Int. J. Radiation Oncology Biol. Phys., Vol. 56, No. 1, pp. 28–39, 2003

0360-3016/03/$–see front matter

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doi:10.1016/S0360-3016(02)04506-6

CLINICAL INVESTIGATION **Pediatrics**

IMPACT OF RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA: A CHILDREN'S CANCER GROUP STUDY

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Purpose: To assess the effect of local radiation administered to primary disease sites in children with high-risk neuroblastoma.

Methods and Materials: A total of 539 eligible patients were entered on protocol CCG-3891, consisting of chemotherapy, primary surgery, and 10 Gy of external beam radiation therapy (EBRT) to gross residual disease, followed by randomized assignment to continuation chemotherapy (CC) or autologous bone marrow transplantation (ABMT). ABMT patients received total body irradiation (TBI).

Results: Estimated event-free survival and overall survival at 5 years were 25% ± 2% and 35% ± 2%, respectively. Estimated 5-year locoregional recurrence rates were 51% ± 5% and 33% ± 7% for CC and ABMT patients ($p = 0.004$). For patients who received 10 Gy of EBRT to the primary, the addition of 10 Gy of TBI and ABMT decreased local recurrence compared with CC (22% ± 12% and 52% ± 8%, $p = 0.022$). EBRT did not increase acute toxicity, except for increased total parenteral nutrition administration.

Conclusions: In combination with EBRT to the primary tumor site, the addition of 10 Gy of TBI as a component of high-dose chemotherapy with ABMT improved local control compared with CC without TBI. Results suggest a dose–response relationship for local EBRT. Short-term toxicity of local EBRT is limited. **© 2003 Elsevier Inc.**

Radiation, Pediatric, High-risk neuroblastoma.

INTRODUCTION

Neuroblastoma, the most common extracranial solid tumor of childhood, is a neoplasm that arises from sympathetic ganglion cells. Approximately 650 children are diagnosed with it in the United States each year, half of them presenting with Stage IV metastatic disease (1). Despite concerted clinical and scientific efforts, prognoses of patients with high-risk neuroblastoma remain poor. Less than 30% of patients with high-risk disease who are older than 1 year survive more than 5 years (2).

The risk of relapse at the primary disease site presents a significant challenge. Patients with Stage IV neuroblastoma usually present with large, invasive primary tumors that are rarely eradicated by chemotherapy alone and pose complex hurdles to surgery (2). As a result, local recurrences occur in 17%–74% of patients (3–8). Although no randomized trials have addressed the role of radiation in children with Stage IV disease, some recent studies reported apparently improved local control rates by adding radiation therapy or increasing radiation doses to primary sites of disease (7–11). Current multimodality protocols for high-risk neuroblastoma patients have incorporated radiation to the primary disease site (12). However, optimal application of radiation to high-risk patients, specifically dosage, timing, and use with macroscopic and microscopic disease, remains elusive.

The recently reported randomized Children's Cancer Group study (CCG-3891) showed superior clinical outcomes for patients with high-risk neuroblastoma who were treated with myeloablative chemotherapy and total body irradiation (TBI) with transplantation of purged autologous

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Supported in part by ASCO Career Development Award (DAH-K) and Pfizer Scholar Grant for New Faculty (DAH-K), Kasle and Tcalcevik Neuroblastoma Research Fund (KKM), and Children's Cancer Group (CA13539), from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Contributing Children's Cancer Group investigators, institutions, and grant numbers are given in the appendix.

Received Aug 20, 2002. Accepted for publication Oct 16, 2002.

bone marrow, followed by treatment with 13-*cis*-retinoic acid (12). External beam radiation therapy (EBRT) was prescribed for all patients with gross residual disease after induction chemotherapy and surgery. Patients randomly assigned to the transplantation arm received additional TBI as a component of the ablative regimen. The purpose of the study described here was to analyze efficacy of radiation administered to residual primary disease sites in children with high-risk neuroblastoma treated on CCG protocol 3891.

METHODS AND MATERIALS

Patients

The CCG-3891 protocol was a randomized study that compared conventional-dosage treatment with ablative chemoradiotherapy supported by purged autologous bone marrow transplantation (ABMT) for patients with high-risk neuroblastoma. 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. Four hundred fifty-three patients had Evans Stage IV disease. Seventy-two had Stage III disease with one or more of the following: amplification of the *MYCN* oncogene (13), unfavorable histopathology by Shimada classification (14, 15), and serum ferritin ≥143 ng/ml (16). One patient older than 1 year at diagnosis had Stage II disease with *MYCN* amplification, and 13 had Stage I or II disease with bone metastases that developed before chemotherapy or radiation treatment. There were no patients with Stage IVS who developed bone metastases before therapy other than surgery, although they would have been eligible for this trial. 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). Patients receiving continuation chemotherapy (CC) and ABMT displayed similar rates of tumor response to treatment, a finding that has been corroborated by a study that documented similar rates of neuroblastoma cells detected in bone marrow of CC and ABMT patients (17). The response rates at the end of induction were essentially identical in the two groups, with complete remissions or very good partial remissions achieved in 67% of patients receiving CC and 70% of patients receiving ABMT (Table 1). Appropriate local institutional review boards approved the protocol, and the children's parents or guardians provided written informed consent. All patients who completed 5 months of induction therapy were included in the analysis of local control, whether or not they completed consolidation with chemotherapy or ABMT. Contributing Children's Cancer Group investigators, institutions, and grant numbers are given in Appendix 1.

Table 1. Patient characteristics of 539 patients on CCG-3891

Patient characteristics	Patients	
	Number	Percent
Median age (range), months	34 (2–208)	
Median follow-up (range), months	66 (2–114)	
Evans stage		
II	1	0
III	72	13
IV	453	84
I or II disease with bone metastases before therapy other than surgery	13	2
MYCN amplified/number tested	156/395	39
Ferritin ≥143 ng/mlinutnber tested	289/487	59
Unfavorable histology/number tested	352/373	94
ABMT (randomized)	189	35
Continuation chemotherapy (randomized)	190	35
Continuation chemotherapy (nonrandomized)	118	22
No randomized or assigned regimen*	42	8
End-induction response†		
ABMT patients		
CR/VGPR	86	70
PR/SD/MR/PD	36	30
CC patients		
CR/VGPR	154	67
PR/SD/MR/PD	76	33
Primary site		
Abdominal	452	84
Thoracoabdominal/thorax	52	10
Pelvis	13	2
Other	22	4

* Patients not assigned to any regimen because of relapse, death, or withdrawal before the first randomized assignment.

† Seventy-nine patients were not evaluable for disease response, most commonly because they did not complete induction therapy, and 108 patients were not included in this response evaluation, because they did not complete CC or ABMT.

Abbreviations: ABMT = autologous bone marrow transplantation; CR/VGPR = complete remission/very good partial remission; PR/SD/MR/PD = partial remission/stable disease/mixed response/progressive disease; CC = continuation chemotherapy.

Therapy

Induction chemotherapy consisted of cisplatin (60 mg/m^2 body-surface area), doxorubicin (30 mg/m^2), etoposide (100 mg/m^2), and cyclophosphamide (1000 mg/m^2) for 5 cycles at 28-day intervals. After induction chemotherapy and thorough evaluation of response, patients without disease progression underwent delayed primary surgery with attempted resection of primary and bulky metastatic lesions greater than 3 cm in diameter. The operative goal was gross total resection, with examination and sampling of all regional lymph nodes associated with the primary tumor.

Local control measures consisted of surgery followed by EBRT to gross residual disease, administered before CC or transplantation (ABMT). Extra-abdominal tumors received 20 Gy, whereas mediastinal and intra-abdominal tumors received 10 Gy, delivered in 2-Gy fractions, once daily. The dose of EBRT was chosen in an effort to treat CC and ABMT patients with the same primary site dose while preventing normal-tissue toxicity in ABMT patients receiving TBI. Physical examination, operative reports, and im-

aging studies 1–2 weeks after surgery delineated areas of gross residual disease. Imaging studies included CT or MRI. Although postoperative changes can impede documentation of disease status, the treating radiation oncologist sought correlations between abnormal soft tissue on imaging studies, abnormal metaiodobenzylguanidine (MIBG) uptake, and operative reports to determine whether gross residual disease was present. Treatment volume consisted of a 1–2-cm margin around all sites of residual disease evident after induction chemotherapy and surgery. Surgery, radiotherapy, and pathology records were reviewed centrally by a team of experienced surgeons and radiotherapists.

After local control measures were completed, patients received continuation chemotherapy or myeloablative chemoradiotherapy followed by infusion of immunomagnetically purged autologous bone marrow (12). Randomization of assignment to CC or ABMT arm was at Week 8 of the protocol, just before the third cycle of induction chemotherapy. Patients who were unable to be randomly assigned (n = 160) because of psychosocial or medical reasons were nonrandomly assigned to the same continuation chemotherapy as the randomized CC group, which consisted of 3 cycles of cisplatin (160 mg/m^2), etoposide (500 mg/m^2), doxorubicin (40 mg/m^2), ifosfamide (2500 mg/m^2), and mesna (600 mg/m^2 per dose). For the transplantation group, chemotherapy consisted of carboplatin (1000 mg/m^2) and etoposide (640 mg/m^2) administered by continuous infusion over 96 h beginning 8 days before transplantation, and melphalan (a bolus of 140 mg/m^2 7 days before transplantation and a bolus infusion of 70 mg/m^2 6 days before transplantation). The conditioning regimen for myeloablative therapy included TBI delivered in 3.33-Gy daily fractions during the 3 days before transplantation. The target volume included the entire patient, treated with equally weighted parallel-opposed beams. The TBI regimen was based on a pilot study with limited toxicity previously conducted by CCG (5, 18). The prescribed dose was not exceeded, and the EBRT was administered before CC or ABMT in all enrolled patients.

A second randomization followed ABMT or CC. Patients without disease progression were assigned randomly to receive 6 cycles of 13-*cis*-retinoic acid (160 mg/m^2 per day administered orally in 2 divided doses for 14 consecutive days in a 28-day cycle) or no further therapy. Clinical evaluations were done with the international criteria for response to treatment of neuroblastoma at diagnosis (19, 20), at the end of induction therapy, continuation chemotherapy or transplantation, and 13-*cis*-retinoic acid therapy.

Statistical analysis

Life-table methods were used to estimate event-free survival (EFS), overall survival (OS), and local disease control probabilities (21). Elapsed time from study entry to an event or to end of follow-up was used to compute EFS and OS probabilities. Several different types of comparisons of EFS and OS according to EBRT therapy were made. To compare outcomes of patients who received EBRT vs. those who did not, elapsed time was computed from time of EBRT (for those who received it) or from 162 days from study entry (for those who did not). The time point of 162 days from the beginning of follow-up for the comparison group was chosen because it was equal to the median time of receiving EBRT. Patients who already had events (relapse) by 162 days were not used in the control group. This approach toward constructing the comparison group was designed to minimize waiting biases in favor of EBRT that would occur if time from study entry were used in life-table analyses (22). In addition to overall comparisons of outcome by EBRT status, we did stratified analyses with strata defined according to extent of resection. In this case, the best resection obtained by the time of EBRT or 162 days (for patients who did not receive EBRT) defined the strata in the analyses. Further comparisons were made of patients who actually received ABMT (n = 129) vs. CC (n = 254). In these cases, follow-up was computed from time of ABMT or from 190 days from study entry for the CC group. The choice of 190 days was made, because it was the median for time of ABMT. Patients with events before 190 days again were not used as controls in this comparison.

Time of local disease control was calculated from the same starting points as EFS for the subgroups described above; however, an event was defined as the first occurrence of progressive disease at the primary site defined at diagnosis, and all other events were considered censored observations. The log-rank statistic was used to compare EFS and local disease control probabilities between subgroups of patients.

Table 2. Radiation therapy given and extent of resection at the time of EBRT

	Continuation chemotherapy		Bone marrow transplantation	
	EBRT	No EBRT	TBI + EBRT	TBI, no EBRT
Gross total resection	36	103	14	68
Incomplete resection or no surgery	43	53	15	23

Abbreviations: EBRT = external beam radiation therapy; TBI = total body irradiation.

RESULTS

For all 539 eligible patients entered, the median follow-up was 66 months (range: 2–114 months), and the estimated EFS and OS rates at 5 years were 25% ± 2% and 35% ± 2%, respectively. In CCG-3891, EBRT was prescribed to the primary disease site for patients who underwent grossly incomplete (partial) resections or had postoperative radiologic evidence of gross residual disease. Radiation therapy is delivered to improve local disease control, so analyses focused on local control at the primary disease site. Table 2 shows the local control measures

delivered to patients with the specified extent of resection (Table 2). The absolute number of patients in the CC group is greater than that in the ABMT group, as evident from Table 2, because in addition to the 190 patients randomized to CC, 118 patients were nonrandomly assigned to continuation chemotherapy for psychosocial or medical reasons (Table 1). Thus, compliance with radiation guidelines in the group of 221 patients with gross total resections was 77%, whereas compliance among 134 patients with incomplete resections or no surgery was 43%.

Relapse at the primary disease site was a major component of unsuccessful treatment. Among 539 patients, 349 had recurrences, including 31 with isolated locoregional relapses, 148 with simultaneous local and distant recurrences, and 150 with distant relapses. At 5 years, the estimated locoregional recurrence rate was 51% ± 5% among patients who received continuation chemotherapy compared with 33% ± 7% among patients who received transplantation ($p = 0.004$, Fig. 1a). The difference in local relapses between the CC and ABMT groups was most pronounced in patients with *MYCN*-amplified tumors. Among patients with *MYCN* amplification ($n = 156$), the estimated 5-year local recurrence rate was 70% ± 10% for those who received CC compared with 25% ± 15% for patients who received ABMT ($p = 0.001$, Fig. 1b). The improved locoregional control rate evident in the ABMT group may in part be the result of a higher proportion of patients in the ABMT group undergoing a complete resection (68% in the ABMT group and 59% in the CC group). The rate of complete resection was similar when only patients with *MYCN* amplification were analyzed (70% in the ABMT group and 62% in the CC group).

The high rate of local recurrence prompted an examination of whether addition of EBRT improved local control rates. However, this question could not be answered directly by this study, because EBRT was not randomly assigned. EBRT was prescribed only to patients who underwent incomplete resections or had evidence of postoperative gross residual disease. Incomplete tumor resection is associated with worse clinical outcome in several published series (23–27), so patients who received EBRT likely represent a worse prognostic group than those who did not. Patients who received EBRT were compared to those who did not. Patients on the CC arm were analyzed separately from those on the ABMT arm. EBRT did not statistically significantly influence time to primary relapse or EFS in either group. Among ABMT patients, local relapse rates at 5 years were 22% ± 12% and 35% ± 10% with and without EBRT, respectively ($p = 0.36$, Fig. 2a). Among CC patients, local relapse rates at 5 years were 52% ± 8% and 50% ± 7% with and without EBRT, respectively ($p = 0.55$, Fig. 2b).

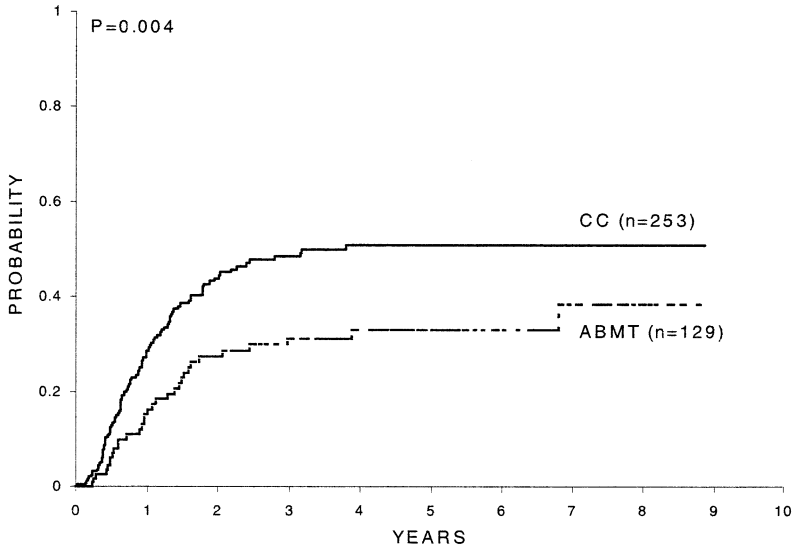
Although the majority of patients had mediastinal and intra-abdominal tumors and therefore received 10 Gy to the primary site, a subgroup of patients received 20 Gy delivered to extra-abdominal primary tumors. Of 36 patients with extra-abdominal primaries, 6 patients received 20 Gy EBRT (2 also received TBI), whereas 30 patients received no EBRT (10 of these received TBI). Local relapse rates at 5 years were 0% ± 0% and 44% ± 15% for patients with and without EBRT, respectively ($p = 0.09$).

An additional analysis examined separately patients who did or did not receive 13-*cis*-retinoic acid. The cohort that received 13-*cis*-retinoic acid included 41 patients who were assigned to 13-*cis*-retinoic acid because of biopsy-proven persistent disease documented after CC or ABMT. For patients who received 13-*cis*-retinoic acid, 5-year EFS rates were 45% ± 9% and 29% ± 6% for those receiving and not receiving primary site EBRT, respectively ($p = 0.05$). For patients who did not receive 13-*cis*-retinoic acid, 5-year EFS rates were 28% ± 14% and 35% ± 7% for those receiving and not receiving primary site EBRT, respectively ($p = 0.40$).

When we assessed the influence of EBRT, we extended analyses to several subgroups, which included patients undergoing gross total resections and those with incomplete resections (patients undergoing partial resections, biopsies only, or no surgery), patients with Stage IV disease, those with Stage III disease, and patients with and without *MYCN* amplification. Within all of these subgroups, EBRT did not statistically significantly influence time to primary relapse or EFS. However, it is noteworthy that in every subgroup of patients receiving ABMT, administration of EBRT was associated with higher 5-year EFS, despite a lack of statistical significance within any subgroup (Table 3A). Similarly, for patients receiving CC, each subgroup, with the exception of Stage III disease, demonstrated improved 5-year EFS associated with EBRT, although, again, this difference was not statistically significant within any subgroup (Table 3B).

The comparison of patients who received EBRT with those who did not carries the inherent bias of nonrandomized indications for EBRT dictated by the protocol (12). To compare groups with more uniform patient characteristics, we evaluated separately the group that received EBRT and the group that did not receive EBRT and asked whether, within each group, the addition of TBI and ABMT improved local control. In patients prescribed EBRT for postoperative gross residual disease, a total of 10 Gy was directed to the primary site and associated lymph nodes. These patients had been randomly assigned to ABMT that included an additional 10 Gy of TBI or CC that included no additional radiation. Thus, the primary sites of patients with postoperative gross residual disease received either 20 Gy as a component of ABMT or 10 Gy in conjunction with CC.

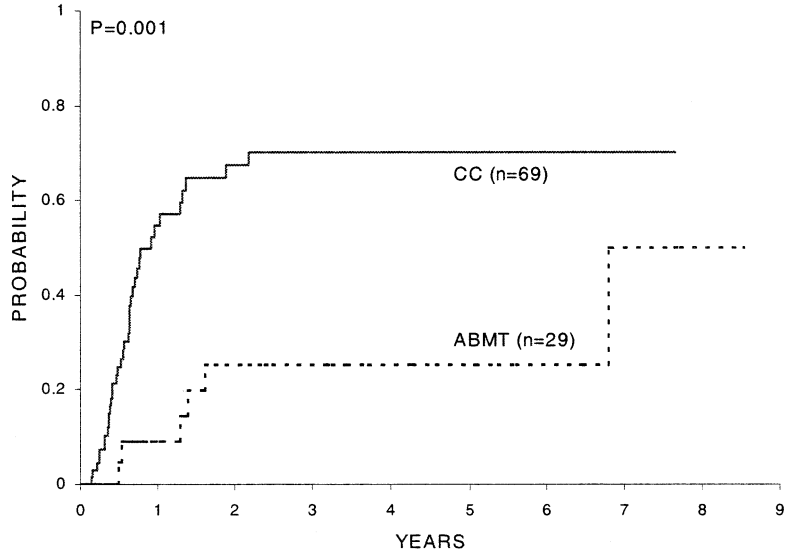
For patients who received EBRT to the primary disease site, the addition of 10 Gy TBI as a component of ABMT resulted in a statistically significant increase in local control rates. The 5-year local recurrence rates were 22% ± 12% and 52% ± 8% for ABMT and CC, respectively ($p = 0.022$, Fig. 3a). When analysis was confined to patients with Stage IV disease who received EBRT to the primary site, a persistent statistically significant increase in local control was evident for patients who received ABMT compared with those who received CC; 5-year local recurrence rates were



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	29	18	13	10	8	6	5	2	1
CC	69	19	12	9	6	5	2	1	0

(a)

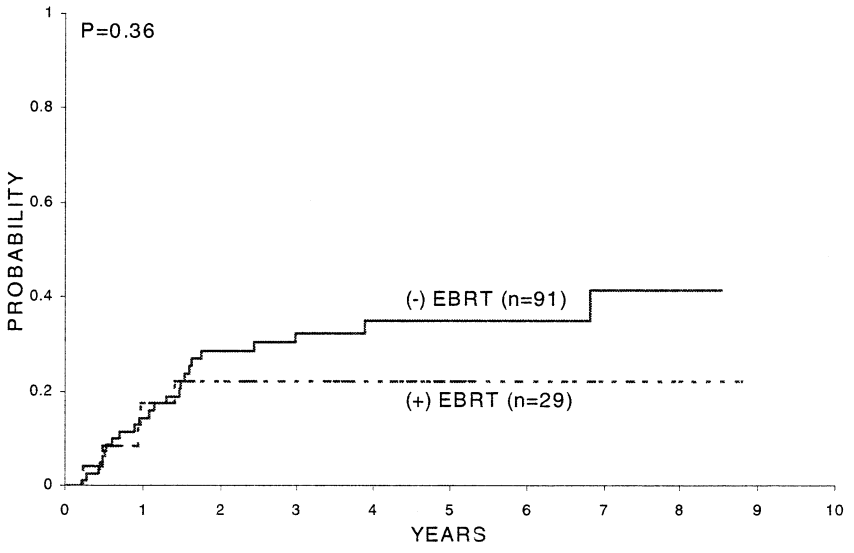


Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	29	18	13	10	8	6	5	2	1
CC	69	19	12	9	6	5	2	1	0

(b)

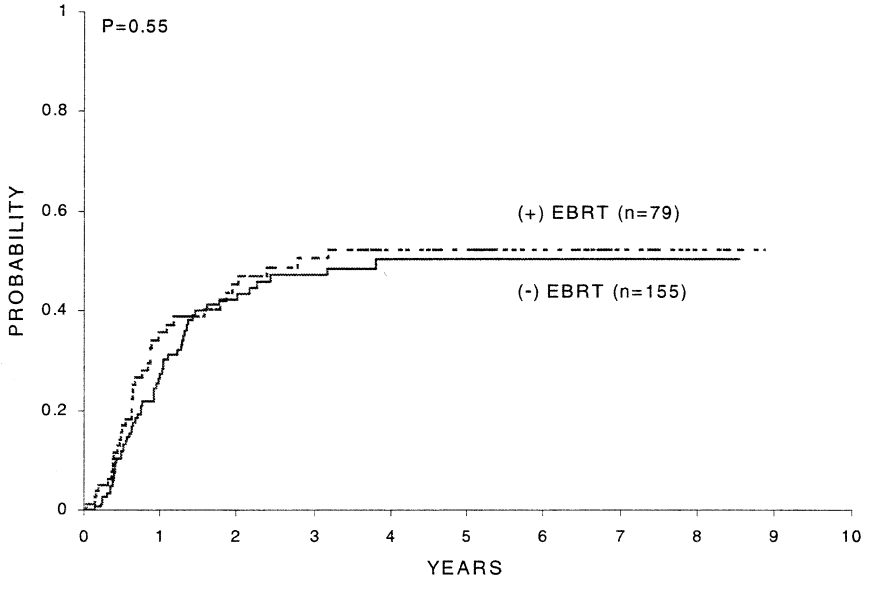
Fig. 1. Actuarial rate of relapse at the primary site according to administered treatment regimen. (a) Relapse rate for all analyzed patients who received either ABMT, $n = 129$ (dashed line) or CC, $n = 253$ (solid line); $p = 0.004$. (b) Relapse rate for patients with *MYCN* amplification who received either ABMT, $n = 29$ (dashed line) or CC, $n = 69$ (solid line); $p = 0.001$.



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	91	57	42	35	25	16	12	7	3
CC	29	18	17	14	14	9	3	2	1

(a)



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	155	77	50	39	26	24	18	11	4
CC	79	42	32	29	23	20	12	4	3

(b)

Fig. 2. Actuarial rate of relapse at the primary site according to whether EBRT was administered to the primary tumor bed. (a) Local relapse rate for patients who underwent ABMT and received, $n = 29$ (dashed line) or did not receive, $n = 91$ (solid line), EBRT to the primary site; $p = 0.36$. (b) Local relapse rate for CC patients who received, $n = 79$ (dashed line) or did not receive, $n = 155$ (solid line), EBRT to the primary site; $p = 0.55$

Table 3A. Five-year event-free survival for patients receiving ABMT

	Patients (*n*)	5-year EFS (%) EBRT (−)	EBRT (+)	*p* value
Gross total resection*	82	37 ± 8	50 ± 18	0.90
Incomplete resection*	25	36 ± 21	49 ± 16	0.79
Stage III	14	74 ± 17	100 ± 0	0.55
Stage IV	102	29 ± 7	50 ± 12	0.21
MYCN amplification	27	42 ± 16	47 ± 20	0.96
No *MYCN* amplification	60	35 ± 10	54 ± 15	0.60

* A total of 107 patients underwent resection; 9 patients had no surgery.

Abbreviations: ABMT = autologous bone marrow transplantation; EFS = event free survival; EBRT = external beam radiation therapy; CC = continuation chemotherapy.

23% ± 12% and 57% ± 9% for ABMT and CC patients, respectively ($p = 0.017$). Among patients who received EBRT to primary sites, separate analyses were done for those who had gross total resections and those who underwent incomplete resections. ABMT, including 10 Gy of EBRT and 10 Gy of TBI, resulted in a trend toward improved local control for all patients, regardless of extent of resection. Among patients who underwent incomplete resections, the 5-year local recurrence rates were 26% ± 15% and 54% ± 11% for patients who received ABMT and CC, respectively ($p = 0.17$, Fig. 3b). For patients who underwent gross total resections, a similar trend in favor of EBRT was evident, with 5-year local recurrence rates of 20% ± 18% and 47% ± 12% for patients who received ABMT and CC, respectively ($p = 0.14$, Fig. 3c). The relative contributions to local control of the higher radiation dose and the more intensive myeloablative therapy cannot be dissected, because all patients assigned to the ABMT arm received additional radiation from TBI and myeloablative chemotherapy.

Grades 3–4 toxicities, most of which were hematologic, occurred in 81% of patients who received EBRT and in 78% of patients who did not ($p = 0.57$). Table 4 delineates toxicity rates according to whether patients received EBRT to the primary site. EBRT was not associated with a significant increase in toxicity, with the exception of parenteral nutrition requirement, which occurred in 55% and 44% of patients who did and did not receive EBRT, respectively ($p = 0.049$). Although not statistically significant, the difference in veno-occlusive disease of the liver was noteworthy in 14% and 7% of patients who did and did not receive EBRT, respectively ($p = 0.26$). Second primary malignancies were seen in 4 patients enrolled in CCG-3891; none were within the EBRT field. Two of those second malignancies, follicular carcinoma of the thyroid and acute myelogenous leukemia, developed in patients who received TBI without EBRT.

Table 3B. Five-year event-free survival for patients receiving CC

	Patients (*n*)	5-year EFS (%) EBRT (−)	EBRT (+)	*p* value
Gross total resection*	139	24 ± 5	36 ± 9	0.35
Incomplete resection*	64	26 ± 13	28 ± 8	0.36
Stage III	38	59 ± 14	52 ± 12	0.91
Stage IV	193	18 ± 4	24 ± 6	0.43
MYCN amplification	66	6 ± 6	17 ± 8	0.42
No *MYCN* amplification	109	36 ± 7	47 ± 9	0.26

* A total of 107 patients underwent resection; 9 patients had no surgery.

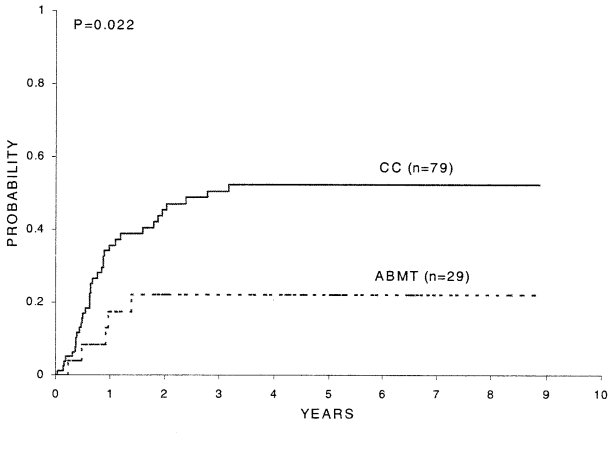
Abbreviations: ABMT = autologous bone marrow transplantation; EFS = event-free survival; EBRT = external beam radiation therapy; CC = continuation chemotherapy.

DISCUSSION

Radiation, like surgery, is therapy to control local, not systemic, disease. As systemic therapy for high-risk neuroblastoma becomes more aggressive, response rates improve, and survival increases, local control becomes a formidable problem (5). This is shown by the high local relapse rates of 51% ± 5% and 33% ± 7% at 5 years for patients in the present report that received continuation chemotherapy and transplantation, respectively. For Stage III and IV neuroblastoma, local relapse is a major component of treatment failure in several published series, all of which included radiation delivered to the site of primary disease (3–5). However, several recent single-institution or small consortium studies reported local control rates substantially better than those reported herein. Wolden *et al.* reported on a series of patients with Stage IV neuroblastoma receiving 1.5 Gy twice a day to 21 Gy to prechemotherapy, presurgery primary tumor volume and regional lymph nodes (10). The actuarial locoregional control rate at 5 years was 84%. A recent update of this experience reported a 10.1% probability of primary-site failure among 99 patients, most of whom (92 patients) had no evidence of disease in the primary site at the time of irradiation (11). Among 7 patients with disease at the primary site at the time of irradiation, 3 had disease that recurred locally. Direct comparison of this experience with our current data is limited by the considerably higher rate of complete total resections in the single-institution study, as well as the various chemotherapy regimens used, none of which resemble the CCG-3891 regimens.

A similar treatment regimen was used by the German multicenter neuroblastoma trial in which 14 of 26 patients with advanced disease had disease that relapsed; 4 of these cases (29%) included the primary sites (6). Similar regimens have resulted in decreased local relapse rates ranging from 0% to 17% (7–9).

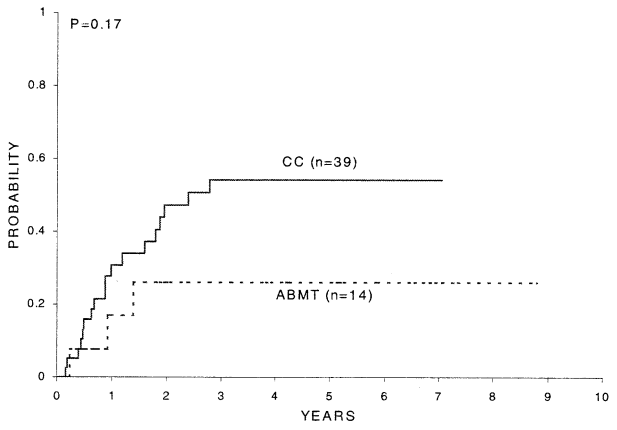
Although the above studies do not detail the extent of resections, they do indicate that many of the patients had only microscopic residual disease at the time of primary site



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	29	18	17	14	14	9	3	2	1
CC	79	42	32	29	20	12	4	3	

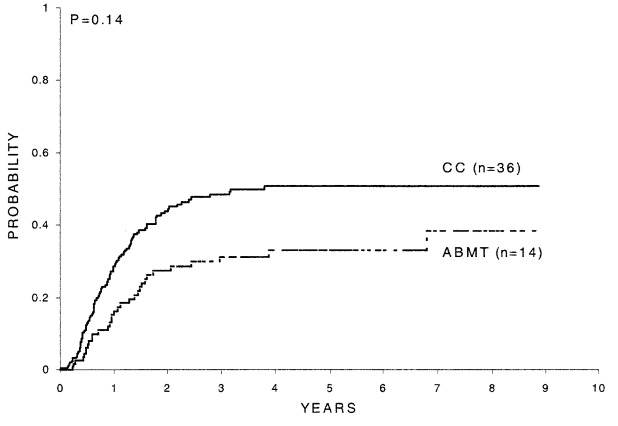
(a)



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	14	9	8	6	6	5	2	2	1
CC	39	22	15	13	10	9	6	1	0

(b)



Number at risk at year

Risk Group	0	1	2	3	4	5	6	7	8
ABMT	14	8	8	7	7	3	1	0	0
CC	36	19	16	15	12	10	5	3	3

(c)

Fig. 3. Actuarial probability of relapse at the primary site according to administered treatment regimen, for patients who received EBRT to the primary site. (a) Probability of relapse at the primary site for patients who received EBRT, followed by CC, $n = 79$ (solid line), or ABMT, $n = 29$ (dashed line); $p = 0.022$. (b) Probability of relapse at the primary site for patients with incomplete resections who received EBRT to the primary site, followed by CC, $n = 39$ (solid line), or ABMT (dashed line), $n = 14$; $p = 0.17$. (c) Probability of relapse at the primary site for patients with gross total resections who received EBRT to the primary site, followed by CC, $n = 36$ (solid line), or ABMT, $n = 14$ (dashed line); $p = 0.14$.

irradiation. The superior local control rates reported in these studies employing 21 Gy or more to the primary site suggest that radiation to the primary tumor bed might benefit patients with gross residual and microscopic residual disease at the time of radiation.

Our results suggest similarly that in the context of local radiation to the primary tumor site, the addition of 10 Gy of TBI as a component of aggressive myeloablative treatment improves local control. Thus, regardless of extent of resection, treatment with 20 Gy with myeloablative chemotherapy produces higher local control rates than 10 Gy given with continuation chemotherapy. The higher radiation dose and the enhanced chemotherapy intensity clearly might contribute to improvement in local control. The relative contributions of these components of myeloablative chemoradiation can only be deciphered by a prospective randomized trial. The benefit of EBRT is substantiated by a statistically significant improvement in EFS evident when EBRT was administered to patients receiving 13-*cis*-retinoic acid. This suggests that the benefit of local control emerges as

Table 4. Toxicity rates according to EBRT administration

Toxicity: Grade 3–4	Toxicity rate (%) EBRT (−)	EBRT (+)	*p* value
All toxicities	78	81	0.57
Nonhematologic toxicities	36	36	0.90
Hematologic toxicities	43	47	0.56
Renal	11	10	1.00
Total parenteral nutrition	44	55	0.05
Abdominal pain	6	7	0.64
Diarrhea	13	12	0.86
Nausea and vomiting	17	19	0.65
Transaminase elevation	6	5	0.80
Decreased creatinine clearance	1	2	0.64
Infection	47	53	0.30
Veno-occlusive disease of the liver	7	14	0.26

Abbreviations: EBRT = external beam radiation therapy.

metastases are better controlled by treatment directed at systemic and minimal residual disease.

A dose response to radiation administered to the primary tumor site is supported by the patients in this study that received 20 Gy for extra-abdominal primary tumors. Whereas in the absence of EBRT to the primary 44% of patients recurred locally, none of 6 patients who received 20 Gy to the primary tumor site experienced a primary relapse ($p = 0.09$). A dose response to radiation is further supported by several publications, most of which describe results in Stage III disease or do not incorporate biologic prognostic markers (4, 28, 29). Our data indicate that 10 Gy delivered to the primary tumor site, whether with TBI or local EBRT, is not sufficient to achieve local control. Although the current study suggests a possible radiation dose response, the appropriate approach to determine the adequate radiation dose to the primary tumor site is a prospective trial that randomly assigns patients to receive different radiation doses to the primary site.

Toxicity of local EBRT was limited, with no evidence that EBRT increased the risk of second malignancy, but longer follow-up is necessary. EBRT was associated with more patients receiving total parenteral nutrition, with no significant effect on the risk of renal, hepatic, or gastrointestinal toxicities. The median follow-up of 66 months in this study precludes meaningful conclusions regarding the late toxicities of the regimens used in CCG-3891. However, in view of established long-term toxicities, particularly of pediatric patients receiving TBI, current high-risk neuroblastoma protocols have shifted toward non–TBI-containing conditioning regimens for ABMT in conjunction with local radiation to the primary tumor site.

It is difficult to assess the biologic equivalent of 10 Gy in 2-Gy daily fractions, followed weeks later by 10 Gy of TBI administered in 3.33-Gy daily fractions. Current protocols for high-risk neuroblastoma include no TBI but prescribe 20 Gy of local EBRT for all patients. The relationship between this recent radiotherapy schema and that prescribed in CCG-3891 is unclear, emphasizing the need for a logical progression of approaches to radiotherapy in high-risk neuroblastoma. A promising novel approach to the treatment of neuroblastoma integrates ^{131}I-MIBG into an aggressive multimodality regimen (30). Thus, in future high-risk neuroblastoma protocols, ^{131}I-MIBG may be incorporated into the conditioning regimen to target radiation to tumor cells (31).

Compliance with radiation guidelines was poor, highlighting two important points. First, quality review was not performed before the initiation of treatment, an intervention that must be incorporated into present cooperative group trials to assure appropriate treatment of patients and reliable interpretation of the results. Second, the poor compliance likely reflects a dearth of information regarding the appropriate use of radiation in high-risk neuroblastoma and resultant investigator biases. Studies such as this one may provide the impetus for high-risk neuroblastoma studies to pose a radiotherapy question that may be answered in a prospective, randomized fashion, in contrast to the nonrandom prescription of local radiation in virtually all recent high-risk protocols.

Radiation therapy in the treatment of high-risk neuroblastoma patients remains controversial. Our study suggests a benefit for radiotherapy, particularly when systemic treatment is optimized with myeloablative therapy and 13-*cis*-retinoic acid. The data further suggest a dose–response relationship with local EBRT, although the optimal dosage to primary tumor sites has not been established. For patients with high-risk neuroblastoma, we recommend EBRT to the primary tumor site in the context of a myeloablative regimen that does not include TBI but incorporates posttransplant therapy for minimal residual disease. A minimum dose of 21.6 Gy in 1.8-Gy daily fractions should be delivered to the tumor volume present before surgical resection. This dose should be adequate for patients with a complete surgical resection, but we propose that in the context of a prospective trial, patients with gross residual disease postoperatively may benefit from a higher radiation dose in an attempt to improve upon poor local control rates reported in the literature. The results of CCG-3891 underscore the need to address indications for radiation in a prospective randomized trial. The urgency of this task increases as systemic chemotherapy and biologic agents improve control of metastatic disease.

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APPENDIX 1

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William Beaumont Hospital	Charles Main	N/A
DeVos Children's Hospital	David Freyer	N/A
Henry Ford Hospital	Hassan Yaish	N/A
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