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Loco-regional Tumor Progression after Radiation Therapy Influences Overall Survival in Pediatric Patients with Neuroblastoma

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Abstract

Purpose—There is renewed attention in primary site irradiation and local control for patients with high-risk neuroblastoma (NB). We conducted a retrospective review to identify factors that might predict for loco-regional tumor control and its impact on overall survival.

Methods and Materials—Between July 2000 through August 2006, 44 pediatric patients with NB received radiation therapy (RT) with curative intent using CT-based treatment planning. The median age was 3.4 years and the median cumulative dose was 23.4 Gy. Overall survival and loco-regional tumor control were measured from the start of RT to the date of death or event as determined by CT/MRI/MIBG. The influence of age at irradiation, gender, race, cumulative radiation dose, INSS stage, treatment protocol and resection status was determined with respect to loco-regional tumor control.

Results—With a median follow-up of 34 months $\pm$ 21 months, loco-regional tumor progression was observed in 11 (25%) and was evenly divided between primary site and adjacent nodal/visceral site failure. The influence of loco-regional control reached borderline statistical significance ($p=0.06$). Age ($p=0.5$), dose ($p=0.6$), resection status ($p=0.7$) and INSS stage ($P=0.08$) did not influence overall survival.

Conclusions—Overall survival in high-risk neuroblastoma is influenced by loco-regional tumor control. Despite CT-based planning, progression in adjacent nodal/visceral sites appears to be common; this requires further investigation regarding target volume definitions, dose and the effects of systemic therapy.

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Keywords

pediatric; neuroblastoma; radiation; loco-regional failure; overall survival

Introduction

High risk neuroblastoma (NB) is a common extra-cranial, sympathoadrenal solid tumor of the pediatric population with a notably poor prognosis. During the past two decades, emphasis has been placed on systemic therapy because the majority of children present with metastatic disease involving bone marrow, bone, lymph nodes and liver. The result has been a gradual improvement in overall survival from 40% to 60%.^{1, 2} As systemic tumor control improves, the proportion of patients who experience loco-regional failure as a component of first failure has naturally increased. These events have prompted a re-examination of loco-regional tumor control and the impact of primary site failure on overall survival.

The role of surgery has been relatively stable during the past decade: judiciously aggressive macroscopic resection remains the primary goal. Although the need for gross total resection is not uniformly demonstrated across all major studies, the current consensus is that improved outcomes are associated with minimal residual loco-regional disease.^{3, 4} Series that include radiation therapy suggest that local control rates in excess of 90% are attainable; however, large randomized trials have shown that local control rates are actually significantly lower, especially for patients with gross residual disease at the primary site.^{5, 6} Institutional and cooperative group protocols have incorporated dose-escalation to the primary tumor bed and residual disease, from 30.6Gy, to 36Gy, based on data suggesting an association between increasing dose and improved loco-regional control.^{5, 7}

We undertook a retrospective review to determine the patterns of treatment failure after primary site irradiation among patients with high risk NB treated at our institution using CT-based treatment planning. Our hypothesis was that loco-regional tumor control impacts overall survival and that accurate evaluation of treatment failures in the primary site and adjacent nodal and visceral sites would identify the need for improved targeting, comprehensive irradiation beyond the currently identified primary site target volume and a cohort of patients for whom survival might be improved. Additionally, we sought to demonstrate that in order to avoid under-estimating local failure, assessment of loco-regional tumor control should consider competing risks, including progression of metastatic disease, treatment toxicity and death.

Methods and Materials

Between July 2000 and August 2006, 44 patients with high-risk (INSS stage 3/4) NB received primary site irradiation with curative intent using CT-based treatment planning. These patients included 41 with non-progressive, metastatic disease and three were classified as stage 3. They were chosen from among 84 patients treated during the same time period because radiation therapy was planned using 3-dimensional methods and their follow-up included modern imaging that could be electronically registered to the treatment planning data for analysis of patterns of failure. Sixteen of 44 patients received irradiation to metastatic sites at the time of primary tumor bed irradiation; one received emergent radiotherapy to the skull base approximately 9 months before irradiation of the primary site. The mean age at the time of irradiation was 3.8 years $\pm$ 1.9 and the median was 3.4 years (range 1.1 to 9.7 years). The mean primary site dose was 24.7Gy $\pm$ 2.9Gy with a median of 23.4Gy (range 21.0 to 30.6Gy). Thirty-four underwent gross total resection, eight were subtotally resected, one underwent biopsy only and the resection status was unknown in one patient. There were 24 female and eleven non-white patients. Twenty-two were younger than 3.36 years at the time of irradiation, 16 received

greater than 23.4Gy to the primary site and 10 had less than 95% tumor resection prior to irradiation. Primary tumor locations were abdominal (n=39), mediastinal (n=2), multilevel mediastinal and abdominal (n=2), and sacrum (n=1).

The sequence of treatment varied according to treatment era. Radiotherapy was administered as part of the current national protocol paradigm—induction chemotherapy, surgical resection, consolidation high-dose chemotherapy with stem cell transplant and primary site irradiation—in 11 of 44 (25%) patients. These 11 patients received therapy on the national protocol, NB02P1 and the St. Jude protocol NB2005. Of the remaining 33, seven were treated on St. Jude protocol NB97 and 26 were not enrolled on a specific protocol for their initial treatment, thereby making comparisons of volume definition across treatment regimens difficult. All patients received radiotherapy in the primary setting. Radiotherapy was not systematically included as a part of the therapeutic plan prior to accrual to protocol NB02P1. For those with protocol-mandated radiotherapy, volumes included a gross tumor volume based on the post-induction, pre-operative tumor. The corresponding clinical target volume incorporated a 1.5 cm margin, and planning target volumes consisted of a 0.5 – 1.0 cm geometric three-dimensional expansion. However, draining lymphatic regions were not routinely treated according to protocol guidelines in NB02P1 and NB2005. In some cases gross residual disease received an additional boost to the appropriate residual volume. The majority received radiotherapy when gross residual disease was noted either peri-operatively or the infiltration of initial disease suggested a significant local control issue. Therapy was most commonly delivered with opposed anterior-posterior, posterior-anterior fields, which required a subsequent off-kidney boost before exceeding renal tolerance constraints. A small minority of patients presented with localized disease amenable to conformal radiotherapy. No case received inverse-planned intensity modulated radiotherapy, because ICRU-62 supplement definitions for pediatric target or avoidance structure motion as impacted by respiration were undefined at the time.⁸ Coverage of the planning target volume (PTV) was thus commonly reduced for the off-kidney phase by 10 – 30%. These reductions were most closely related to the dimensions of the PTV, and resulted in worse PTV coverage particularly for tumor volumes displaying a high degree of concavity around the renal structures.

Pattern of First Failure Analysis

Pertinent imaging (CT, MRI, FDG-PET, MIBG and bone scintigraphy) demonstrating first progression was evaluated and when possible, registered to the original treatment planning CT to determine the pattern of first failure with respect to the original planning target volume. Most frequently, CT and CT/MIBG data were sufficient to determine first failure. These data were registered to treatment planning data to establish the location of the progressive disease relative to the irradiated volume. In the rare case of MIBG non-avid tumors MRI, FDG-PET and bone scintigraphy contributed to the definition of the volume of first failure. *Infield failure* was defined as progression of disease within the PTV. *Adjacent failure* was defined as progression of disease in nodal or visceral regions contiguous with the primary site and outside the PTV that received less than 5% of the prescribed dose. *Distant failure* was the appearance of new disease or disease progression at sites that were not contiguous with the primary site. *Marginal failure* was defined as progression at sites outside of the PTV that received less than 95% and more than 5% of the prescribed dose. For purposes of analysis, loco-regional failure was defined as the combination of infield failure and adjacent failure.

Statistical Analysis

The statistical endpoints for this retrospective study were the Kaplan-Meier estimates of event-free (EFS) and overall (OS) survival measured from the start of RT. EFS was measured from the date of starting radiotherapy to the date of event, inclusive of infield failure, adjacent failure, distant failure and death. OS was measured from the first day of irradiation to death. The log-

rank test was used to evaluate the differences in EFS and OS based on sex, race, disease stage, age, radiation dose, tumor stage, treatment protocol and extent of tumor resection. The cumulative incidence of infield failure, adjacent failure and distant failure were calculated using Gray's method. The cumulative incidence of failure was measured from the first day of irradiation to the date of first failure, while any other failures occurring prior to the failure are considered competing events.

Results

Loco-regional and distant tumor progression were observed in 11 (25%) and 13 (29.6%) patients, respectively. All failures were infield, adjacent or distant; there were no cases of marginal failure. The cumulative incidence of loco-regional and distant failure at 5 years was $25.3\% \pm 6.7\%$ and $33.9\% \pm 7.6\%$, respectively. Figure 1a Loco-regional failure was evenly divided by infield ($n=5$, 5 yr CI $11.6\% \pm 5.0\%$) and adjacent ($n=6$, 5 yr CI $13.6\% \pm 5.2\%$) failure. Figure 1b With a median follow-up of 34 months $\pm$ 21 months, the 5 year EFS and OS were $36.2\% \pm 11.8\%$ and $40.9 \pm 12.8\%$, respectively. Age (greater or less than 3 years, $p=0.5$), sex ($p=0.9$), race ($p=0.5$), radiation dose (greater or less than 23.4Gy, $p=0.6$), extent of resection (greater or less than 95%, $p=0.7$), INSS stage (3 vs. 4, $p=0.08$) and treatment protocol ($p=0.4$) did not influence event-free or overall survival; however, the influence of loco-regional tumor control on overall survival reached borderline statistical significance ($p=0.06$). Overall survival at 5 years was $48.3\% \pm 14.2\%$ for patients without loco-regional failure versus $21.8 \pm 19.3\%$ for patients with loco-regional failure. Figure 2

Discussion

Primary site irradiation is considered requisite for high risk NB consolidation therapy^{5, 9–12} and may be validated in the Children's Oncology Group protocol¹³ where current studies include irradiation for all patients and dose-escalation for patients with residual disease after induction chemotherapy and surgery. Current standard of care conventions using local irradiation for high-risk NB were empirically derived with few modifications in recent years. Given the widespread use of CT-based treatment planning and 3-dimensional treatment methods, sufficient experience has been gained to examine the patterns of failure, assess the manner in which patients are targeted for radiation therapy, and evaluate disease progression, especially for those who suffer local failure as the first site of failure.

Our analysis confirms the importance of loco-regional tumor control by suggesting an influence on overall survival. Although our findings were borderline significant, they are strengthened by the detailed nature of our patterns of failure method that co-registered follow-up volumetric imaging to treatment planning data and identified adjacent nodal and visceral failures. The results are further strengthened by the conservative method of statistical analysis that more accurately describes loco-regional failures by considering distant metastases and other events as competing risks.

Our reported infield failure rate of 11.6%, event-free survival rate of 36.2% and overall-survival rate of 40.9% at 5 years parallels recent contemporary series including that reported by Wolden et al in 2000. They reported local failure rates of 16% and 5 year overall survival of 45%. This was achieved using hyperfractionated irradiation to 21 Gy and comprehensive coverage of the initial tumor volume and regional lymph nodes in conjunction with autologous bone marrow transplant or immunotherapy. In a follow-up report that included 99 high risk patients from the same institution treated with the same fractionation regimen, the 36 month local failure rate was only $10.1 \pm 5.3\%$. None of the 23 patients had primary site recurrence after gross total resection, but 3 of 7 recurred after irradiation with subtotal resection.¹⁰ These and other studies indicate the important roles of both surgery and local irradiation in optimizing local control;

however, they lack characterizing information about non-primary site failures and the competing risk of distant failure in their assessment of local tumor control. This series reports a 77% rate of gross total resection and a 20% rate of subtotal resection (with one receiving biopsy alone). The impact of surgical resection status did not yield a statistically significant effect on overall survival in this series. One explanation may be related to the sample size in this analysis. Additionally, the non-standard role of radiotherapy may function as a bridge to improving local control at the primary site in cases of subtotally resected disease.

A more recent study by George et al reported only 3 loco-regional failures out of 97 patients at 7 years.² Five patient deaths were recorded after a tandem regimen of high-dose chemotherapy with stem cell support and total body irradiation (TBI) using 12 Gy. Prior to tandem transplant, but following a 5 cycle course of induction chemotherapy with peripheral blood stem cell harvest and surgery, local irradiation using 10.8–18Gy was delivered. The initial design for the study included 18Gy local irradiation, however, due to toxicity concerns, the non-TBI primary site dose was subsequently reduced to 10.8Gy.^{14, 15} These results appear to yield the best loco-regional control rates, albeit at a considerable cost in terms of patient mortality. The actual local failure rate might be higher considering competing risks and the contribution of TBI. Despite the relatively low dose of the TBI regimens, its contribution to regional tumor control in adjacent sites should not be underestimated. An earlier study that relied upon TBI, CCG-321P3, delivered local irradiation limited to the sites of gross residual disease. Disease progression at the primary site was demonstrated in 22 of 41 patients.¹⁶ The implication of these data is that loco-regional irradiation may have a significant impact on local disease control, regardless of the presence of gross residual disease. Furthermore, the use of TBI in addition to focal irradiation, while reducing local failure rates, is also responsible for increased myelosuppression, and potentially significantly increased mortality.²

The overall survival and loco-regional control results demonstrated in this series are comparable to several other series published within the last decade. However, 75% of patients reviewed in this study did not receive radiotherapy—either total body or focal irradiation—as a systematic part of the standard of care. Nine of these 33 (27%) developed loco-regional failure. Of the 11 (25%) patients with planned post-transplant irradiation, only one child with highly MYCN amplified disease failed loco-regionally. These results suggest the possibility of obtaining similarly high levels of loco-regional control with single transplant and dose-escalated focal irradiation as have been attained with tandem transplant. Furthermore, no treatment related mortality was noted in any of the cases receiving single transplant and focal irradiation, and recovery from therapeutic toxicity was generally uncomplicated.

Although the institutional protocol, NB97, had no designated role for radiotherapy, towards the latter phases of accrual, therapy was amended to incorporate focal irradiation as standard therapy. The non-protocol patients prior to NB97 received consideration for radiation only when the presence of significant gross residual disease was thought to merit additional local control measures. This method tended to select a more infiltrative disease subset of the total population. Therefore, it becomes difficult to make sweeping generalizations regarding the role of radiotherapy. However, despite the bias of a non-systematic radiotherapeutic approach in 75% of these patients, loco-regional control did demonstrate considerable impact on overall survival. The impact of the inherent negative selection bias associated with 75% of patients receiving off-protocol primary site irradiation because of poor prognostic factors (resection status, locally infiltrative disease) is difficult to quantify. Furthermore, even though a variety of different treatment regimens were utilized across time, including hyperfractionation with accelerated delivery, the volume definitions have been relatively constant. These factors increase the importance of radiotherapy in these patients and its impact on loco-regional tumor control and overall survival. These conclusions are especially relevant for those with subtotally resected or infiltrative tumors.

The current role of radiotherapy in high risk neuroblastoma at our institution parallels current cooperative group regimens of induction chemotherapy, surgery, high-dose chemotherapy consolidation with stem cell support and focal irradiation with dose-escalation for residual disease. Critical to the future use of radiotherapy in high-risk NB and especially patients with residual tumor is the definition of target volumes, critical avoidance structures and the RT delivery method. Target volume coverage and adherence to treatment guidelines is highly dependent on the initial extent of tumor and allowable normal tissue tolerances.

Conclusions

Benefits from current treatment regimens with improvements in event-free survival and gains in systemic tumor control have increased the importance of primary site tumor control due to its influence on overall survival. Local irradiation, by contributing to local control, provides a strong impact on overall survival. In this series, loco-regional control is demonstrated to exert a more significant effect on overall survival than INSS stage, age and resection status.

Conventional irradiation is potentially limited in efficacy by the capacity to identify loco-regional microscopic disease, and therefore, the ability to fully target areas at risk; target dose may be further compromised by toxicity to productive bone marrow. Target dose may also be limited by physiologic organ motion in predominantly abdominal primary sites. Further refinement in radiation dose delivery can be accomplished and may be necessary to improve local control and hence, overall survival.

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Figure 1.

a. Cumulative Incidence of Local and Distant Failure

b. Cumulative Incidence of Infield and Adjacent Failure

Figure 2.
Overall Survival by Presence or Absence of Loco-regional Failure