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Radiation Therapy as Part of Local Control of Metastatic Neuroblastoma: the St. Jude Children's Research Hospital Experience

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Abstract

Purpose—To compare outcomes of pediatric patients with high-risk metastatic neuroblastoma who received radiotherapy (RT) with those of patients who did not.

Patients and Methods—We reviewed the records of 63 patients with newly diagnosed metastatic neuroblastoma treated at our institution (1989–2001) to investigate their characteristics at presentation, dose and field of RT, treatment response and failure patterns.

Results—Seventeen patients received RT, and 46 did not. In the RT group, a greater percentage of patients had residual disease prior to consolidation than did those in the no-RT group (88.2% vs. 69.6%; $p=0.008$). Gross total resection was achieved less often in the RT group (65% vs. 89%, $p=0.055$), but the 5-year cumulative incidences of local failure were similar ($35.3\% \pm 12.4\%$ vs. $32.6\% \pm 7.1\%$). Although there was no difference in 5-year event-free survival, overall survival was better in the no-RT group ($47.8\% \pm 7.2\%$ vs. $23.5\% \pm 9.2\%$; $p=0.026$).

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Conflicts of Interest

None of the authors have any financial or personal relationships that would affect or be affected by the results of this study.

Conclusion—The addition of RT to the therapy of a group of patients with more residual locoregional disease appeared to improve the local failure rate to approximately that of patients with less residual disease. RT may provide even greater benefit to those with less residual disease prior to consolidation.

Keywords

neuroblastoma; radiotherapy; neoplasm recurrence; local; survival

Introduction

The 5-year survival rates for pediatric patients with high-risk neuroblastoma who receive multimodality therapy, i.e., chemotherapy, surgery, and radiation therapy (RT), range from 28% to 44% [1–4]. A large randomized study performed by the Children's Cancer Group (CCG-3891) [4] demonstrated improved survival of patients who received myeloablative chemotherapy, total body irradiation (TBI), and subsequent autologous bone marrow transplantation (ABMT). In a separate randomization, patients who received maintenance chemotherapy comprising 13-*cis*-retinoic acid also showed improved survival. The 5-year estimates of survival of patients who received ABMT and maintenance therapy was 59% $\pm$ 8% from the time of the second randomization. Although this CCG study has helped guide treatment decisions about chemotherapy for patients with high-risk neuroblastoma, data on the other treatment modalities (surgery and RT) remain unclear.

Surgical resection is the standard treatment for localized neuroblastoma [5], but the role and optimal timing of surgery remain controversial for older patients with advanced-stage disease. Recent studies [6–9] have tried to assess the importance of complete resection of the primary tumor in the management of metastatic neuroblastoma, but there is no clear consensus. This matter will continue to be debated, as no randomized study has been designed to address this question.

RT has been used for local control [10–16] and symptom control [17,18] in patients with neuroblastoma. As noted above, TBI was previously included in myeloablative regimens with autologous hematopoietic stem cell (HSC) support in patients with high-risk disease. Today, TBI is used less often because chemotherapy-alone regimens have shown similar results [1] with less toxicity [19]. Because a variety of interventions are used to treat high-risk metastatic neuroblastoma in children, the contribution of RT to local control and survival remains unclear.

The objective of this study was to define the role of RT in treating high-risk metastatic neuroblastoma. We identified 63 patients older than 1 year with metastatic neuroblastoma who were treated on consecutive protocols at our institution from 1989–2001. RT was not a prescribed part of protocol therapy, but 17 patients received RT as part of their treatment. Thus all patients received similar chemotherapy and surgical approaches but only a subset received RT. We compared the outcome measures (local failure rate, overall failure rate, and survival) of patients who received RT to the primary site with those of patients who did not.

Patients and Methods

Patients

This retrospective study was approved by the Institutional Review Board of St. Jude Children's Research Hospital, which also approved all institutional treatment protocols. We reviewed the records of 75 children older than 1 year at the time of diagnosis of INSS stage 4 neuroblastoma who were treated on one of three consecutive institutional protocols at St. Jude between June 1989 and February 2001. Twelve patients were excluded from the analysis: one patient with

an initial diagnosis of resectable, localized disease in whom metastatic neuroblastoma developed; one 13-month-old patient with limited metastatic disease, favorable histology (Shimada classification), and a DNA index of 1.76 (not high risk); and 10 patients with progressive disease during induction chemotherapy.

Therapy comprised six cycles of induction chemotherapy, followed by surgical resection of remaining disease and consolidation with either chemotherapy (NB88) or intensive chemotherapy and autologous HSC rescue (NB91 and NB97), as previously described [7]; RT was not prospectively prescribed in these protocols. No significant difference in outcome was found among these three protocols (data not shown).

The following data were extracted from the patients' records: demographic, clinical, and tumor data; serum lactate dehydrogenase (LDH) values; ferritin concentration; and *MYCN* status. Diagnostic imaging, operative, and pathology reports were reviewed to confirm that each patient's disease stage was consistent with the revised INSS criteria [20]. For patients who underwent an initial resection, Shimada histologic risk classification [21] was determined retrospectively for those treated on the NB88 or NB91 protocols and prospectively for those on NB97.

MYCN amplification was defined as more than three copies of the gene determined by Southern blot [22,23] in samples obtained before 1990 and by fluorescence in situ hybridization (FISH) in samples obtained after January 1990 [22,24]. Serum LDH activity >1500 U/L and ferritin concentration >142 ng/mL were considered elevated. The extent of tumor resection was determined by the operating surgeon and defined as follows: *gross total resection* (GTR), removal of more than 95% of visible tumor from the primary site; *less than GTR* (<GTR), removal of less than 95% of visible tumor. All resections included the removal of involved lymph nodes.

All patient records were reviewed with respect to the indications for, timing (during initial therapy or after relapse/progression), features (field, dose), and intent (curative or palliative) of RT. Sites of disease relapse were coded as local, distant, or both (local+distant). For patients with an abdominal primary site, any relapse in the abdomen was considered local. For patients who received RT to the primary site, a radiation oncologist (MJK) reviewed all local relapses in relation to the RT field.

Statistical analysis

Fisher's exact test, the exact Wilcoxon rank sum test, and the exact chi-square test were used to compare patient characteristics of those who received RT and those who did not. Cumulative incidence analysis [25] was used to compare local control rates between the two groups. Local or local+distant relapse were considered events. All deceased patients had a relapse date prior to death. Therefore, distant relapse was the only event considered a competing risk in the cumulative incidence analysis. The analysis was then repeated with only local relapse considered an event and local+distant or distant relapse considered competing risks. Event-free survival (EFS) analysis included any relapse as an event. Overall survival (OS) analysis considered death the only event. EFS and OS distributions were estimated by the Kaplan and Meier method [26]. Standard errors were calculated by the Peto and Pike method [27]. Duration of EFS was defined as the interval between diagnosis and relapse or last follow-up. Duration of OS was defined as the interval between diagnosis and death or last follow-up. EFS and OS distributions were compared between groups using the exact log-rank test.

Results

Patient characteristics

The characteristics of the 63 pediatric patients included in this study are shown in Table 1. The median age at the time of diagnosis was 3.09 years (range, 1.16–16.84 years). At the time of analysis, 18 patients were alive with a median follow-up of 10.7 years (range, 5.3–17.5 years). Fourteen survivors had undergone follow-up within the last year.

Radiation therapy

As part of their initial therapy, 17 patients received external beam RT to their primary tumor sites as detailed in Table 2. These sites included the abdomen (n=15) and thorax (n=2). Indications for RT included persistent primary tumor and/or locoregional nodal disease prior to consolidation therapy in 14 patients and clinician preference in one patient with no evidence of primary disease but extensive metastatic disease at the end of induction. Two patients received RT as part of their consolidation therapy at other institutions. The dose administered ranged from 20.1 to 36 Gy (median, 30 Gy) in 1.5 or 1.8 Gy fractions with AP/PA fields prior to 1999 and by conformal techniques starting in 1999. For the abdominal AP/PA fields, therapy was adjusted to spare the kidneys after 15 Gy. Generally, the RT was well tolerated; the main acute effects were mild nausea, dry skin, hyperpigmentation, and diarrhea.

Differences in the characteristics of the two patient groups

Characteristics of the 46 patients who did not receive primary RT (no-RT group) were compared with those of the 17 patients who did (RT group) (Table 3). The two groups were similar in terms of age at diagnosis, site of primary disease, *MYCN* status, and sites of metastatic disease. There was a trend toward an association between the extent of surgical resection and the choice to administer RT. Patients in the RT group did not undergo GTR as often as did those in the no-RT group (64.7% vs. 89.1%; $p=0.055$). Also, a greater percentage of patients in the RT group showed evidence of residual disease at the end of induction than did those in the no-RT group (88.2% vs. 50%; $p=0.008$).

Effects of radiation therapy

Treatment failure rates are outlined in Table 4. Of the 17 patients in the RT group, 15 (88.2%) experienced relapse: nine had distant relapse, and six had local or local+distant relapse. Of the 46 patients in the no-RT group, 32 (69.6%) experienced relapse: 17 had distant relapse, and 15 had local or local+distant relapse. There was no difference in the 5-year estimates of cumulative incidence of local failure (isolated or in conjunction with distant failure) between the RT group and no-RT group ($35.3\% \pm 12.4\%$ vs. $32.6\% \pm 7.1\%$, respectively; $p=0.74$) (Figure 1). It may be more appropriate to use local+distant relapse as a competing event when analyzing local control rates, because the timing of local reoccurrence is uncertain. For these reasons, we performed another analysis of isolated local control using local+distant relapse as a competing event. The isolated local control rate for the RT group was $17.7\% \pm 9.6\%$, and that of the no-RT group was $13.0\% \pm 5.0\%$ ($p=0.573$).

Five-year EFS estimate appeared to be better in the no-RT group ($30.4\% \pm 6.6\%$) than in the RT group ($11.8\% \pm 6.4\%$), but no significant difference was detected ($p=0.106$) (Figure 2a). However, the 5-year OS estimate was significantly better in the no-RT group than in the RT group ($47.8\% \pm 7.2\%$ vs. $23.5\% \pm 9.2\%$, respectively; $p=0.026$) (Figure 2b).

Discussion

In this retrospective study of outcome in pediatric patients with high-risk metastatic neuroblastoma treated on one of three St. Jude protocols, we found that patients who received

RT did not experience improved local disease control. To interpret these results, we considered the characteristics of these nonrandomly selected groups. Patients in the RT group were less likely to have undergone GTR and were more likely to have residual disease at the end of induction chemotherapy. Intuitively, this group would be more likely to experience local failure than those in the no-RT group. The fact that the local control rates of the two groups were similar suggests that the RT group benefitted from the therapy to the point that they experienced local control similar to that of the no-RT group, whose disease was controlled by chemotherapy and surgery.

A second interesting finding is that patients in the RT group experienced worse survival than those in the no-RT group. Of note, all patients died after relapse of neuroblastoma; no deaths were caused by the toxicity of treatment. Therefore, one cannot attribute the decreased survival to the effects of RT. Instead, the decreased survival is another indication of the selection bias in this cohort. The patients selected to receive RT not only had more local disease at the end of induction chemotherapy but also were more likely to succumb to their disease despite similar local control rates.

The initial relapse in approximately one third of our patients involved locoregional disease. This rate is similar to those reported by the CCG-321P3 [28] and CCG-3891 [11] studies. In CCG-321P3, all patients received 10 Gy of TBI. An additional 20 Gy of RT (10 Gy if abdominal) was administered to sites of residual disease after several cycles of induction chemotherapy. The 3-year local relapse rates were 26% for those who received primary-site RT and 31% for those who received only TBI [28]. Patients treated on CCG-3891 received induction chemotherapy followed by external-beam radiation therapy (EBRT) to gross residual disease. The patients then were randomized to receive continuation chemotherapy (CC) or high-dose chemotherapy with ABMT. All patients treated on the ABMT arm received 10 Gy of TBI. The 5-year estimated locoregional recurrence rates were $51 \pm 5\%$ in the CC group and $33 \pm 7\%$ in the ABMT group [11]. There was a trend toward improved local control rates for the patients treated on the ABMT arm who received additional EBRT, although it was not statistically significant. For the patients with stage 4 neuroblastoma treated on CCG-3891, the 5-year EFS ranged from $18\% \pm 4\%$ for those in the CC group who did not receive EBRT to $50\% \pm 12\%$ for those who received ABMT and EBRT. These rates are similar to the ones reported in our series. Thus, intensive chemotherapy, surgery, and RT administration to selected patients result in local treatment failure rates and 5-year survival estimates that are comparable to those measures in patients with lower-risk disease.

More recent single- and limited-institution studies have reported improved local control rates. Memorial Sloan-Kettering Cancer Center has reported several series of patients treated with intensive induction chemotherapy, surgery, and hyperfractionated RT [12,16,29]. These patients also received either immunotherapy or myeloablative chemotherapy without TBI followed by ABMT. In the first report of 16 patients with stage 4 disease receiving initial therapy, only one experienced treatment failure in the primary site [29]. In one of the more recent studies, the 5-year estimated local failure rate was 16%, and the EFS was 40% [16]. In another study, the probability of primary-site failure 3 years after RT was $10.1\% \pm 5.3\%$, and EFS was $45.7\% \pm 5.5\%$ [12]. The amount of overlap between these patient populations is unclear. In another single-institution study, Bradfield et al [10] described 21 patients with high-risk neuroblastoma who received a regimen of chemotherapy, delayed surgery, and ABMT. Seventeen patients received the planned 21 Gy of EBRT to the primary site. The 2-year estimated local failure rate was 7%, and the 2-year EFS was $48\% \pm 22\%$. Another study using induction chemotherapy, surgery, 10.8 Gy of EBRT to the primary site (omitted if patients had complete resection with negative margins) followed by tandem autologous HSC transplantation, that included 12 Gy TBI, reports an actuarial probability of local control of 97% with a 3-year EFS of 63% [13]. All of these studies reported improved local control rates

of >80% when RT was prescribed for all patients and not reserved for only those who had visible evidence of residual disease.

The concept that RT may be most beneficial for those patients with microscopic residual disease is supported by a report from Rosen et al [15] who described 22 patients (older than 1 year) with metastatic neuroblastoma who entered complete or near-complete remission after chemotherapy and surgery. Six of the 15 (40%) patients who received RT experienced a primary site failure, and 6 of 7 (86%) who did not receive RT had a primary failure. Of note, although local control appears to be improved when intense multimodality therapy is administered to patients with high-risk neuroblastoma, distant control shows significant failure that needs to be addressed.

Another matter that should be addressed when evaluating the escalation of therapy is the increased toxicity that may occur. In our series, none of the patients died of treatment toxicity, and the patients who were selected to receive RT did not experience excess short-term toxicity. In CCG-3891, the overall rate of grade 3–4 toxicities was similar in patients who received EBRT and those who did not [11]. However, in the ERBT group, significantly more patients needed total parenteral nutrition, and there was a trend toward increased veno-occlusive disease of the liver. The most common acute toxicity of RT reported was mild gastrointestinal symptoms [11,12]. Myelosuppression also appears to be problematic in patients who receive RT after HSC transplantation. In one series, 13 of 16 patients received a second infusion of peripheral blood stem cells upon completion of RT [10]. Late toxicities are emerging in survivors. These have included hypothyroidism [12], leg-length discrepancy [10], scoliosis [16], and poor growth [12]. At this time, treating the primary site with RT does not appear to produce excess toxicity, given the already intense regimen to which these patients are subjected. However, as RT use becomes more widespread and more patients survive, this issue should be reassessed.

In summary, we report a group of pediatric patients older than 1 year with metastatic neuroblastoma who were treated on consecutive protocols at our institution. RT was not a prescribed part of protocol therapy, but 17 patients received RT as part of their treatment. Our aim was to determine whether RT affected local control and survival by comparing these outcomes in a group of patients who received RT to those in a group who did not. We found that the two groups were similar in terms of initial disease characteristics but differed with respect to the extent of residual disease after induction chemotherapy and surgery. Patients in the RT group were more likely to have visible residual primary disease. By using RT, we achieved a local control rate in the group with higher-risk neuroblastoma and more residual disease that was similar to that of the no-RT group, which had less residual disease at the end of therapy.

There is evidence from the literature that all patients with high-risk neuroblastoma may benefit from local RT, and those with only microscopic residual disease may benefit the most. Thus, our current high-risk neuroblastoma protocol incorporates RT for all patients. We are carefully evaluating local control rates and toxicity with this change in institutional approach. Unfortunately, distant failure remains problematic. A variety of approaches such as targeted RT with MIBG [30], immunotherapy [31–33] or novel therapies based on a better understanding of the biology of the tumor such as antiangiogenic therapy [34], or inhibition of the *ALK* gene product [35] is needed to improve the outcome of these patients.

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References

- Berthold F, Hero B, Kremens B, et al. Long-term results and risk profiles of patients in five consecutive trials (1979–1997) with stage 4 neuroblastoma over 1 year of age. *Cancer Lett* 2003;197(1–2):11–17. [PubMed: 12880954]
- De Bernardi B, Nicolas B, Boni L, et al. Disseminated neuroblastoma in children older than one year at diagnosis: comparable results with three consecutive high-dose protocols adopted by the Italian Co-Operative Group for Neuroblastoma. *J Clin Oncol* 2003;21(8):1592–1601. [PubMed: 12697885]
- 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(8):613–621. [PubMed: 12439032]
- Matthay KK, Reynolds CP, Seeger RC, et al. Long-Term Results for Children With High-Risk Neuroblastoma Treated on a Randomized Trial of Myeloablative Therapy Followed by 13-cis-Retinoic Acid: A Children's Oncology Group Study. *J Clin Oncol* 2009;27(7):1007–1013. [PubMed: 19171716]
- Nitschke R, Smith EI, Shochat S, et al. Localized neuroblastoma treated by surgery: a Pediatric Oncology Group Study. *J Clin Oncol* 1988;6(8):1271–1279. [PubMed: 3411339]
- Adkins ES, Sawin R, Gerbing RB, et al. Efficacy of complete resection for high-risk neuroblastoma: A children's cancer group study. *J Pediatr Surg* 2004;39(6):931–936. [PubMed: 15185228]
- McGregor LM, Rao BN, Davidoff AM, et al. The impact of early resection of primary neuroblastoma on the survival of children older than 1 year of age with stage 4 disease: the St. Jude Children's Research Hospital Experience. *Cancer* 2005;104(12):2837–2846. [PubMed: 16288490]
- von Schweinitz D, Hero B, Berthold F. The impact of surgical radicality on outcome in childhood neuroblastoma. *Eur J Pediatr Surg* 2002;12(6):402–409. [PubMed: 12548494]
- La Quaglia MP, Kushner BH, Su W, et al. The impact of gross total resection on local control and survival in high-risk neuroblastoma. *J Pediatr Surg* 2004;39(3):412–417. [PubMed: 15017562]
- Bradfield SM, Douglas JG, Hawkins DS, et al. Fractionated low-dose radiotherapy after myeloablative stem cell transplantation for local control in patients with high-risk neuroblastoma. *Cancer* 2004;100(6):1268–1275. [PubMed: 15022296]
- 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(1):28–39. [PubMed: 12694821]
- 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(11):2821–2828. [PubMed: 11387353]
- Marcus KJ, Shamberger R, Litman H, et al. Primary tumor control in patients with stage 3/4 unfavorable neuroblastoma treated with tandem double autologous stem cell transplants. *J Pediatr Hematol Oncol* 2003;25(12):934–940. [PubMed: 14663275]
- Paulino AC, Mayr NA, Simon JH, Buatti JM. Locoregional control in infants with neuroblastoma: role of radiation therapy and late toxicity. *Int J Radiat Oncol Biol Phys* 2002;52(4):1025–1031. [PubMed: 11958898]
- Rosen EM, Cassady JR, Frantz CN, et al. Neuroblastoma: the Joint Center for Radiation Therapy/ Dana-Farber Cancer Institute/Children's Hospital experience. *J Clin Oncol* 1984;2(7):719–732. [PubMed: 6737018]
- 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(4):969–974. [PubMed: 10705019]
- De Bernardi B, Pianca C, Pistamiglio P, et al. Neuroblastoma with symptomatic spinal cord compression at diagnosis: treatment and results with 76 cases. *J Clin Oncol* 2001;19(1):183–190. [PubMed: 11134211]
- Paulino AC. Palliative radiotherapy in children with neuroblastoma. *Pediatr Hematol Oncol* 2003;20(2):111–117. [PubMed: 12554522]

19. Flandin I, Hartmann O, Michon J, et al. Impact of TBI on late effects in children treated by megatherapy for Stage IV neuroblastoma. A study of the French Society of Pediatric oncology. *Int J Radiat Oncol Biol Phys* 2006;64(5):1424–1431. [PubMed: 16427213]
20. Brodeur GM, Pritchard J, Berthold F, et al. Revisions of the international criteria for neuroblastoma diagnosis, staging, and response to treatment. *J Clin Oncol* 1993;11(8):1466–1477. [PubMed: 8336186]
21. Shimada H, Ambros IM, Dehner LP, et al. The International Neuroblastoma Pathology Classification (the Shimada system). *Cancer* 1999;86(2):364–372. [PubMed: 10421273]
22. Alvarado CS, London WB, Look AT, et al. Natural history and biology of stage A neuroblastoma: a Pediatric Oncology Group Study. *J Pediatr Hematol Oncol* 2000;22(3):197–205. [PubMed: 10864050]
23. Brodeur GM, Seeger RC, Schwab M, et al. Amplification of N-myc in untreated human neuroblastomas correlates with advanced disease stage. *Science* 1984;224(4653):1121–1124. [PubMed: 6719137]
24. Shapiro DN, Valentine MB, Rowe ST, et al. Detection of N-myc gene amplification by fluorescence in situ hybridization. Diagnostic utility for neuroblastoma. *Am J Pathol* 1993;142(5):1339–1346. [PubMed: 7684192]
25. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics* 1988;16(3):1141–1154.
26. Kaplan EL, Meier P. Nonparametric-estimation from incomplete observations. *Journal of the American Statistical Association* 1958;53(282):457–481.
27. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical-trials requiring prolonged observation of each patient.2. Analysis and examples. *British Journal of Cancer* 1977;35(1):1–39. [PubMed: 831755]
28. Matthay KK, Atkinson JB, Stram DO, et al. Patterns of relapse after autologous purged bone marrow transplantation for neuroblastoma: a Childrens Cancer Group pilot study. *J Clin Oncol* 1993;11(11):2226–2233. [PubMed: 8229138]
29. Kushner BH, O'Reilly RJ, Mandell LR, et al. Myeloablative combination chemotherapy without total body irradiation for neuroblastoma. *J Clin Oncol* 1991;9(2):274–279. [PubMed: 1899111]
30. Matthay KK, Yanik G, Messina J, et al. Phase II study on the effect of disease sites, age, and prior therapy on response to iodine-131-metaiodobenzylguanidine therapy in refractory neuroblastoma. *J Clin Oncol* 2007;25(9):1054–1060. [PubMed: 17369569]
31. Yu AL, Uttenreuther-Fischer MM, Huang CS, et al. Phase I trial of a human-mouse chimeric anti-disialoganglioside monoclonal antibody ch14.18 in patients with refractory neuroblastoma and osteosarcoma. *J Clin Oncol* 1998;16(6):2169–2180. [PubMed: 9626218]
32. Kushner BH, Kramer K, Cheung NK. Phase II trial of the anti-G(D2) monoclonal antibody 3F8 and granulocyte-macrophage colony-stimulating factor for neuroblastoma. *J Clin Oncol* 2001;19(22):4189–4194. [PubMed: 11709561]
33. Osenga KL, Hank JA, Albertini MR, et al. A phase I clinical trial of the hu14.18-IL2 (EMD 273063) as a treatment for children with refractory or recurrent neuroblastoma and melanoma: a study of the Children's Oncology Group. *Clin Cancer Res* 2006;12(6):1750–1759. [PubMed: 16551859]
34. Dickson PV, Hamner JB, Sims TL, et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res* 2007;13(13):3942–3950. [PubMed: 17606728]
35. George RE, Sanda T, Hanna M, et al. Activating mutations in ALK provide a therapeutic target in neuroblastoma. *Nature* 2008;455(7215):975–978. [PubMed: 18923525]

Figure 1.

Cumulative incidence of local treatment failure (isolated or concurrent with distant failure) in pediatric patients with high-risk metastatic neuroblastoma. No difference was seen between patients groups based on whether they were treated with radiation therapy (red dashed line) or not (black solid line).

Figure 2.

Survival of pediatric patients with high-risk metastatic neuroblastoma. The probabilities of event-free survival (**a**) and overall survival (**b**) were determined in patient groups that were either treated with radiation therapy (red dashed line) or not (black solid line). No significant difference was seen in event-free survival, but overall survival was better in the no-RT group than in the RT group.

Table 1

Characteristics of 63 pediatric patients with metastatic high-risk neuroblastoma

Characteristic	No. patients (%)
Sex	
Male	38 (60.3)
Female	25 (39.7)
Race	
White	46 (73)
Black	13 (20.6)
Other	4 (6.3)
St. Jude Protocol	
NB88	20 (31.7)
NB91	25 (39.7)
NB97	18 (28.6)
Primary disease site	
Left adrenal gland	30 (47.6)
Right adrenal gland	22 (34.9)
Abdomen	8 (12.7)
Thorax	3 (4.8)
<i>MYCN</i> status	
Amplified	18 (28)
Not amplified	38 (60.3)
Missing	7 (11.1)
Ferritin concentration	
≥ 142 ng/mL	40 (63.5)
≤ 141 ng/mL	16 (25.4)
Missing data	7 (11.1)
Surgery	
Gross total resection	52 (82.5)
<Gross total resection	11 (17.5)
Lactate dehydrogenase	
≥1500 U/L	9 (14.3)
≤1499 U/L	51 (81)
Missing data	3 (4.8)

Table 2

Details regarding the extent of disease and radiation therapy of patients in the RT group

Patient	Primary site	Metastatic Sites at Diagnosis			GTR	Residual Disease Prior to Consolidation		Delivery of EBRT			Pattern of Failure	Toxicity
		Lymph Node(s)	Bone	Bone Marrow		Locoregional	Distant	Site	Technique	Dose		
1	Adrenal	+	+	-	No	Extensive Primary	None	Upper middle/left abdomen	AP/PA	34.5 Gy	Local	Anorexia
2	Adrenal	+	-	+	Yes	lymph nodes	None	Upper middle/left abdomen	AP/PA	36 Gy	Distant	Diarrhea Vomiting Abdominal pain
3	Adrenal	-	+	+	Yes	lymph nodes	None	Paraortic	AP/PA/lateral	30 Gy	Distant	
4	Adrenal	+	+	+	Yes	lymph nodes	None	Upper middle/right abdomen	AP/PA	36 Gy	Distant	
5	Adrenal	+	+	+	Yes	lymph nodes	bone	Paraortic/ left abdomen	AP/PA	30 Gy	Distant	
6	Adrenal	+	+	+	Yes	Small residual primary, lymph nodes	bone	Paraortic and upper pelvis	AP/PA	33.6 Gy	Distant	
7	Adrenal	+	+	+	Yes	lymph nodes	bone	Paraortic	AP/PA	30 Gy	Local + Distant	
8	Adrenal	+	+	+	No	Unresectable primary, lymph nodes	bone	Paraortic	AP/PA	36 Gy	Distant	Diarrhea
9	Abdomen (nonadrenal)	+	+	+	No	Unresectable primary	none	Paraortic	AP/PA	30 Gy	None	
10	Thorax	-	+	-	Yes	Small residual primary	bone	Left paraspinal	3DCRT	30.6 Gy	Local	Odynophagia
11	Adrenal	+	+	+	Yes	lymph nodes	bone	Right upper abdomen	AP/PA	20.1 Gy	Distant	
12	Adrenal	+	+	+	No	Small residual primary, lymph nodes	Bone, thoracic lymph nodes	Left supraclavicular, mediastinal and retrocrural nodes	3DCRT	30.6 Gy	Local + Distant	
13	Adrenal	+	+	-	No	lymph nodes	none	Paraortic	3DCRT	25.2 Gy	Local	
14	Thorax	+	+	+	Yes	Small residual primary	bone	Thorax	3DCRT	25.2 Gy	Distant	
15	Adrenal	-	+	+	Yes	none	none	Abdomen	AP/PA	21.6 Gy	None	Anorexia
16	Adrenal	+	-	+	No	Lymph nodes	none	Abdomen to 21 Gy, then boost to gross	3DCRT	30 Gy	Local	Nausea

Patient	Primary site	Metastatic Sites at Diagnosis			GTR	Residual Disease Prior to Consolidation		Delivery of EBRT			Pattern of Failure	Toxicity
		Lymph Node(s)	Bone	Bone Marrow		Locoregional	Distant	Site	Technique	Dose		
17	Adrenal	+	+	+	Yes	none	Bone, bone marrow	Right abdomen	3DCRT	23.4 Gy	Distant	Nausea

Abbreviations: AP/PA –anteroposterior/posteroanterior radiation fields; 3DCRT–three-dimensional conformal radiation therapy

Table 3

Comparison of the characteristics of patients who received radiation therapy (n=17) with those of patients who did not (n=46)

Characteristic	RT group	No-RT group	P-value
	No. patients (%)	No. patients (%)	
Age at Diagnosis (years)			0.300
Median	3.37	2.94	
Range	(1.79, 16.84)	(1.16, 9.38)	
Sex			0.883
Male	10 (58.8)	28 (60.9)	
Female	7 (41.2)	18 (39.1)	
Race			1.000 ^a
White	13 (76.5)	33 (71.7)	
Black	3 (17.6)	10 (21.7)	
Other	1 (5.9)	3 (6.5)	
St. Jude Protocol			0.113
NB88	5 (29.4)	15 (32.6)	
NB91	4 (23.5)	21 (45.7)	
NB97	8 (47.1)	10 (21.7)	
Primary disease site			0.175 ^b
Adrenal gland	14 (82.4)	38 (82.6)	
Abdomen	1 (5.9)	7 (15.2)	
Thorax	2 (11.8)	1 (2.2)	
NMYC status			0.338 ^c
Amplified	3 (17.6)	15 (32.6)	
Not amplified	12 (70.6)	26 (56.5)	
Missing	2 (11.8)	5 (10.9)	
Ferritin concentration			0.741 ^c
≥ 142 ng/mL	10 (58.8)	30 (65.2)	
≤ 141 ng/mL	5 (29.4)	11 (23.9)	
Missing	2 (11.8) ()	5 (10.9)	
Surgery			0.055
Gross total resection	11 (64.7)	41 (89.1)	
<Gross total resection	6 (35.3)	5 (10.9)	
Residual disease prior to consolidation			0.008
Yes	15 (88.2)	23 (50)	
No	2 (11.8)	23 (50)	
Lactate dehydrogenase			0.423 ^c
≥1500 U/L	1 (5.9)	8 (17.4)	
≤1499 U/L	16 (94.1)	35 (76.1)	
Missing	0 (0)	3 (6.5)	

Characteristic	RT group	No-RT group	P-value
	No. patients (%)	No. patients (%)	
Bone Marrow involvement			1.000
Yes	14 (82.4)	38 (82.6)	
No	3 (17.6)	8 (17.4)	
Bone involvement			0.315
Yes	15 (88.2)	34 (73.9)	
No	2 (11.8)	12 (26.1)	
Nodal disease at diagnosis			0.741
Yes	14 (82.4)	35 (76.1)	
No	3 (17.6)	11 (23.9)	

^aWhite race versus other races

^bFavorable sites (pelvic or thorax) versus unfavorable sites (adrenal, nonadrenal, or cervical)

^cMissing data were excluded from the test

Table 4

Rates of neuroblastoma relapse and progression in patients who received radiation therapy (n=17) and those who did not (n=46)

Measure	RT group	No-RT group
	No. patients (%)	No. patients (%)
Relapse or progression of neuroblastoma		
Yes	15 (88.24)	32 (69.57)
No	2 (11.76)	14 (30.43)
Site of initial disease progression		
Local	4 (26.7)	9 (28.1)
Distant	9 (60)	17 (53.1)
Local+distant	2 (13.3)	6 (18.8)