Published in final edited form as:
Lancet Oncol. 2009 March ; 10(3): 258–266. doi:10.1016/S1470-2045(08)70342-5.

A Prospective Study of Conformal Radiation Therapy for Pediatric Ependymoma

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Abstract

Background—Successful therapy for ependymoma includes aggressive surgical intervention and radiation therapy administered using methods which minimize the risk of side effects. We extended this treatment approach to include children under the age of 3 years.

Methods—Between July 1997 and 2007, 153 pediatric patients (median age 2·9 years, range 0·9–22·9 years) with localized ependymoma received conformal radiation therapy after definitive surgery. Doses of 59·4 (n=131) or 54·0 Gy (n=22) were prescribed to a 10mm clinical target volume margin surrounding the post-operative residual tumor and/or tumor bed. The patients had the following characteristics: anaplastic ependymoma (n=85), infratentorial location (n=122), prior chemotherapy (n=35) and extent of resection (gross-total=125, near-total=17, subtotal=11). Disease control, patterns of failure and complications were recorded for patients followed through 10 years.

Findings—With a median follow-up of 5·3 years (range 0·4 to 10·4 years), death was recorded in 23 patients and tumor progression in 36, including local (n=14), distant (n=15) and combined failure (n=7). Tumor grade predicted overall (OS) and event-free (EFS) survival and distant failure. Extent of resection predicted OS, EFS and local failure. Race predicted OS. The 7 year local control, event-free and overall survival were 83·7% (95% CI: 73·9–93·5%), 69·1% (95% CI: 56·9–81·3%) and 81·0% (95% CI: 71·0–91·0%), respectively. The cumulative incidence of local and distance failure were 16·3% (95% CI: 9·6–23·0%) and 11·48% (95% CI: 5·9–17·1%), respectively. Considering only those patients treated with immediate post-operative CRT (without delay or chemotherapy) the 7 year OS, EFS and CI of local and distant failure were 85·0% (95% CI: 74·2–95·8%), 76·9% (95% CI: 63·4–90·4%), 12·59% (95% CI: 5·1–20·1%)and 8·56% (95%

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The authors declared no conflicts of interest.

Contributors
TM was principal investigator of the study and participated in the concept and design, collection and assembly of data, data analysis and interpretation, manuscript writing and editing. CL and XX participated in the concept and design, collection and assembly of data, and data analysis and interpretation. LK, FB and RS participated in the provision of study materials/patients and editing of the manuscript. All authors participated in the final approval of the manuscript.

CI: 2·8–14·3%), respectively. The incidence of secondary malignant brain tumor at 7 years was 2·3% (95% CI: 0–5·6%) and brainstem necrosis 1·6% (95% CI: 0–4·0%).

Interpretation—This study provides new disease control benchmarks and a unifying approach for the treatment of ependymoma that should include surgery with the aim of gross-total resection and conformal, high-dose, post-operative irradiation even for the youngest children. Future trials might consider treatment stratification based on gender and age as female patients are more likely to be long-term survivors and younger patients have higher rates of failure.

INTRODUCTION

Newer methods of radiotherapy administration have combined with advances in neurosurgery to increase tumor control and reduce side effects in pediatric patients with localized ependymoma. Preliminary results from contemporary series using conformal, intensity-modulated, and proton beam radiation therapy support this thesis with reduced side effects and improved rates of local tumor control, event-free and overall survival.[1–4] These results are especially relevant for ependymoma is commonly diagnosed in young patients and radiotherapy avoidance has had limited success. [5–7] Fear of radiation-related side effects has driven radiotherapy avoidance and the use of chemotherapy in young children. Recent data suggest that 42% of patients might avoid irradiation 5 years after diagnosis using chemotherapy.[5] Others suggest that fewer than 22% might benefit from this approach[6] and that the role of chemotherapy is unproven.[8] At stake is the overall survival and functional outcome; patients treated with post-operative radiation therapy have superior event-free and overall survival.

Improved disease control provides a new opportunity to evaluate prognostic factors, patterns of failure and late effects of treatment. To our knowledge, we were the first to report on the use of conformal radiation therapy for ependymoma in a prospective trial that included 88 pediatric patients treated using a 10mm clinical target volume margin.[4] The 3 year event free survival estimate was 74·7% (95% CI: 63·5–85·9%), the median age at irradiation was 3 years and limited side effects were observed. In the present report, we describe our results with extended follow-up of these patients and include a total of 153 patients from our single institution series. This study provides unique insight into the role of radiation therapy in the initial management of young children and establishes a baseline for disease control and major adverse events. The information will be useful in the design and analysis of future trials.

METHODS

Patients

The study included 153 patients treated with conformal or intensity-modulated radiation therapy between July 1997 and December 2007. The data were current on April 20, 2008. The initial 88 patients were prospectively treated on an IRB approved phase II trial between July, 1997 and January, 2003. The study was amended, with IRB approval, to included similarly treated patients who were enrolled for prospective follow-up once they completed treatment using the same target volume guidelines during the time period from February, 2003 through December, 2007. Eligibility criteria included localized ependymoma without evidence of dissemination (MR brain and spine and CSF cytology negative for metastases within 3 weeks of irradiation) or prior radiation therapy. The minimum age at the time of irradiation was 12 months until February, 2003 after which it was removed as an eligibility requirement. Prior treatment with chemotherapy was allowed and there was no limit for the interval from time of first surgery to irradiation.

Surgery and Imaging Follow-up

Neurosurgery was routinely consulted prior to irradiation to assess eligibility for additional tumor resection. Gross-total resection was defined as intraoperatively assessed macroscopically complete resection and no evidence of MR imaging residual tumor. Near-total resection was defined as less than 5mm residual tumor in greatest dimension. Sub-total resection included all other cases and no patient had more than 1ml residual tumor at the time of irradiation. Imaging follow-up included brain MRI every 3 months for the first two years (1997–2002), every 4 months for the first three years (2003–2007), every 6 months through five years, and then annually. Spinal MRI was performed annually unless symptoms developed.

Conformal Radiation Therapy

We have used the term conformal radiation therapy (CRT) to refer to conformal and intensity-modulated radiation therapy. The latter was used selectively for supratentorial tumors to reduce dose to the orbit and for infratentorial tumors to reduce dose to the cochleae. CT planning was used for all cases and post-operative MR imaging data (post-contrast T1 and T2-weighted sequences) were registered to CT data beginning in 1998. MR imaging was performed in the treatment position using a dedicated MR system beginning in 2004 which improved registration, in particular, of the anatomy of the upper cervical spinal cord and lower brainstem in patients with infratentorial tumors treated in the prone position. The advent of transferable digital imaging from referring institutions during the last three years of the study permitted registration of pre-operative imaging data to further assist in target volume definition. Patients treated prone used vacuum molds; those treated supine used a thermoplastic mask with or without a radiocamera monitoring. Approximately 70% of children under the age of 7 years required general anesthesia administered IV.

ICRU report 50 definitions were used for target volume definitions.[9] The description of the gross-tumor volume (GTV) was modified to include gross residual tumor and/or the post-operative tumor bed. The clinical target volume (CTV) was a 10mm anatomically confined expansion of the GTV. The planning target volume (PTV) was a 3–5mm geometric expansion of the CTV. Treatment methods included multi-field non-coplanar step and shoot using multi-leaf collimation (5–10mm). Target volume coverage was −5% and +10%. There were no dose-volume limits for the brainstem and the dose to the spinal cord and optic chiasm were limited to approximately 54Gy for the first 30 fractions and were allowed to receive < 70% of the prescribed dose for the remaining 3 fractions. (Figure 1) The prescribed dose was 59·4Gy for all patients except those under the age of 18 months who achieved gross-total resection and selected patients early in our series.

Statistical Methods

We evaluated the overall survival, event free survival, cumulative incidence of local recurrences, and cumulative incidence of distant recurrences. The variables considered include tumor grade, tumor location, race, gender, age at CRT, total RT dose, surgery number, surgery extents, and pre-RT chemotherapy. Overall survival (OS) was defined as the time interval from the initiation of CRT to death from any cause or last known date of survival. Event-free survival (EFS) was defined as the time interval from the initiation of CRT to the date of tumor progression, determined by MRI, death without tumor progression or last MRI follow up, whichever occurred first; patients alive at last follow up were censored. Kaplan-Meier survival estimates were obtained;[10] standard errors were calculated using the method described by Peto et al.[11, 12] In the univariate analysis of OS and EFS, the survival distributions among the groups of each variable were compared using Mantel-Haenszel Statistics,[13] and the hazard ratio was estimated using the Cox proportional hazards model.[14] Multiple regression analysis of OS and EFS were performed using the Cox

proportional hazards model. The cumulative incidence function for local or distant tumor progression was estimated based on the methods of Kalbfleisch and Prentice.[15] Local failure included local only tumor progression or combined local and distant tumor progression. The length of time at risk for local failure was determined from the CRT start date to the date of MRI identification of any component of local failure. Distant-only tumor progression and death from other causes were considered competing events. Local failure was considered a competing event in the estimation of cumulative incidence of distant only tumor progression. In the univariate analysis of cumulative incidence for local or distant tumor progression, Gray's method[16] was used to compare the cumulative incidence functions between subgroups within each variable. Multiple regression analysis of cumulative incidence functions was conducted based on Fine and Gray's estimator with the incorporation of competing events.[17] The survival and incidence were reported in the format of estimate (95% confidence interval). All P-values reported are for two-sided tests. No adjustment was made for multiple comparisons. Analyses were performed using SAS and Splus package.

The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation or writing of this report. The corresponding author had full access to all of the study data and had final responsibility for the decision to submit for publication.

RESULTS

All patients were treated with post-operative CRT. Thirty-five (22·9%) received chemotherapy prior to CRT and 11 (8·1%) had a delay to treatment of more that 4·4 months due to complications, parental indecision or planned observation. All remaining patients defined a group treated with CRT alone following definitive surgery. Two patients treated with chemotherapy and two observed after first surgery experienced local progression and underwent resection prior to CRT. Only 21 of 153 (13·7%) patients had their initial surgery at our institution and most who required second surgery had their definitive resection in Memphis, Tennessee. Chemotherapy was administered with the intent of improving second surgery in two patients, the remaining received chemotherapy based on referring institution preference to administer chemotherapy to very young children, perceived high-risk status based on extent of resection or other reasons including the lack of CRT experience with young children. The deployed regimens and interval of chemotherapy were not systematic. The most common regimen was cisplatin-cyclophosphamide-etoposide-vincristine (n=10) or the same combination substituting cisplatin (n=9). Regimens of cis- and carboplatin with various combinations of etoposide and vincristine (n=7) were used. The remainder received various combinations of agents. Only 5 patients did not receive a platinum-containing agent. None of the patients received post-CRT chemotherapy. The interval from first surgery to CRT was 7.0 months for patients treated with chemotherapy compared to 1.7 months for those who did not receive chemotherapy. No patient with newly diagnosed localized ependymoma referred to our institution during the time period of this study was excluded from this series. Clinical and treatment characteristics are included in Table 1.

With a median follow-up of 5·3 years (range 0·4 to 10·4 years). The 7 year estimates of local control, event-free and overall survival were 83·7 % (95% CI: 73·9–93·5%), 69·% (95% CI: 56·9–81·3%) and 81·0% (95% CI: 71·0–91·0%), respectively. Local control, event-free and overall survival curves are presented in Figure 2. Death was recorded in 23 patients and tumor progression in 36, including local failure for 14, distant failure for 15 and combined local and distant failure in 7. The median time to progression from diagnosis was 22·5 months (range 5·0–90·9) and from start of CRT was 20·3 months (range 3·1–75·4). All local failures were confined to the 95% isodose volume determined by image registration. Spinal

metastatic failure was diagnosed only in symptomatic patients or those evaluated at the time of intracranial failure.

Multiple regression analysis revealed that overall survival was influenced by tumor grade, extent of resection, and race. Gross-total resection was associated with a lower risk of death from any cause (HR: 0·16, 95% CI: 0·07 to 0·37, P=<0·0001) compared with near- or sub-total resection. The risk of death was greater in patients with anaplastic tumors compared to differentiated tumors (HR: 3·98, 95% CI: 1·51 to 10·48, P=0·0052) and non-white versus white patients (HR: 3·0, 95% CI: 1·21 to 7·44, P=0·018). Extent of resection was not associated with tumor grade nor was race associated with tumor grade, extent of resection or any of the clinical factors listed in Table 1. The use of chemotherapy prior to CRT was associated with lower overall survival in univariate analysis (66·9%, 95% CI 43·0–90·8% versus 85·3%, 95% CI 75·1–95·5%, P=0·038) but not multiple regression analysis. The latter may be explained, in part, by the correlation between pre-CRT chemotherapy and extent of resection (P=0·022). A smaller percentage of patients had pre-CRT chemotherapy in the gross-total resection group (19·2%) compared to the near- or sub-total resection group (39·3%). There was no association between pre-CRT chemotherapy and race or tumor grade. Tumor grade was associated with tumor location with a higher percentage of differentiated tumors with infratentorial location (P=0·019). Death from necrosis did account for a lower survival rate in the non-white patient group. When we excluded the two patients who died of necrosis, the comparison of race was not significant for overall survival P=0·19. Univariate statistics of overall survival by significant clinical factor are presented in Table 2.

Multiple regression analysis revealed that event-free survival was influenced by tumor grade, extent of resection, and gender. Gross-total resection was associated with a lower risk of death from any cause (HR: 0·20, 95% CI: 0·11 to 0·39, P=<0·0001) compared with near- or sub-total resection. The risk of progression was greater in patients with anaplastic tumors compared to differentiated tumors (HR: 2·52, 95% CI: 1·27 to 5·01, P=0·008) and male versus female patients (HR: 2·19, 95% CI: 1·03 to 4·66, P=0·042). Gender was not associated with tumor grade, extent of resection or any of the clinical factors listed in Table 1. The use of chemotherapy prior to CRT was associated with lower event-free survival in univariate analysis but not multiple regression analysis. The latter may be explained, as noted previously, by the correlation between pre-CRT chemotherapy and extent of resection. The number of surgery procedures prior to irradiation was borderline significant with values of 74·4% (95% CI: 60·3–88·5%) versus 62·0% (95% CI: 41·2–82·8%) (P=0·056). Although the time interval of this study include more than ten years, there was no difference in 3-year event-free survival comparing patients treated from 1997–2003 to those treated from 2003–2007, 78·3% (95% CI: 67·9–88·7%) versus 82·0% (95% CI: 65·5–98·5%)(P=0·84). Univariate statistics of event-free survival by clinical factor are presented in Table 2.

The cumulative incidence of local failure was 16·3% at 7 years. Multiple regression analysis revealed that the cumulative incidence of local failure was influenced by extent of resection, gender and age at the time of irradiation. Gross-total resection was associated with a lower risk of local failure (HR: 0·16, 95% CI: 0·067 to 0·38, P<0·0001) compared with near- or sub-total resection. The risk of local failure was greater in male patients (HR: 3·85, 95% CI: 1·10 to 13·.52, P=0·035) compared to female patients. And patients under the age of 3 years at the time of CRT had a greater risk of local failure (HR: 3·25, 95% CI: 1·.30 to 8·16, P=0·.012) compared to older patients. Age was not associated with extent of resection, gender or any of the factors listed in Table 1. As noted previously, gender was not associated with extent of resection or any of the factors listed in Table 1. Even though 18 of the 22 children treated with 54Gy were under the age of 3 years at the time of irradiation, there was no difference in local failure by total dose. The cumulative incidence of distant only failure at 7 years (11·48%, 95% CI: 5·9–17·1%) was influenced by tumor grade (HR 4·11, 95%CI 1·21

to 14·04, P=0·017) but not tumor location, gender, race, age or extent of resection. The cumulative incidence at 7 years was 17·08% (95% CI: 8·1–26·1%) for anaplastic tumors versus 5·17% (95% CI: 0–11·0%) for differentiated tumors.

Considering the favorable prognostic factors of female gender and gross-total resection in the setting of 59·4Gy, the overall survival at 7 years would be 90·3% (95% CI: 77·8–100·0%) with a cumulative incidence of any failure or local failure of 15·2% (95% CI: 3·8–26·6%) and 5·1% (95% CI: 0–12·2%), respectively. Excluding those with anaplastic tumors and prior treatment with chemotherapy would result in even higher rates of survival and disease control.

In a separate analysis we excluded those patients treated with any prior chemotherapy or who incurred a delay from first surgery to irradiation. The resulting 107 patients treated with post-operative radiation therapy within a median of 1·5 months (range 0·6 to 4·4 months) of first surgery had fewer prognostic factors for overall and event-free survival and local and distant failure. By multiple regression analysis, gender was no longer significant for overall and event-free survival and local failure; age no longer influenced local failure. Overall survival was influenced by race, extent of resection and tumor grade. Event-free survival was influenced by extent of resection and tumor grade. Local failure was influenced by extent of resection and distant failure by tumor grade.

With this group, infratentorial tumor location was associated with anaplastic ependymoma (P=0·031) and age under three years at the time of irradiation (P=0·006). Overall survival at 5 and 7 years was 88·6% (95% CI: 81·0–96·2%) 85·0% (95% CI: 74·2–95·8%). Multiple regression analysis showed that overall survival was lower in patients with anaplastic ependymoma (HR: 5·41, 95% CI: 1·39 to 21·15, P=0·015) and non white patients (HR: 3·70, 95% CI: 1·05 to 13·01, P=0·041) and higher after GTR (HR: 0·17, 95% CI: 0·05 to 0·56, P=0·004). Event-free survival at 5 and 7 years was 79·2% (95% CI: 69·2–89·2%) and 76·9% (95% CI: 63·4–90·4%). Multiple regression analysis showed that event-free survival was lower in patients with anaplastic ependymoma (HR: 4·28, 95% CI: 1·54 to 11·91, P=0·005) and higher after GTR (HR: 0·15, 95% CI: 0·06 to 0·36, P<0.0001). Incidentally, univariate analysis, female patients had a borderline significantly improved survival (HR: 2·74, 95% CI: 0·92 to 8·17, P=0·07); at 7 years 88·2% (95% CI: 73·3–100·0%) and 69·2% (95% CI: 49·0–89·4%). The cumulative incidence of local recurrence was 12·59% (95% CI: 5·1–20·1%) when measured at 7 years. This was influenced by extent of resection (HR: 0·11, 95% CI: 0·03 to 0·37, P=0.0003), 7·78% (95% CI: 0·5–15·0%) for GTR and 40·0% (95% CI: 13·9–66·1%) for NTR or STR. The cumulative incidence of distant failure was 8·56% (95% CI: 2·8–14·3%) when measured at 7 years. This was influenced by tumor grade (HR: 6·16, 95% CI: 0·79 to 55·53, P=0·082) 2·22% (95% CI: 0–6·6%) for differentiated ependymoma and 14·60% (95% CI: 4·4–24·8%) for anaplastic ependymoma. The difference was significant using the log-rank test (P=0.039).

Four female patients with infratentorial tumor location developed secondary tumors. Three were attributed to radiation therapy including one case of papillary thyroid cancer at 7 years and two cases of fatal high-grade glioma involving the brainstem/cerebellum at 60 and 66 months, respectively. One patient developed a low-grade glioma of the cerebral cortex at 24 months unrelated to CRT. The tumor was resected and the patient remains disease-free 10 years after CRT. All secondary tumor patients were under the age of the age of four years at the time of irradiation and two had prior exposure to chemotherapy. Excluding the unrelated low-grade glioma, the cumulative incidence of a secondary malignancy at 7 years was 4·07% (95% CI: 0–8·7%) and malignant glioma 2·33% (95% CI: 0.9–5·6%)at 7 years.

There were four cases of clinically significant cervical subluxation. Three cases have required surgical stabilization. All were patients with infratentorial ependymoma treated with more than one surgical resection and had cervical laminotomy of at least one level. Necrosis of the brainstem, as determined by MR imaging and clinical signs and symptoms, was observed in two patients with infratentorial ependymoma 9 and 12 months after the initiation of CRT. Both were treated with corticosteroids and hyperbaric oxygen therapy. The patient that presented earliest died from necrosis. The patient that presented later was stabilized and remains progression-free 4 years after CRT. She is functional with moderate to severe unilateral cranial nerve, motor and cerebellar deficits. One additional patient died within 3 weeks of completing radiation therapy after a seizure episode. His autopsy showed residual tumor and signs of ischemia and necrosis within the brainstem attributed to the evolving brainstem stroke that occurred during the first of two surgical procedures six months earlier. He required mechanical ventilation and was inpatient during radiation therapy. All three patients were African-American, had infratentorial tumor location and experienced significant perioperative morbidity including evidence of brainstem ischemia on post-operative T2-weighted MR imaging, required tracheostomy, had post-operative hypertension requiring medication and two of the three had history of a post-operative seizure. There were no other cases of necrosis and no other patients had a similar constellation of clinical signs and symptoms prior to or during radiation therapy. Considering the three patients, the cumulative incidence of brainstem necrosis was 2·5% (95% CI: 0–5·2%). Considering only the two cases that presented with typical signs and symptoms, the cumulative incidence was 1·6% (95% CI: 0–4·0%). Seizure disorders required chronic medication in five patients with supratentorial tumor location. Two required epilepsy surgery and were able to reduce or eliminate medication. There was one case of radiation-related cerebral vasculopathy in a patient with infratentorial tumor location that required revascularization surgery. He was age 12 months at the time of irradiation and the high-dose volume encompassed the Circle of Willis.

DISCUSSION

Our findings show that the highest rates of overall survival and event-free survival in childhood ependymoma depend on treatment with gross-total resection and lower tumor grade. Higher rates of event-free survival were found for female patients. Local tumor control was greatest in female patients treated with gross total resection and those greater than 3 years of age at the time of irradiation. These findings further support the known prognostic factors of extent of resection and tumor grade, and provide further evidence that the independent clinical factors of gender and age are prognostic for event-free survival and local tumor control.

This study shows the long-term benefits of radical surgery and focal post-operative irradiation and provides a unifying theme for the treatment of children with localized ependymoma. The high rates of local tumor control, event-free and overall survival highlight the importance of gross-total resection, the use of second surgery and the management strategy to administer high-dose postoperative radiation therapy even for young children. The pattern of failure has been shifted from predominantly local to nearly evenly divided rates of local and distant failure. These results point to the need to identify subclinical metastatic disease, develop new strategies to treat disseminated disease and find ways to prevent adverse events including secondary tumors. It is important to understand the pitfalls that limit comparison between this and other series including the high rate of gross-total resection, the single institution nature of the study, and modern staging and surgical procedures to respectively exclude patients with metastatic disease and increase the rate of gross-total resection

The available statistics on local tumor control for ependymoma are limited because most series have not differentiated between local and distant failure in their estimates of event-free survival. Local failure has been the greatest obstacle to improving overall survival in ependymoma; prior reports have the proportion of patients with local failure at 59–97%.[18–25] Isolated local failure accounted for 40% of failures in our series. Local failure may be attributed to a variety of factors. Our results firmly demonstrate the impact of extent of resection.

Because our estimates of local tumor control exceed those expected from contemporary series using prescribed doses ≥ 54Gy, and with similar rates of gross-total resection,[1–3] consideration must be given to the prospective nature of this work, systematic targeting and our procedures that included image registration, and relatively high prescribed doses and normal tissue tolerances. Future efforts to increase local tumor control in ependymoma should prioritize increasing the rate of gross total resection, using second surgery when required and avoiding treatment delays. Consideration should also be given to higher total doses and combining synergistic agents with irradiation because the cumulative incidence of local failure remains high at 16%. Future studies should also consider reducing the clinical target volume margin from 10mm to 5mm to limit dose to normal tissues and improve the safety of high-dose irradiation. The limited invasive nature of ependymoma should make further volume reduction feasible.

Series comprised of adequate patient numbers and follow-up (Table 3) have reported event-free survival after irradiation, ranging from 45–58% when measured at 5 years to 30–49% at 10 years. [4, 18–26] Overall survival has ranged from 54–75% at 5 years to 45–55% at 10 years. Our event-free and overall survival estimates at 5 years were 74% and 85%, respectively. Although some of the differences may be attributable to treatment era and the distribution of major prognostic factors; the improved outcome persists when considering the most favorable patients including those treated with gross-total resection, early post-operative irradiation and prescribed doses ≥ 54Gy. Those treated in our series with gross-total resection had 5 year event-free survival estimates of 82%. These estimates increased to 84·9% (95% CI: 75·5–94·3%) when patients treated with immediate post-operative irradiation, and without chemotherapy, were considered.

St. Jude Children's Research Hospital is located in Memphis, Tennessee and occupies most of Shelby County, Tennessee (population 910,100). With an annual US incidence of 0·76 cases per 100,000 individuals ages 0–19 years, and fewer than 274,000 individuals in this age group, Shelby county yields fewer than one case of ependymoma/anaplastic ependymoma per calendar year. Patients were recruited for treatment on this protocol from 37 of the 50 United States with two countries other than the US. Thirteen (8·5%) of patients were from Tennessee. Seven or more patients were recruited from 8 states including Mississippi, Louisiana, Kentucky, Missouri, Texas, Ohio, Florida and New York. Referral from beyond the geographic region is nearly always associated with bias toward more difficult cases (initial subtotal resection), aggressive tumor (anaplastic ependymoma) and younger patients. Poignant examples include the number of patients who presented with residual tumor or that that required more than one resection, the excess number of anaplastic tumors compared to other series, and the proportion of children under the age of 3 years at the time of irradiation. The lack of required time interval from first surgery to irradiation facilitated recruitment and may also have contributed to a referral bias and negative selection. St. Jude accepts regional patients for treatment regardless of disease status; however, those from beyond the immediate region were required to fulfill the enrollment criteria for our protocol to be accepted for treatment. Thus, a minority of patients had their first surgical resection in Memphis and our series does not include patients with metastatic disease.

While disease control for all patients remains the primary objective, treatment of pediatric patients places heavy emphasis on minimizing therapy whenever possible and the identification of favorable groups. The estimates of survival and disease control may, for example, be increased using the favorable prognosis associated with gross-total resection, differentiated ependymoma and female gender. There were 24 female patients with differentiated ependymoma who underwent gross-total resection prior to CRT. There have been only two events and deaths in this group.

The improved event-free and overall survival rates in our study can be linked to an increase in local tumor control suggesting a benefit from aggressive resection and high-dose post-operative irradiation. We have narrowed the number of prognostic factors by the systematic irradiation of very young children. Age is no longer a prognostic factor for event-free and overall survival when chemotherapy is not given and treatment delays are not incurred. The metastatic failure rate increased relative to local failure and accounted for nearly half of all failures. The overall rate of metastatic failure appears to depend on the number of patients with anaplastic tumors. Although the role of craniospinal irradiation has been discounted in historical series due to the high rate of local failure, future treatment strategies for patients with ependymoma might consider craniospinal irradiation for patients with subclinical metastatic disease or anaplastic tumors.

Patients with metastatic failure have been treated with a variety of treatment approaches. Because we have not observed sequential local failure in these patients, it may be concluded that the development of metastatic disease was not related to the inability of radiation therapy to achieve disease control at the primary site. Future efforts should focus on detecting subclinical metastatic disease and identifying patients who might benefit from systemic therapy or craniospinal irradiation.

The benefit of improved disease control may be realized only if the rate and magnitude of clinically significant side effects and adverse events is reasonable as determined on an individual basis as well as from the entire patient cohort. Because of the large number of patients treated over a relatively short period of time, strict compliance to protocol directed follow-up and the extended period of evaluation, we have had the opportunity to document the incidence and time course of a broad range of treatment-related side effects and observe a variety of rare adverse events. We have reported separately the neurologic, endocrine and cognitive effects in this patient cohort.[27–29] Our recent report assessing the academic abilities[28] of these patients is contemporary with the submission of this manuscript for publication and highlights the vulnerability of reading compared to other academic skills. This is representative of our effort to include all patients in our evaluation of the effects of irradiation subject to the objectives of the given report. This recent longitudinal investigation included 87 patients and 309 evaluations using an instrument with the minimum age requirement of 5 years. This is notable considering that 44 of the 87 were under the age of 5 years at the time of irradiation and have survived long enough to contribute to an assessment of academic competence. Institutional funding allows us to pay for patient travel for follow-up studies. This promises a high rate of compliance even for patients who have had major treatment related toxicities. In the present report we have chosen to focus on the more severe complications of therapy including those that are life-threatening or might affect quality of life. Our report is limited to patients who were progression-free at the time of the event.

Radiation therapy for childhood ependymoma will continue to evolve even as investigators search for means to reduce local and neuraxis treatment failure. Newer methods of radiation therapy delivery promise further reductions in dose to normal tissues and increased conformity of the highest doses to the targeted volume. New methods will also allow for modulation of toxicity base on improved understanding of the relationship between dose,

irradiation volume and clinically significant side effects. Lacking objective information about normal tissue dose constraints in this patient cohort, we applied dose limits only for the irradiation of optic chiasm and cervical spinal cord. Our treatment planning goals were to globally minimize dose to normal tissues. With long-term follow-up, we are modeling dose, volume and normal tissue effects longitudinally hoping to further optimize treatment. [32]

We have confirmed in a large single institution experience, both contemporary and perspective, that local tumor control and event free survival can be achieved with a high rate of success using aggressive surgery and high dose focal irradiation. Local tumor control and event free survival depend on tumor grade, extent of resection, and patient gender. Although this information is not entirely new, it confirms the importance of efforts to achieve gross total resection including second surgery as a requisite for patients with macroscopically incomplete resection after initial surgery and identifies the importance of tumor grade even among patients where gross total resection has been achieved. That female patients fare better than male patients was identified previously.[30] New is the finding that gender also effects local control. These three prognostic factors provide an opportunity for risk stratification.

Even though we have reported overall survival as a measured outcome, overall survival may not be a measure of success, for patients who fail radiation therapy have limited curative options and overall survival is dependent on the pattern of failure and subsequent aggressive management. We have had some success with surgery and a second course of irradiation in selected cases.[32] The lack of side effects from limited volume irradiation provides new salvage options for these patients.

This study is special because of the length and quality of follow-up. Failure after three years is infrequent making 3 year event free survival a good measure of success with radiation therapy. Of course, late failures are known to occur for this disease and our improved survival is now demonstrating the rare but clinically significant development of somatic effects and secondary malignancies. The relatively low rate of local failure compared to historic series, combined with an estimated rate of distant only failure exceeding 10%, suggests that improving the detection of subclinical metastases at the time of diagnosis should be given priority.

Acknowledgments

This work was supported in part by the American Cancer Society and by the American Lebanese Syrian Associated Charities (ALSAC)

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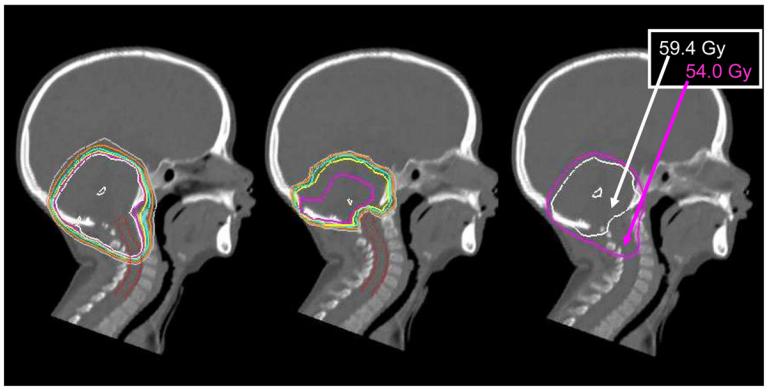

Figure 1.
Sagittal CT reconstruction showing 0–54Gy (left), 54–59.5Gy (center) and composite (right) radiation dose contours for a case of infratentorial ependymoma.

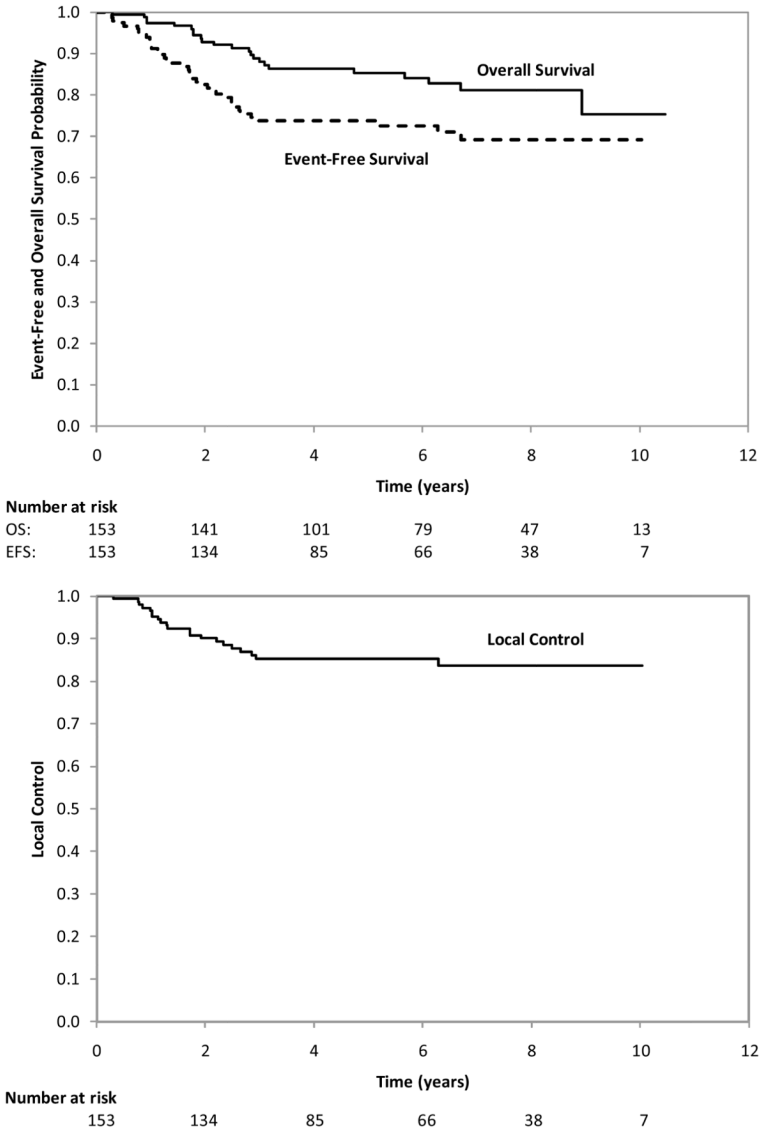

Figure 2.

Local control, event-free and overall surgical curves for 153 patients with localized ependymoma treated with conformal radiation therapy.

Table 1

Patient Characteristics (N=153)

Variable	Group	N	%
Age at CRT (year)	Mean 4·9 SD 4·4		
	Median 2·9 range 0·9 to 22·9		
Age at Diagnosis (year)	Mean 4·4, SD 4. ·4		
	Median 2·4, range 0 to 22·7		
Elapsed days of CRT	Mean 44, SD 2·5		
	Median 44, range 37 to 56		
Age	< 3 years	78	51.0
	≥ 3 years	75	49.0
Tumor Grade	Differentiated	68	44·4
	Anaplastic	85	55·6
Tumor Location	Infratentorial	122	79·7
	Supratentorial	31	20·3
Race	White	126	82·4
	Black	19	12·4
	Hispanic	6	3·92
	Asian	2	1·31
Gender	Female	58	37·9
	Male	95	62·1
Total dose	54	22	14·4
	59·4	131	85·6
Surgery number	1	87	56·9
	2	51	33·3
	3	11	7·19
	4	4	2·61
Surgery extent	GTR	125	81·7
	NTR	17	11·1
	STR	11	7·19
Pre-CRT chemotherapy	yes	35	22·9
	no	118	77·1
Death	No	130	85
	Yes	23	15
Recurrence	distant only	15	9·8
	local and distant	7	4·58
	local only	14	9·15
	none	117	76·5

Legend: CRT, conformal radiation therapy; GTR, gross-total resection; NTR, near-total resection; STR, sub-total resection.

Table 2

Univariate analysis of event-free (upper table) and overall survival (lower table).

			Event-Free Survival (%)							Overall Survival (%)						
Factors	**Sub-Group**	**N**	**5-Year**		**7-year**			**Hazards Ratio**		**5-Year**		**7-year**			**Hazards Ratio**	
			estimate	**95% CI**	**estimate**	**95% CI**	**P-Value**	**Estimate**	**95% CI**	**estimate**	**95% CI**	**estimate**	**95% CI**	**P-Value**	**Estimate**	**95% CI**
Tumor grade	Differentiated	68	86·4	76·8–96·0	79·2	69·6–88·8	0·005	1·0		91·9	84·3–99·5	89·4	81·8–97·0	0·006	1·0	
	Anaplastic	85	61·3	46·4–76·2	61·3	46·4–76·2		2. ·58	1·30–5·12	78·3	66·3–90·3	71·8	59·8–83·8		3·56	1·37–9·22
Tumor Location	Infratentorial	122	71·1	60·5–81·7	65·8	55·2–76·4	0·16	1·0		84·0	75·6–92·4	80·5	72·1–88·9	0·6	1·0	
	Supratentorial	31	82·9	66·6–99·2	82·9	66·6–99·2		0·52	0·20–1·32	89·5	76·8–100·0	83·1	70·4–95·8		0·75	0·25–2·22
Race	White	126	75·5	66·3–84·7	70·4	61·2–79·6	0·26	1·0		87·7	80·6–94·8	84·5	77·4–91·6	0·017	1·0	
	Other	27	64·5	30·8–98·2	64·5	30·8–98·2		1·55	0·71–3·38	72·9	44·9–100·0	60·7	32·7–88·7		2·84	1·16–6·92
Gender	Female	58	84·7	73·9–95·5	81·0	70·2–91·8	0·018	1·0		91·8	83·8–99·8	88·6	80·6–96·6	0·091	1·0	
	Male	95	66·7	53·4–80·0	61·0	47·7–74·3		2·4	1·13–5·06	81·1	70·1–92·1	76·0	65·0–87·0		2·2	0·86–5·61
Age at CRT	≥ 3 years	75	79·0	66·8–91·2	69·4	57·2–81·6	0·37	1·0		90·1	81·1–99·1	81·7	72·7–90·7	0·46	1·0	
	< 3 years	78	68·6	55·7–81·5	68·6	55·7–81·5		1·34	0·71–2·52	80·4	69·8–91·0	80·4	69·8–91·0		1·37	0·60–3·12
Total Dose	54	22	80·7	61·5–99·9	70·6	51·4–89·8	0·67	1·0		85·4	68·9–100·0	77·7	61·2–94·2	0·82	1·0	
	59·4	131	72·4	62·4–82·4	68·8	58·8–78·8		1·04	0·87–1·24	85·0	77·0–93·0	81·6	73·6–89·6		0·98	0·80–1·19
Surgery Number	1	87	79·7	69·3–90·1	74·4	64·0–84·8	0·056	0·55	0·29–1·02	90·1	82·7–97·5	83·9	76·5–91·3	0·15	0·56	0·24–1·26
	2~4	66	65·6	49·5–81·7	62·0	45·9–78·1		1·0		78·4	64·5–92·3	78·4	64·5–92·3		1·0	
Surgery Extent	GTR	125	81·5	72·7–90·3	77·3	68·5–86·1	<0·0001	0·21	0·11–0·40	93·0	87·3–98·7	88·0	82·3–93·7	<0·0001	0·16	0·07–0·36
	NTR or STR	28	41·0	17·7–64·3	34·2	10·9–57·5		1·0		52·4	25·5–79·3	52·4	25·5–79·3		1·0	
Pre-CRT Chemotherapy	Yes	35	59·4	39·6–79·2	48·7	28·9–68·5	0·008	1·0		73·6	55·6–91·6	66·9	48·9–84·9	0·038	1·0	
	No	118	78·1	68·3–87·9	75·9	66·1–85·7		0·43	0·22–0·81	88·6	81·3–95·9	85·3	78·0–92·6		0·42	0·18–0·98

Table 3

Event-free and overall survival estimates from selected radiotherapy series reporting 5 and 10 year outcomes.

Series	Time Period	Patients	5yr EFS	10yr EFS	5yr OS	10yr OS
Akyuz	1972–1991	62	-	36%	-	50%
Perilongo	1977–1993	92	-	35%	-	56%
Shu	1980–2000	49	41%	31%	66%	56%
Oya	1961–1999	48	42%	42%	62%	47%
Pollack	1975–1993	40	46%	36%	57%	45%
Jaing	1985–2002	43	46%	-	54%	-
V. Veelan	1980–1999	83	48%	46%	73%	51%
Robertson	1986–1992	32	50%	-	64%	-
Mansur	1964–2000	60	58%	46%	71%	55%
Merchant	1997–2007	153	74%	69%	85%	75%

Legend: EFS, event-free survival; OS, overall survival