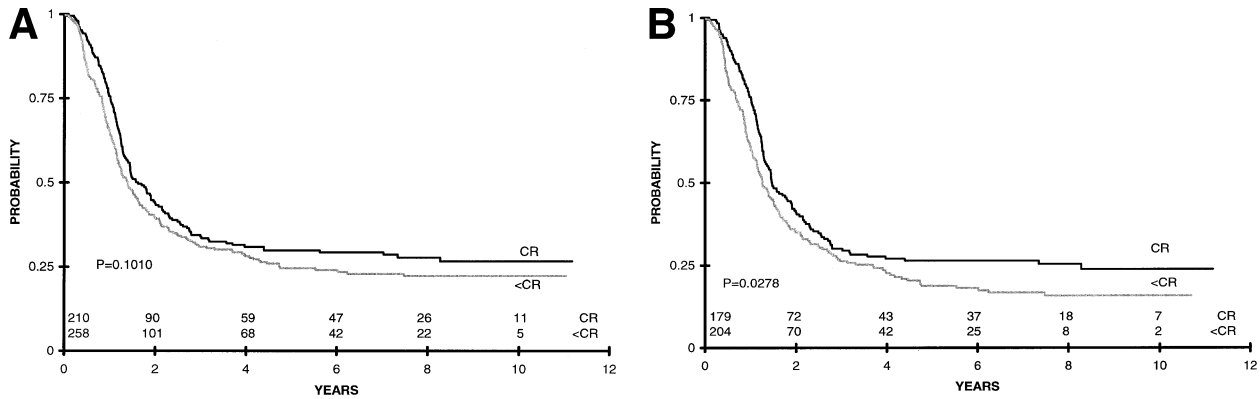

Fig 1. Kaplan-Meier event-free survival curves. (A) By best resection achieved: CR (n = 210) versus <CR (n = 258); *P* = .1010. (B) By best resection achieved for stage 4 tumors: CR (n = 179) versus <CR (n = 204); *P* = .0278.

survival with more complete resection of the primary tumor, but this advantage is not statistically significant ($P = .2352$). When OS was examined by tumor stage, a trend toward improved OS with complete resection was found but again was not statistically significant for either stage 3 tumors ($P = .2852$ for CR [66% +/− 10%] *v.* <CR [48% +/− 9%]) or for stage 4 tumors ($P = .2024$ for CR [36% +/− 4%] *v.* <CR [31% +/− 3%]). A multivariate analysis was performed to determine the impact of surgery by treatment category. Degree of resection was not significant in either CC or ABMT.

At initial operation, only 88 of 323 (28%) patients had a significant resection (CR or MR) performed (Table 3). Only 54 (17%) achieved complete resection. When surgery was delayed until after chemotherapy, the CR rate increased to 46%, with 73% achieving either CR or MR. Notably, second-look procedures achieved similar success rates as delayed resection. Second-look procedures often were performed after IR when resection was less than CR. There were insufficient resections after DR to gauge the effectiveness of secondary resection in this circumstance.

Complications

In patients who achieved a CR for their overall best extent of resection, normal organs were removed in approximately 19% of patients. Although a lower proportion of patients had complications in the CR group, the difference was not statistically significant ($P = .1556$ [Table 4]). Major intraoperative hemorrhage occurred in 7% of cases and was similar by degree of resection. Renal injury was the only other frequent complication, which occurred in 8% of patients and was often caused by a vascular injury during dissection. The overall complication rate was similar for all resection categories. When complications were evaluated as a function of timing of surgery, the proportion of patients with complications was similar at IR (32%), DR (33%), and SL (34%).

DISCUSSION

In patients with stage 3 and 4 neuroblastoma, the primary tumor usually is large and locally invasive. Chemotherapy alone is unlikely to eradicate such disease. Surgery for these large and invasive tumors is technically challenging. All past and current clinical trials for neuroblastoma patients have incorporated surgical resection of the primary disease site. In low-risk disease, the efficacy of surgical therapy is well established[10-14]; however, the benefits of complete resection in high-risk patients, especially in current intensive multimodality treatment protocols, are not clear.

This study shows a trend toward improved survival for complete resection. That benefit is not statistically significant. When survival was evaluated by tumor stage, the trend toward improved survival rate with complete

Table 3. Effectiveness of Surgical Procedure

	Initial Resection (IR), No. (%)	Delayed Initial Resection (DR), No. (%)	Second-Look Surgery (SL) After IR, No. (%)	Second-Look Surgery (SL) After DR, No. (%)
CR	54 (17)	86 (46)	57 (47)	2 (20)
MR	34 (11)	51 (27)	30 (25)	3 (30)
PR	30 (9)	38 (20)	17 (14)	4 (40)
Bx	205 (63)	13 (7)	18 (15)	1 (10)
Total	323	188	122	10

Table 4. Number of Patients with Complications by Extent of Surgical Procedure (n = 399)

Complication	No. of Patients With Complication With a Best Resection of: CR = 210 No. (%)	MR = 115 No. (%)	PR = 74 No. (%)	Total No. (%)
Normal organs removed with tumor	39 (19)	26 (23)	11 (15)	76 (19)
Major hemorrhage intraoperatively	11 (5)	8 (7)	7 (9)	26 (7)
Major hemorrhage postoperatively	1 (0)	0 (0)	0 (0)	1 (0)
Renal injury	14 (7)	14 (12)	6 (8)	34 (8)
Bowel obstruction	1 (0)	0 (0)	3 (4)	4 (1)
Pulmonary complications	3 (1)	1 (1)	4 (5)	8 (2)
Wound complications	0 (0)	2 (2)	3 (4)	5 (1)
Other	8 (4)	5 (5)	7 (10)	20 (5)
Total Complications*	77	56	41	174
Total patients with at least 1 complication	60 (29)	44 (38)	27 (36)	131 (33)

Abbreviations: PR, Gross tumor remaining (greater than 50% resection).

*The same patient may be reporting more than one complication.

resection persisted but was significant only for EFS in stage 4 tumors. This finding contrasts with Matthay's report[15] showing improved survival of stage III tumors with unfavorable biology when resection was complete or near complete. Differences in the findings could be caused by nonrandom use of EBRT at the primary site and the subjectivity of assessment of degree of resection. Standardization of EBRT and radiographic confirmation of degree of resection may eliminate these factors and permit cleaner analysis of the benefits of surgery. Moreover, the effect of tumor biology on resectability confounds this and all studies in which degree of resection is not randomized.

This series confirms prior findings of improved resectability after chemotherapy. Achievement of CR or MR was 3 times more likely after chemotherapy than before. The reasons for this are many: chemotherapy reduces tumor vascularity, leads to reduction in the size of the primary tumor, leads to tumor maturation, and decreases invasion of adjacent organs.

Second-look procedures are very effective at achieving tumor resection and local control. These data suggest that secondary resection is only performed in half of the patients with less than CR at initial resection and a smaller percentage after DR. The reasons for this are likely 2-fold: with large, invasive tumors, many surgeons are reluctant to proceed with further surgery, and radiation is effective in controlling residual disease. Indeed, Haas-Kogan et al[16] in their analysis of EBRT in this protocol, concluded that treatment with 20 Gy enhances local control and survival.

Complications

The incidence of complications in this study is higher than reported in other studies.[17-19] This is because we have chosen to include resection of normal organs as a listed complication. It was unexpected to find that complications were unrelated to extent of resection. The most likely explanation for this finding is that heroic resections to achieve complete resection were not performed at the expense of complications and that in many situations, complete resection may have been abandoned after one or more complications occurred.

The study failed to confirm previous findings of higher complications with operations performed before chemotherapy. This likely represents an educational effect—surgeons are now less likely to perform aggressive resections "up front" because of the prevailing belief that delayed resection is safer.

This study has shown the following: (1) there was no statistically significant improvement in EFS or OS by achieving complete resection, although there was a trend toward increased survival with CR; (2) delayed resection after chemotherapy is more likely to achieve complete resection than initial resection; (3) second-look procedures converted half of patients who initially failed to achieve CR to CR; (4) second-look procedures were performed in only half of patients with less than CR after resection; (5) complication rate and the types of complications were similar with CR, MR, and PR; (6) complication rate is independent of timing of resection—similar complications were seen with IR, DR, and SL procedures.

The question of efficacy of complete resection in high-risk neuroblastoma is not settled. In the next generation of studies, higher intensity treatment may control metastatic disease so well that surgical control of the primary tumor becomes more important. Protocols with routine use of EBRT for the primary tumor may enhance or diminish the effect of surgical resection. Routine review of postsurgical status with MIBG and CT scan will objectify the resection categories.

Appendix I. Participating Investigators—Children's Cancer Group 3891

Institution	Investigator	Grant No.
Children's Hospital Medical Center-Akron, Ohio	Jeffrey Hord	N/A
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