Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–7, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.04.006

CLINICAL INVESTIGATION

LONG-TERM OUTCOME AND TOXICITIES OF INTRAOPERATIVE RADIOTHERAPY FOR HIGH-RISK NEUROBLASTOMA

Amy M. Gillis, M.D.,* Elizabeth Sutton, M.D.,† Kelly D. DeWitt, M.D.,* Katherine K. Matthay, M.D.,‡ Vivian Weinberg, Ph.D.,§ Benjamin M. Fisch, M.D.,* Albert Chan, R.T.T., C.M.D.,* Charles Gooding, M.D.,† Heike Daldrup-Link, M.D., Ph.D.,† William M. Wara, M.D.,* Diana L. Farmer, M.D.,‖ Michael R. Harrison, M.D.,‖ and Daphne Haas-Kogan, M.D.*

Departments of *Radiation Oncology, †Radiology, ‡Pediatrics, §Biostatistics Core, and ‖Surgery, University of California, San Francisco, School of Medicine, San Francisco, CA

Purpose: To review a historical cohort of consecutively accrued patients with high-risk neuroblastoma treated with intraoperative radiotherapy (IORT) to determine the therapeutic effect and late complications of this treatment.
Methods and Materials: Between 1986 and 2002, 31 patients with newly diagnosed high-risk neuroblastoma were treated with IORT as part of multimodality therapy. Their medical records were reviewed to determine the outcome and complications. Kaplan-Meier probability estimates of local control, progression-free survival, and overall survival at 36 months after diagnosis were recorded.
Results: Intraoperative radiotherapy to the primary site and associated lymph nodes achieved excellent local control at a median follow-up of 44 months. The 3-year estimate of the local recurrence rate was 15%, less than that of most previously published series. Only 1 of 22 patients who had undergone gross total resection developed recurrence at the primary tumor site. The 3-year estimate of local control, progression-free survival, and overall survival was 85%, 47%, and 60%, respectively. Side effects attributable to either the disease process or multimodality treatment were observed in 7 patients who developed either hypertension or vascular stenosis. These late complications resulted in the death of 2 patients.
Conclusions: Intraoperative radiotherapy at the time of primary resection offers effective local control in patients with high-risk neuroblastoma. Compared with historical controls, IORT achieved comparable control and survival rates while avoiding many side effects associated with external beam radiotherapy in young children. Although complications were observed, additional analysis is needed to determine the relative contributions of the disease process and specific components of the multimodality treatment to these adverse events. © 2007 Elsevier Inc.

Neuroblastoma, High-risk, Pediatric, Intraoperative radiotherapy, IORT, Local control.

INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for approximately 10% of all pediatric malignancies (1, 2). The prognosis of patients with high-risk neuroblastoma has improved dramatically during the past 20 years. Historically, the progression-free survival (PFS) rates for high-risk neuroblastoma patients have been 10–25% (3–5). With increasingly aggressive myeloablative therapy and stem cell transplantation, the current PFS rates are >30% (4, 6–15).

In this evolving multimodality setting, controversy persists regarding the importance of radiotherapy (RT) in achieving locoregional control (16). In many studies, local failure has represented a dominant form of disease relapse (8, 17). Therapy aimed at achieving local control in patients with high-risk neuroblastoma has evolved during the past decade. In conjunction with myeloablative therapy that included total body irradiation (TBI), local external beam radiotherapy (EBRT) was reserved for patients with postoperative residual disease. However, as the standard has shifted away from TBI, EBRT to the primary site has been incorporated into the therapy for all high-risk patients. The currently recommended radiation fields encompass the primary tumor volume and regional positive lymph nodes after induction chemotherapy, but before surgery (18).

Reprint requests to: Daphne Haas-Kogan, M.D., Department of Radiation Oncology, University of California, San Francisco, School of Medicine, 1600 Divisadero St., Suite H1031, San Francisco, CA 94115-1708. Tel: (415) 353-7175; Fax: (415) 353-9884; E-mail: hkogan@radonc17.ucsf.edu

Supported in part by National Institutes of Health Grant M01RR01271 and the Kasle & Tkalcevic Neuroblastoma Research Fund, Thrasher Fund, and Nancy and Stephen Grand Philanthropic Fund (D.A.H.-K.).

Conflict of interest: none.

Received Jan 31, 2007, and in revised form April 3, 2007. Accepted for publication April 4, 2007.

Although EBRT appears to contribute to locoregional control, significant acute and late side effects can result, particularly in young children. The EBRT dose is limited by the normal tissue tolerances. Furthermore, even with optimal use of local EBRT, the most favorable published series nevertheless reported local recurrence rates of 10–15%, with yet greater local recurrence rates reported in most multi-institutional studies. We sought to maximize local control while avoiding additional toxicities by using intraoperative RT (IORT), either alone or in combination with EBRT. Our experience with complex or recurrent patients has been previously reported and demonstrated promising local control rates (4).

Our initial experience using IORT began in the 1980s with recurrent disease in children for whom previous RT precluded additional EBRT because of the tolerance of the normal structures. As favorable outcomes emerged, the use of IORT evolved to include tumors whose sizes and locations rendered EBRT particularly toxic because of the adjacent normal tissues. We now report the results of a more homogeneous cohort restricted to newly diagnosed high-risk neuroblastoma patients treated with IORT at the University of California, San Francisco Medical Center. Longer follow-up and a larger and more uniform cohort of newly diagnosed patients have provided a sounder basis for recommendations regarding RT.

METHODS AND MATERIALS

Between 1986 and 2002, 31 patients with newly diagnosed high-risk neuroblastoma were treated with IORT at primary tumor resection. Of these 31 patients, 23 were reported on in a previous study (4). High-risk disease was defined by the International Neuroblastoma Staging System (19, 20) and the biologic features of the tumor according to the following classification: patients >1 year old at diagnosis with Stage 4 disease, Stage 3 with unfavorable histopathologic features as determined by the Shimada classification, *MYCN* amplification, or a serum ferritin level of ≥143 ng/mL; patients with Stage 2 disease with *MYCN* amplification; and patients <1 year old at diagnosis with Stage 4 or 4S and *MYCN* gene amplification. One patient was 10 months old at diagnosis, with Stage 4 disease and no *MYCN* amplification and was considered to have high-risk disease because of tumor progression during induction chemotherapy. The stage was determined using magnetic resonance imaging or computed tomography, ^{123}I-meta-iodobenzylguanidine scan, bone scan, and bilateral bone marrow biopsy. The *MYCN* copy number was determined by semiquantitative immunohistochemistry. Ten patients had an unknown *MYCN* status, most likely because routine analysis of *MYCN* amplification was less common in the earlier part of this study. All parents or caregivers provided informed consent before surgical resection, and our institution's committee on human research approved the study. The surgical intent was to achieve gross total resection (GTR) whenever possible. The extent of surgery was determined by reviews of the operative reports and postoperative radiologic studies. Tumor margin status and lymph node involvement were determined by a review of the pathology reports.

Descriptive statistics were used to characterize the patients accrued to this study. The Kaplan-Meier product-limit method was used to estimate the probabilities of local recurrence, PFS, and overall survival—all reported at 36 months. All durations were determined from the time of diagnosis. Comparisons of the distributions for subset analyses were performed using the log–rank test. The Cox proportional hazards model was used to identify independent predictors of outcome. A forward stepwise approach was performed, with the final model limited to the three most important independent predictors as determined by the likelihood ratio test because of the total sample size. Significance was defined as a probability of <0.05.

The indication for IORT in this study was high-risk disease that required RT to the primary tumor site (4, 21, 22). Additional treatment with EBRT was selectively given to those patients with residual disease after tumor resection or multiple positive lymph nodes. Before 1997, IORT was given in the radiation oncology department, transporting patients either at surgery or reopening the resection cavity within 3 days after surgery (9 patients). Patients treated during or after 1997 (22 patients) were treated at primary resection, using a dedicated mobile linear accelerator (Mobetron) in the operating room (23). RT using electron beams was delivered through Lucite or aluminum cones 2.1–9.5 cm in interior diameter. Intraoperatively, the surgeon and radiotherapist assessed the depth at risk of disease involvement. Beam energies of 4–16 MeV were used to limit the depth of absorbed dose to the areas at risk, while encompassing the target volumes within the 80–90% isodose line. The median dose was 10 Gy (range, 7–15) delivered in a single fraction. One to four separate IORT fields were used to cover the entire target volume.

The target volume was the area of preoperative tumor as determined by the preoperative imaging, operative, and intraoperative frozen section findings, when necessary. All patients had undergone induction chemotherapy before surgical excision of the primary tumor. Of the 31 patients, 10 received additional EBRT to the primary site, with a dose range of 6–41.4 Gy. Six patients were treated with TBI before receiving hematopoietic cell transplantation (HCT). Finally, 27 patients underwent myeloablative chemotherapy and HCT subsequent to the local control measures.

On review of all medical records, any adverse events attributable to either the disease process itself or the multimodality treatment were noted. Specifically, the presence or absence of hypertension and vascular complications, such as renal artery stenosis, mesenteric vascular insufficiency, or middle aortic syndrome, were noted. We attempted to examine the risk factors for developing these complications, including the number of IORT fields, use of EBRT, and patient age at IORT.

RESULTS

The patient characteristics are summarized in Table 1. The median follow-up from diagnosis for all patients was 43.7 months and for surviving patients was 69.2 months (range, 1.5–16.7 years). Twenty-seven patients presented with Stage 4, one with 4S, and three with Stage 3 disease. All 31 patients were classified as high risk according to the criteria, and all patients had an abdominal component of disease, a site associated with decreased survival (24–26). In general, because of the selection criteria for IORT early in the study period, the patient characteristics of this cohort represent a particularly unfavorable prognostic group.

All patients underwent induction chemotherapy before surgical resection and IORT. Of the 31 patients, 27 received HCT after primary resection and IORT. An estimated 65% of

Table 1. Patient characteristics and treatment details

Variable	Value
Age (mo)	
Median	46
Range	10–161
Gender (*n*)	
Male	18
Female	13
INSS stage (*n*)	
3	3
4	27
4S	1
MYCN status (*n*)	
Amplified	10
Nonamplified	11
Unknown	10
HCT (*n*)	
Yes	27
No	4
Resection extent (*n*)	
GTR	22
STR	9

Abbreviations: INSS = International Neuroblastoma Staging System; HCT = hematopoietic cell transplantation; GTR = gross total resection; STR = subtotal resection.

patients who underwent HCT were alive at 36 months. Only 1 of the 4 patients who did not undergo HCT was still alive 45 months after the diagnosis. The other 3 had died within 8 months of surgery.

At primary surgery, 22 patients underwent GTR and 9 underwent subtotal resection (STR). All IORT was delivered without acute complications. One patient who had undergone GTR developed a local recurrence within the IORT field despite receiving EBRT in addition to IORT. Of the 9 patients with STRs, 3 developed a recurrence within the IORT field ($p = 0.01$; Fig. 1). Two of these three recurrences were in patients who had undergone EBRT after IORT. The third patient with a local recurrence within the IORT field after STR had immediate distant progression and underwent EBRT to the metastatic sites. At 36 months after diagnosis, an estimated 64% of patients who had undergone GTR were free of recurrence at any site compared with only 3 of the 9 patients who had undergone STR; these 3 patients were disease free for 8, 69, and 146 months (Fig. 2). An estimated 72% of patients who had undergone GTR were alive at 36 months. Three of the patients who had undergone STR were alive at 69, 73, and 146 months after diagnosis (Fig. 3).

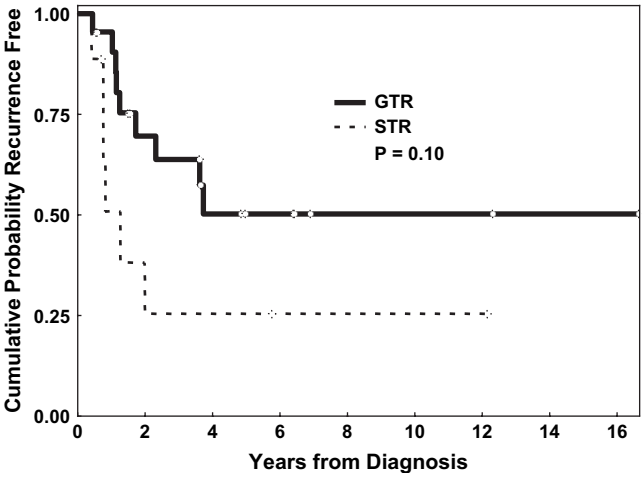

Fig. 2. Recurrence free rate (any type) according to extent of resection. STR = subtotal resection; GTR = gross total resection.

Only 10 patients received EBRT to the primary site. The indications for EBRT included extensive lymph node involvement in 5 patients, STR in 3 patients, and both STR and lymph node involvement in 2 patients. Of the 10 patients who received EBRT to the primary site, 3 had treatment failure within the radiation field, 2 of whom had received a STR. Of the 17 patients who had undergone GTR who did not receive EBRT to the primary site, none had local recurrence. Of these 17 patients, 4 had *MYCN* amplification. For the entire group of 31 high-risk patients, the 36-month estimate of local control, PFS, and overall survival from diagnosis was 85%, 47%, and 60%, respectively; rates that compare favorably with those of published series.

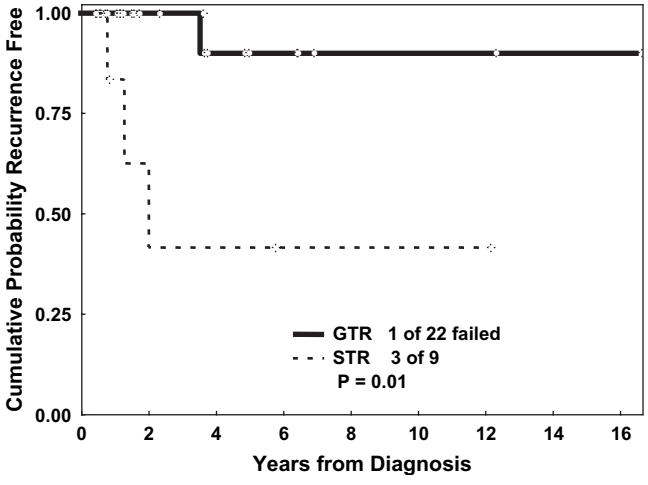

Fig. 1. Local recurrence-free rate according to extent of resection. STR = subtotal resection; GTR = gross total resection.

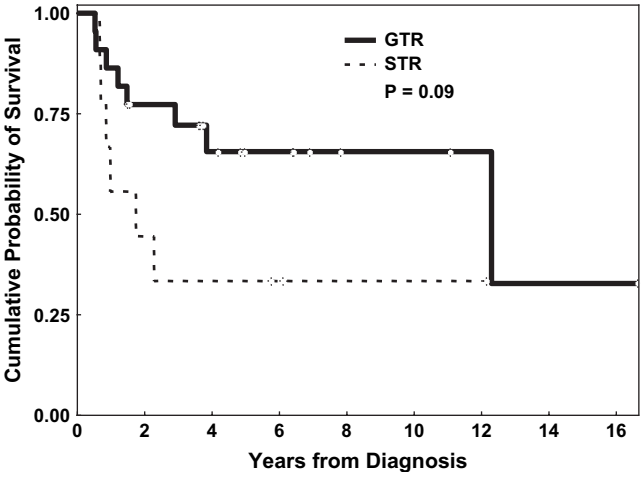

Fig. 3. Overall survival according to extent of resection. STR = subtotal resection; GTR = gross total resection.

Table 2. Post-treatment complications

Pt. No.	Complication	Age at IORT (y)	IORT dose (Gy)	IORT fields (n)	EBRT dose (Gy)	Follow-up after IORT (mo)	Disease outcome	Clinical outcome
1	Aortic stenosis (imaging finding, asymptomatic)	4	10	1	None	72.0	NED	Alive
2	HTN, vascular stenosis	2.5	10	3	10 (TBI)	143.3	NED	Dead; surgical intervention/ vascular graft for MAS and ischemic bowel
3	HTN	1.8	10	1	None	38.2	NED	Alive
4	HTN	4.3	10	1	None	2.6	NED	Dead; sepsis
5	HTN, renal artery stenosis	14	IORT 1, 10 IORT 2, 15	IORT 1, 1 IORT 2, 1	41.4	44.4	Local and distant recurrence	Alive
6	HTN, renal artery stenosis	5	IORT 1, 10 IORT 2, 15	IORT 1, 4 IORT 2, 1	10 (TBI); 10 (local)	140.5	NED	Alive, dilation of renal artery by angioplasty
7	Vascular stenosis	4.3	14	1	None	3.9	NED	Dead; massive ascites

Abbreviations: Pt. No. = patient number; IORT = intraoperative radiotherapy; EBRT = external beam radiotherapy; NED = no evidence of disease; HTN = hypertension; TBI = total body irradiation; MAS = middle aortic syndrome.

The late toxicities experienced by patients in this cohort are shown in Table 2. Two patients had documented hypertension before treatment that was controlled medically preoperatively and resolved after surgical resection and IORT. Seven patients developed hypertension or vascular stenosis after treatment.

Two patients with vascular compromise died of causes potentially related to this finding. The first was a patient with vascular compromise but no hypertension who developed massive ascites, ultimately resulting in death only 3.9 months after surgery and IORT. At resection, this patient's tumor was found to encase both the aorta and inferior vena cava. Vascular insufficiency might have contributed to the massive ascites that developed, although documentation regarding specific vessels was not available. The second death occurred in a patient with hypertension and vascular complications. This patient presented with hypertension before surgical resection and IORT; however, it was unknown whether he also had renal artery stenosis preoperatively. He later developed middle aortic syndrome and mesenteric ischemia owing to vascular insufficiency and died of bowel necrosis immediately after unsuccessful attempts at aortic bypass. Three separate IORT fields had been used in this patient, suggesting a significant risk of radiation field overlaps. Although it is possible that the number of IORT fields, the use of EBRT, or the patient's age could have played a role in the etiology of the vascular complications or hypertension, such an association could not be definitively established.

DISCUSSION

In this study, we sought to evaluate the efficacy and potential toxicities of IORT administered to a relatively homogeneous group of children with newly diagnosed high-risk neuroblastoma. In the evolving multimodality setting of myeloablative chemotherapy and aggressive surgical resection, the role of RT for high-risk neuroblastoma continues to be reassessed. In patients with high-risk disease, RT is recommended to the primary tumor bed to prevent local disease relapse (15, 27).

The RT typically takes the form of EBRT, although this can result in significant toxicities, particularly in young children. In this historical cohort study, we sought to assess the safety and efficacy of IORT delivered to the primary tumor site in patients with newly diagnosed high-risk neuroblastoma.

Many studies (22, 28–32) have reported promising results of IORT for pediatric patients (Table 3). IORT has been used for more than two decades in the treatment of pediatric malignancies; however, the small numbers of long-term survivors have impeded documentation of late toxicities. In assessing the contribution of IORT to local control, one must review the local recurrence rates reported in published studies.

The local recurrence rates have varied widely in published series. A recent study reported the results of 99 consecutively accrued high-risk patients who had undergone EBRT to the primary site after aggressive multimodality therapy (33). That study revealed a high probability of local control at 36 months of 89.9% $\pm$ 5.3%. Although this compares favorably with historical local control rates of 60–70% (8), noteworthy was their finding that of 7 patients with residual primary site disease at EBRT, 3 developed local relapse. Moreover, no local failures occurred in the 23 patients whose tumors were completely excised at diagnosis (before induction chemotherapy) (33). In contrast, no patient in our series

Table 3. Pediatric IORT studies

Study	Patient population	Treatment in addition to surgery	*n*	Conclusions
Kaufman *et al.*, 1984 (28)	Various pediatric malignancies	IORT	2	IORT well tolerated in children and might be beneficial in pediatric malignancies
Haase *et al.* 1994 (29)	Both benign and malignant disease; neuroblastoma, $n = 25$	IORT	59	IORT safe; LC benefit (LC rate for malignant disease, 75%)
Zelefsky *et al.* 1996 (30)	Various pediatric malignancies	IORT, Phase I/II study	10	IORT safe and beneficial in patients at high risk of local recurrence (2-y local RFS, 80%)
Aitken *et al.* 1995 (22)	Advanced neuroblastoma	IORT	8	IORT safe; no complications from IORT
Kuroda *et al.* 2003 (31)	Neuroblastoma with macroscopic residual disease	IORT	33	LC rate, 100% DFS rate, 51.7%
Oertel *et al.* 2006 (32)	Neuroblastoma ($n = 9$) and sarcoma	IORT and EBRT	18	LC rate, 100%; combination of IORT and EBRT safe and effective; complications noted, but tolerable (included ureteral stenosis, kidney hypertrophy, fracture due to osteoradionecrosis)

Abbreviations: LC = local control; RFS = relapse-free survival; DFS = disease-free survival; other abbreviations as in Table 2.

had a primary tumor that was amenable to excision at the initial diagnosis.

Although single-institution studies have achieved local control rates as great as 90%, multi-institutional studies have reported more guarded figures. A recent report from the Children's Cancer Group (CCG-3891) estimated the 5-year locoregional recurrence rate at 51% ± 5% and 33% ± 7% for patients who had received continuation chemotherapy and HCT, respectively. Their results suggested a benefit for RT administered to the primary site and highlighted a potential dose response for such therapy. Specifically, in combination with EBRT to the primary tumor site, the addition of 10 Gy of TBI as a component of HCT improved local control compared with continuation chemotherapy without TBI. However, because of concern of the long-term toxicities of TBI in pediatric patients, current protocols have abandoned the use of TBI and prescribed 21.6 Gy of local EBRT for all high-risk patients (27).

Although the local control rate of 85% with IORT in our report compares favorably with those of previously published series of high-risk neuroblastoma, the potential morbidity incurred by this treatment must be considered. Accurate assessment of toxicities directly related to RT is complicated because identical signs and symptoms are caused by the tumor itself and by several elements of the multimodality therapy. Of the 31 patients in this series, 7 had either hypertension or vascular complications. It is not clear whether these complications were due to the disease process itself or the multimodality treatment. In all of the present cases, the tumors were intimately involved with great vessels within the abdomen, resulting in a risk of vascular narrowing directly from the tumor and a heightened risk of vascular injury at surgical resection. In addition, the risk of microscopic residual disease surrounding the vasculature is great, necessitating inclusion of these structures in the radiation field. The patients who received IORT were at the greatest risk of vascular injury from the tumor and surgery, because they were selected for IORT by virtue of having the most invasive, surgically challenging tumors. Therefore, it was nearly impossible to dissect the direct causes of vascular injury, whether the disease process, surgical intervention, or RT, and thus, all must be considered potential culprits. In our study, hypertension existed before treatment in some patients, suggesting a prominent role for the tumor itself. Although a subset of these patients had resolution of their hypertension after tumor removal, others had progression of symptoms after treatment. A complex interaction exists between tumor behavior and the elements of multimodality treatment that can lead to serious vascular complications, as highlighted in this report.

Our study has addressed issues of balancing local control with potential long-term sequelae of RT. Little has been published regarding the long-term toxicities of IORT, in part because children undergoing IORT have typically been at great risk of disease recurrence and their high mortality rates have curtailed the acquisition of data regarding long-term side effects. However, vascular complications of IORT have been previously noted. Early documentation of possible vascular complications in patients with neuroblastoma treated with multimodality treatment were identified by Zachariou *et al.* (34) in 2002 and included 1 case of renal artery stenosis and 1 case of mesenteric artery occlusion. Nevertheless, these complications were limited to 2 of the 13 patients they examined, and, therefore, they concluded that IORT was safe in patients with neuroblastoma. In addition, in our previous report of IORT for neuroblastoma, we reported 1 patient who had narrowing of the abdominal aorta, an atrophic kidney, and hypertension (4).

We believe IORT given as a single fraction contributes to local control in patients with high-risk neuroblastoma, as evident by the low local recurrence rate in patients who had undergone IORT. Furthermore, the use of IORT mitigates the toxicities of EBRT, such as secondary malignancies and hematologic, renal, gastrointestinal, musculoskeletal,

and hepatic side effects that have been extensively reported (33). However, given the potential vascular toxicity that has emerged from our experience, certain measures should be used to diminish the risk of vascular injuries. Whenever possible, only a single IORT field should be used to reduce the risk of field overlaps. Although the small numbers precluded demonstration of an association between young age and an increased risk of vascular complications, it is recommended that extreme caution be used in delivering IORT to the great vessels of younger children, because of greater increase in the vascular diameter that is required over time as these young children grow. Patients who undergo STR or have multiple positive nodes should receive additional therapy with EBRT delivered in daily fractions of 1.8 Gy to a total dose of 21.6 Gy, because of the greater risk of local recurrence. Greater local doses might be possible with more precise treatment techniques such as intensity-modulated RT, which would be expected to cause less toxicity to normal tissues than standard EBRT. High-risk patients with no evidence of residual tumor had a 95% local control rate with IORT alone; therefore, we do not recommend postoperative EBRT for these patients. Although controversy exists regarding the prognostic significance of the extent of resection, patients with STRs had inferior outcomes, perhaps reflecting a poor response to chemotherapy, which has previously been shown to correlate with inferior disease control and survival (15, 35, 36). This study has highlighted the significant complications as part of multimodality treatment that included IORT for the treatment of children with high-risk neuroblastoma. Clearly, the excellent local control rates achieved by IORT for high-risk neuroblastoma and the avoidance of the toxicities associated with EBRT must be weighed against the significant sequelae observed in this cohort.

REFERENCES

1. Matthay KK, Yamashiro D. Neuroblastoma. In: Bast RC, Kufe DW, Pollock RE, *et al*., editors. Cancer medicine. London, England: BC Decker; 2000. p. 2185–2197.
2. Goldsby RE, Matthay KK. Neuroblastoma: Evolving therapies for a disease with many faces. *Paediatr Drugs* 2004;6:107–122.
3. Cheung NV, Heller G. Chemotherapy dose intensity correlates strongly with response, median survival, and median progression-free survival in metastatic neuroblastoma. *J Clin Oncol* 1991;9:1050–1058.
4. Haas-Kogan DA, Fisch BM, Wara WM, *et al*. Intraoperative radiation therapy for high-risk pediatric neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000;47:985–992.
5. Kiely EM. The surgical challenge of neuroblastoma. *J Pediatr Surg* 1994;29:128–133.
6. Kushner BH, O'Reilly RJ, Mandell LR, *et al*. Myeloablative combination chemotherapy without total body irradiation for neuroblastoma. *J Clin Oncol* 1991;9:274–279.
7. Ladenstein R, Lasset C, Hartmann O, *et al*. Impact of megatherapy on survival after relapse from stage 4 neuroblastoma in patients over 1 year of age at diagnosis: A report from the European Group for Bone Marrow Transplantation. *J Clin Oncol* 1993;11:2330–2341.
8. Matthay KK, Atkinson JB, Stram DO, *et al*. Patterns of relapse after autologous purged bone marrow transplantations for neuroblastoma: A Children's Cancer Group pilot study. *J Clin Oncol* 1993;11:2226–2233.
9. Matthay KK, Seeger RC, Reynolds CP, *et al*. Allogenic versus autologous purged bone marrow transplantation for neuroblastoma: A report from the Children's Cancer Group. *J Clin Oncol* 1994;12:2382–2389.
10. Matthay KK, O'Leary MC, Ramsay NK, *et al*. Role of myeloablative therapy in improved outcome for high risk neuroblastoma: Review of recent Children's Cancer Group results. *Eur J Cancer* 1995;31A:572–575.
11. Matthay KK, Villablanca JG, Seeger RC, *et al*. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. *N Engl J Med* 1999;341:1165–1173.
12. Ohnuma N, Takahashi H, Kaneko M, *et al*. Treatment combined with bone marrow transplantation for advanced neuroblastoma: An analysis of patients who were pretreated intensively with the protocol of the Study Group of Japan. *Med Pediatr Oncol* 1995; 24:181–187.
13. Philip T, Zucker JM, Bernard JL, *et al*. Improved survival at 2 and 5 years in the LMCE1 unselected group of 72 children with stage IV neuroblastoma older than 1 year of age at diagnosis: Is cure possible in a small subgroup? *J Clin Oncol* 1991;9: 1037–1044.
14. Pole JG, Casper J, Elfenbein G, *et al*. High-dose chemoradiotherapy supported by marrow infusions for advanced neuroblastoma: A Pediatric Oncology Group study. *J Clin Oncol* 1991;9: 152–158.
15. Wolden SL, Gollamudi SV, Kushner BH, *et al*. Local control with multimodality therapy for stage 4 neuroblastoma. *Int J Radiat Oncol Biol Phys* 2000;46:969–974.
16. Matthay KK. Neuroblastoma: Biology and therapy. *Oncology* 1997;11:1857–1866.
17. Garaventa A, Boni L, Lo Piccolo MS, *et al*. Localized unresectable neuroblastoma: Results of treatment based on clinical prognostic factors. *Ann Oncol* 2002;13:956–964.
18. Marcus KC, Tarbell NJ. The changing role of radiotherapy in the treatment of neuroblastoma. *Semin Radiat Oncol* 1997;7: 195–203.
19. Brodeur GM, Seeger RC, Barrett A, *et al*. International criteria for diagnosis, staging, and response to treatment in patients with neuroblastoma. *Prog Clin Biol Res* 1988;271:509–524.
20. Brodeur G, Pritchard J, Berthold F, *et al*. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 1993;11:1466–1477.
21. Leavey PJ, Odom LF, Poole M, *et al*. Intra-operative radiation therapy in pediatric neuroblastoma. *Med Pediatr Oncol* 1997; 28:424–428.
22. Aitken DR, Hopkins GA, Archambeau JO, *et al*. Intraoperative radiotherapy in the treatment of neuroblastoma: Report of a pilot study. *Ann Surg Oncol* 1995;2:343–350.
23. Meurk ML, Goer DA, Spalek G, *et al*. The Mobetron: A new concept for IORT. *Front Radiat Ther Oncol* 1997;31:65–70.
24. Matthay KK, Perez C, Seeger RC, *et al*. Successful treatment of stage III neuroblastoma based on prospective biologic staging: A Children's Cancer Group study. *J Clin Oncol* 1998;16: 1256–1264.
25. Powis MR, Imeson JD, Holmes SJ. The effect of complete excision on stage III neuroblastoma: A report of the European Neuroblastoma Study Group. *J Pediatr Surg* 1996;31:516–519.
26. Bowman LC, Castleberry RP, Cantor A, *et al*. Genetic staging of unresectable or metastatic neuroblastoma in infants: A

Pediatric Oncology Group study. *J Natl Cancer Inst* 1997;89: 373–380.
27. Haas-Kogan DA, Swift PS, Selch M, *et al*. Impact of radiotherapy for high-risk neuroblastoma: A Children's Cancer Group study. *Int J Radiat Oncol Biol Phys* 2003;56:28–39.
28. Kaufman BH, Gunderson LL, Evans RG, *et al*. Intraoperative irradiation: A new technique in pediatric oncology. *J Pediatr Surg* 1984;19:861–862.
29. Haase GM, Meagher DP, McNeely LK, *et al*. Electron beam intraoperative radiation therapy for pediatric neoplasms. *Cancer* 1994;74:740–747.
30. Zelefsky MJ, LaQuaglia MP, Ghavimi F, *et al*. Preliminary results of phase I/II study of high-dose-rate intraoperative radiation therapy for pediatric tumors. *J Surg Oncol* 1996;62: 267–272.
31. Kuroda T, Saeki M, Honna T, *et al*. Clinical significance of intensive surgery with intraoperative radiation for advanced neuroblastoma: Does it really make sense? *J Pediatr Surg* 2003;38: 1735–1738.
32. Oertel S, Niethammer AG, Krempien R, *et al*. Combination of external-beam radiotherapy with intraoperative electron-beam therapy is effective in incompletely resected pediatric malignancies. *Int J Radiat Oncol Biol Phys* 2006;64:235–241.
33. Kushner BH, Wolden S, LaQuaglia MP, *et al*. Hyperfractionated low-dose radiotherapy for high-risk neuroblastoma after intensive chemotherapy and surgery. *J Clin Oncol* 2001;19: 2821–2828.
34. Zachariou Z, Sieverts H, Eble MJ, *et al*. IORT (intraoperative radiotherapy) in neuroblastoma: Experience and first results. *Eur J Pediatr Surg* 2002;12:251–254.
35. Klaassen RJ, Trebo MM, Koplewitz BZ, *et al*. High risk neuroblastoma in Ontario: A report of experience from 1989 to 1995. *J Pediatr Hematol Oncol* 2003;25:8–13.
36. Kaneko M, Tsuchida Y, Mugishima H, *et al*. Intensified chemotherapy increases the survival rates in patients with stage 4 neuroblastoma with MYCN amplification. *J Pediatr Hematol Oncol* 2002;24:613–621.