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).
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. 123I-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 (Mobotron) 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, 1.5–167.7 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
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).

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.

### Table 1. Patient characteristics and treatment details

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

Abbreviations: INSS = International Neuroblastoma Staging System; HCT = hematopoietic cell transplantation; GTR = gross total resection; STR = subtotal resection.
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% ± 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...
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 much lower 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 and, therefore, they concluded that IORT was safe in pediatric patients with neuroblastoma. In addition, in our previous report, patients with neuroblastoma 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 much lower 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 and, therefore, they concluded that IORT was safe in pediatric patients with neuroblastoma. In addition, in our previous report, patients with neuroblastoma 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 much lower 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 and, therefore, they concluded that IORT was safe in pediatric patients with neuroblastoma. In addition, in our previous report, patients with neuroblastoma had a primary tumor that was amenable to excision at the initial diagnosis.

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

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

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


