



Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study

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Summary

Background Therapy for ependymoma includes aggressive surgical intervention and radiotherapy administered by use of methods that keep the risk of side-effects to a minimum. We extended this treatment approach to include children under the age of 3 years with the aim of improving tumour control.

Methods Between July 11, 1997, and Nov 18, 2007, 153 paediatric patients (median age 2.9 years [range 0.9–22.9 months]) with localised ependymoma were treated. 85 patients had anaplastic ependymoma; the tumours of 122 were located in the infratentorial region, and 35 had received previous chemotherapy. Patients received conformal radiotherapy after definitive surgery (125 patients had undergone gross total, 17 near total, and 11 subtotal resection). Doses of 59.4 Gy (n=131) or 54.0 Gy (n=22) were prescribed to a 10 mm margin around the target volume. Disease control, patterns of failure, and complications were recorded for patients followed over 10 years. Overall survival, event-free survival (EFS), cumulative incidence of local recurrences, and cumulative incidence of distant recurrences were assessed. Variables considered included tumour grade, tumour location, ethnic origin, sex, age when undergoing conformal radiotherapy, total radiotherapy dose, number of surgical procedures, surgery extent, and preradiotherapy chemotherapy.

Findings After a median follow-up of 5.3 years (range 0.4–10.4), 23 patients had died and tumour progression noted in 36, including local (n=14), distant (n=15), and combined failure (n=7). 7-year local control, EFS, and overall survival were 87.3% (95% CI 77.5–97.1), 69.1% (56.9–81.3), and 81.0% (71.0–91.0), respectively. The cumulative incidences of local and distant failure were 16.3% (9.6–23.0) and 11.5% (5.9–17.1), respectively. In the 107 patients treated with immediate postoperative conformal radiotherapy (without delay or chemotherapy), 7-year local control, EFS, and overall survival were 88.7% (77.9–99.5), 76.9% (63.4–90.4), and 85.0% (74.2–95.8), respectively; the cumulative incidence of local and distant failure were 12.6% (5.1–20.1), and 8.6% (2.8–14.3), respectively. The incidence of secondary malignant brain tumour at 7 years was 2.3% (0–5.6) and brainstem necrosis 1.6% (0–4.0). Overall survival was affected by tumour grade (anaplastic vs differentiated: HR 3.98 [95% CI 1.51–10.48]; p=0.0052), extent of resection (gross total vs near total or subtotal: 0.16 [0.07–0.37]; p<0.0001), and ethnic origin (non-white vs white: 3.0 [1.21–7.44]; p=0.018). EFS was affected by tumour grade (anaplastic vs differentiated: 2.52 [1.27–5.01]; p=0.008), extent of resection (gross total vs near total or subtotal: 0.20 [0.11–0.39]; p<0.0001), and sex (male vs female: 2.19 [1.03–4.66]; p=0.042). Local failure was affected by extent of resection (gross total vs near total or subtotal: 0.16 [0.067–0.38]; p<0.0001), sex (male vs female: 3.85 [1.10–13.52]; p=0.035), and age (<3 years vs ≥3 years: 3.25 [1.30–8.16]; p=0.012). Distant recurrence was only affected by tumour grade (anaplastic vs differentiated: 4.1 [1.2–14.0]; p=0.017).

Interpretation Treatment of ependymoma should include surgery with the aim of gross-total resection and conformal, high-dose, postoperative irradiation. Future trials might consider treatment stratification based on sex and age.

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Introduction

Newer methods of delivering radiotherapy combined with advances in neurosurgery have increased tumour control and reduced side-effects in paediatric patients with localised ependymoma. Preliminary findings from contemporary series using conformal, intensity-modulated, and proton-beam radiotherapy support this conclusion, with reduced side-effects and improved rates of local tumour control, event-free survival (EFS), and overall survival.^{1–4} These results are especially relevant because 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 for up to 5 years after diagnosis by use of chemotherapy.⁵ Others suggest that fewer than 22% might benefit from this approach⁶ and that the role of chemotherapy is unproven.⁸ At stake is overall survival and functional outcome; patients treated with postoperative radiotherapy have better EFS and overall survival than those treated with chemotherapy.

Improved disease control provides a new opportunity to assess prognostic factors, patterns of failure, and late effects of treatment. We previously reported on the use of conformal radiotherapy for ependymoma in a

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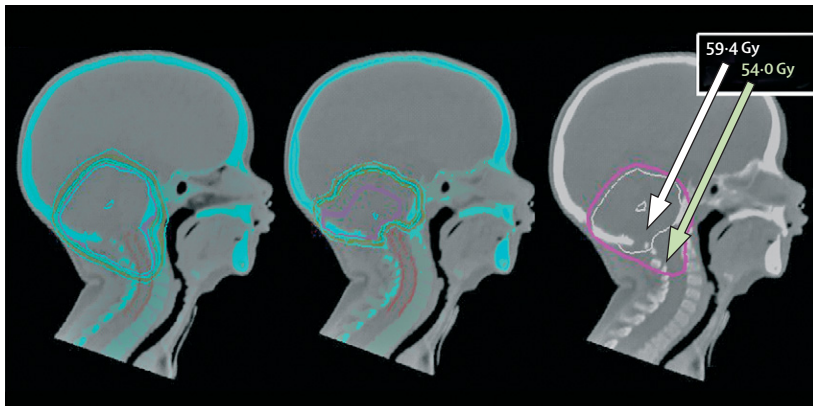


Figure 1: Sagittal CT reconstruction showing 0–54 Gy (left), 54–59.4 Gy (centre), and composite (right) radiation dose contours for a case of infratentorial ependymoma

prospective trial that included 88 paediatric patients treated by use of a 10 mm margin around the target volume with a median follow-up of 38 months.⁴ The 3-year EFS estimate was 74.7% (95% CI 63.5–85.9), median age at irradiation was 3 years (range 1.1–22.9), and few side-effects were noted. In the current report, we describe our findings with extended follow-up of these original patients and extend our single-institution series to now include a total of 153 patients.

Methods

Patients

Between July 11, 1997, and Nov 18, 2007, 153 patients were treated with conformal or intensity-modulated radiotherapy, with written informed consent from a parent or guardian. The data presented were current on April 20, 2008. The initial 88 patients were prospectively treated in a phase II trial, approved by the institutional review board (IRB), between July 11, 1997, and Feb 5, 2003. The study was amended, with IRB approval, to include 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 Feb 5, 2003, through to Nov 18, 2007. Eligibility criteria included localised ependymoma without evidence of dissemination (ie, negative for metastases within 3 weeks of irradiation by use of MRI of the brain and spine and CSF cytology) or previous radiotherapy. The minimum age at the time of irradiation was 12 months until Feb 5, 2003, after which it was removed as an eligibility requirement. Previous 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 before irradiation to assess eligibility for additional tumour resection. Gross-total resection was defined as intraoperatively assessed macroscopically complete resection and no evidence of residual tumour on MRI. Near-total resection was defined

as less than 5 mm residual tumour in greatest dimension. Subtotal resection included all other cases. Imaging follow-up included brain MRI every 3 months for the first 2 years (1997–2002) or every 4 months for the first 3 years (2003–07), then every 6 months up to 5 years, and then annually. Spinal MRI was done annually unless symptoms developed.

Conformal radiotherapy

We have used the term conformal radiotherapy to refer to conformal and intensity-modulated radiotherapy. The latter was used selectively for supratentorial tumours to reduce the dose to the orbit and for infratentorial tumours to reduce the dose to the cochleae. CT planning was used for all patients and postoperative MRI data (postcontrast T1 and T2-weighted sequences) were registered to CT data beginning in 1998. MRI was done in the treatment position using a dedicated magnetic resonance 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 tumours treated in the prone position. The advent of transferable digital imaging from referring institutions during the past 3 years of the study allowed registration of preoperative imaging data to further assist in target-volume definition. Vacuum moulds were constructed to immobilise patients treated prone; those treated supine had a customised thermoplastic mask with or without radiocamera monitoring. About 70% of children under the age of 7 years needed general anaesthesia (propofol was administered intravenously).

Definitions from the International Commission on Radiation Units and Measurements report 50 were used for target-volume definitions.⁹ The description of gross tumour volume (GTV) was modified to include gross residual tumour, or the postoperative tumour bed, or both. The clinical target volume (CTV) was a 10 mm anatomically confined expansion of the GTV. The planning target volume (PTV) was a 3–5 mm geometric expansion of the CTV. Treatment methods included multifield non-coplanar step and shoot using multileaf collimation (5–10 mm). 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 about 54 Gy for the first 30 fractions and were allowed to be less than 70% of the prescribed dose for the remaining three fractions (figure 1). The prescribed dose was 59.4 Gy for all patients except those under the age of 18 months who achieved gross-total resection and selected patients early in our series who received 54 Gy.

Statistical analysis

We assessed overall survival, EFS, cumulative incidence of local recurrences, and cumulative incidence of distant recurrences. Variables included tumour grade, tumour location, ethnic origin, sex, age when undergoing

conformal radiotherapy, total radiotherapy dose, number of surgical procedures, surgical extent, and preradiotherapy chemotherapy. Overall survival was defined as the time interval from the initiation of conformal radiotherapy to death from any cause or last known date of survival. EFS was defined as the time interval from the initiation of conformal radiotherapy to date of tumour progression (determined by MRI), death without tumour 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 and colleagues.^{11,12} Local control time was from the initiation of conformal radiation to recurrences, death, or last follow-up, whichever occurred first. Local only recurrences were events; patients free of local only recurrences were censored at the time of local and distant recurrences, distant recurrences, death, or last follow-up. In the univariate analysis of overall survival and EFS, survival distributions in the groups of each variable were compared by use of Mantel-Haenszel statistics,¹³ and hazard ratios (HR) were estimated by use of the Cox proportional hazards model.¹⁴ Multiple regression analysis of overall survival and EFS were done by use of the Cox proportional hazards model. The cumulative incidence function for local or distant tumour progression was estimated using the methods of Kalbfleisch and Prentice.¹⁵ Local failure included only local tumour progression or combined local and distant tumour progression. The length of time for risk of local failure was determined from the start date of conformal radiotherapy to the date of MRI identification of any component of local failure. Distant tumour progression without local 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 tumour progression without local progression. In the univariate analysis of cumulative incidence for local or distant tumour progression, Gray's method¹⁶ was used to compare the cumulative incidence functions between subgroups within each variable. Multiple regression analysis of cumulative incidence functions was done based on Fine and Gray's estimator with the incorporation of competing events.¹⁷ The survival and incidence were reported in the format of estimates (95% CI). The level of significance was set at 0.05 and all p values reported are for two-sided tests. No adjustment was made for multiple comparisons. Analyses were done using SAS (version 9.1.3) and S-plus (version 7.0 for Windows).

Role of the funding source

The sponsors 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

Clinical and treatment characteristics are shown in table 1. All patients were treated with postoperative conformal radiotherapy. 35 of 153 patients (22.9%) received chemotherapy before conformal radiotherapy and 11 of 153 patients (7.2%) had a delay before treatment of more than 4.4 months because of complications, parental indecision, or planned observation. Two patients treated

Patients (N=153)	
Age at CRT (years)	
Mean (SD)	4.9 (4.4)
Median (range)	2.9 (0.9–22.9)
Age at diagnosis (years)	
Mean (SD)	2.9 (4.4)
Median (range)	2.4 (0.0–22.7)
Elapsed days of CRT	
Mean (SD)	44 (2.5)
Median (range)	44 (37–56)
Age (years), n (%)	
<3	78 (51.0)
≥3	75 (49.0)
Tumour grade, n (%)	
Differentiated	68 (44.4)
Anaplastic	85 (55.6)
Tumour location, n (%)	
Infratentorial	122 (79.7)
Supratentorial	31 (20.3)
Ethnic origin, n (%)	
White	126 (82.4)
Black	19 (12.4)
Hispanic	6 (3.9)
Asian	2 (1.3)
Sex, n (%)	
Female	58 (37.9)
Male	95 (62.1)
Total dose (Gy), n (%)	
54	22 (14.4)
59.4	131 (85.6)
Number of surgical procedures, n (%)	
1	87 (56.9)
2	51 (33.3)
3	11 (7.2)
4	4 (2.6)
Surgical extent, n (%)	
GTR	125 (81.7)
NTR	17 (11.1)
STR	11 (7.2)
Pre-CRT chemotherapy, n (%)	
Yes	35 (22.9)
No	118 (77.1)
CRT=conformal radiotherapy. GTR=gross-total resection. NTR=near-total resection. STR=subtotal resection.	

Table 1: Patient characteristics

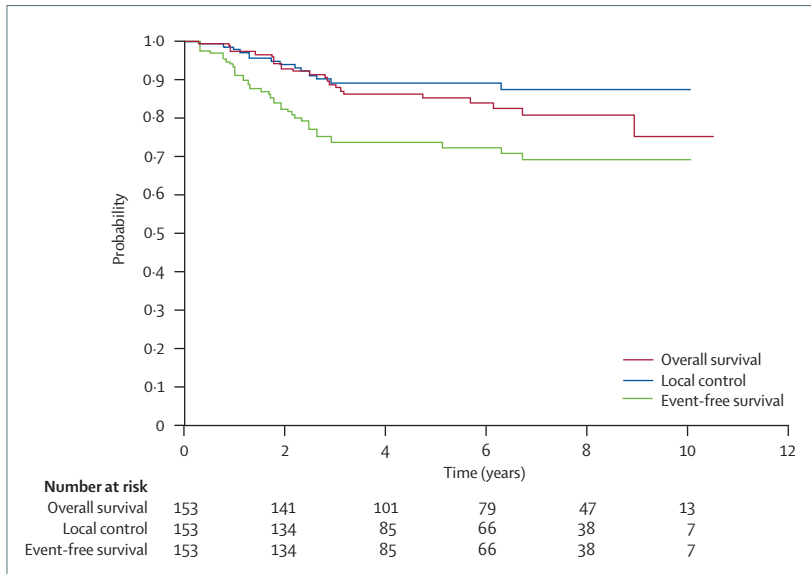


Figure 2: Event-free survival, overall survival, and local control for 153 patients with localised ependymoma treated with conformal radiotherapy

with chemotherapy and two observed after first surgery had local progression and underwent resection before conformal radiotherapy. Only 21 of 153 patients (13.7%) had their initial surgery done at our institution, and most of those who needed second surgery had definitive resection done at LeBonheur Children's Medical Center in Memphis, TN, USA. Chemotherapy was administered with the intent of improving second surgery in two patients; the remaining patients received chemotherapy on the basis of the preference of the referring institution to administer chemotherapy to very young children, the perceived high-risk status based on extent of resection, or other reasons including a lack of experience of conformal radiotherapy in young children. Various chemotherapy regimens were used. The most common regimen was cisplatin–cyclophosphamide–etoposide–vincristine ($n=10$) or the same combination substituting cisplatin with carboplatin ($n=9$). Regimens of cisplatin and carboplatin with various combinations of etoposide and vincristine were used to treat seven patients. The remainder received various combinations of agents. Only five patients who received chemotherapy did not receive a platinum-containing agent. None of the patients received chemotherapy after conformal radiotherapy. The interval from first surgery to conformal radiotherapy was 7.0 months for patients treated with chemotherapy compared with 1.7 months for those who did not receive chemotherapy. No patient with newly diagnosed localised ependymoma referred to our institution during the time of this study was excluded from this series.

The clinical factors presented in table 1 were independent of one another, except tumour grade, which was associated with tumour location (a higher percentage of differentiated tumours were located in the infratentorial

region [60 of 122] than in the supratentorial region [eight of 31]; p for association=0.019).

After a median follow-up of 5.3 years (range 0.4–10.4), 23 patients had died; tumour progression was noted in 36, including local failure in 14 patients, distant failure in 15 patients, and combined local and distant failure in seven patients. 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 assessed at the time of intracranial failure. Spinal metastatic failure as a component of failure occurred in 13 patients: seven patients that had combined local and distant failure, two that had both spinal and intracranial metastases, and four that had isolated spinal metastases. Four female patients, with a primary tumour in the infratentorial region, had a second tumour. Three of these four cases were attributed to radiotherapy, including one case of papillary thyroid cancer at 7 years after radiotherapy and two cases of fatal high-grade glioma involving the brainstem or cerebellum at 60 and 66 months after radiotherapy, respectively. One patient developed a low-grade glioma of the cerebral cortex at 24 months unrelated to conformal radiotherapy. The tumour was resected and the patient remains disease-free 10 years after conformal radiotherapy. All patients with second tumours were under the age of 4 years at the time of irradiation and two had previous exposure to chemotherapy. Excluding the unrelated low-grade glioma, the cumulative incidence of a secondary malignancy at 7 years was 4.1% (95% CI 0.0–8.7) and of a malignant glioma at 7 years was 2.3% (0.9–5.6).

There were four cases of clinically significant cervical subluxation. Three cases have required surgical stabilisation. All were in patients with infratentorial ependymoma treated with more than one surgical resection and who had cervical laminotomy of at least one level. Necrosis of the brainstem, as determined by MRI and clinical signs and symptoms, was noted in two patients with infratentorial ependymoma at 9 and 12 months, respectively, after the initiation of conformal radiotherapy. Both were treated with corticosteroids and hyperbaric oxygen therapy. The patient that presented earliest died from necrosis. The patient that presented later was stabilised and remains progression-free 4 years after conformal radiotherapy. This patient is functional with moderate to severe unilateral cranial nerve, motor, and cerebellar deficits. Another patient died within 3 weeks of completing radiotherapy after a seizure; autopsy showed residual tumour and signs of ischaemia and necrosis within the brainstem attributed to an evolving brainstem stroke that occurred during the first of two surgical procedures 6 months earlier. The patient needed mechanical ventilation and was an inpatient during radiotherapy. All three patients were African-American, had infratentorial tumour location, had substantial perioperative morbidity, including evidence of brainstem ischaemia on postoperative T2-weighted

	N	Event-free survival (%)				Overall survival (%)			
		5 years (95% CI)	7 years (95% CI)	HR (95% CI)	p	5 years (95% CI)	7 years (95% CI)	HR (95% CI)	p
Tumour grade									
Differentiated	68	86.4 (76.8–96.0)	79.2 (66.1–92.3)	1.0	0.005	91.9 (84.3–99.5)	89.4 (79.6–99.2)	1.0	0.006
Anaplastic	85	61.3 (46.4–76.2)	61.3 (38.8–83.8)	2.58 (1.30–5.12)	..	78.3 (66.3–90.3)	71.8 (52.6–91.0)	3.56 (1.37–9.22)	..
Tumour location									
Infratentorial	122	71.1 (60.5–81.7)	65.8 (52.7–78.9)	1.0	0.16	84.0 (75.6–92.4)	80.5 (69.5–91.5)	1.0	0.6
Supratentorial	31	82.9 (66.6–99.2)	82.9 (57.6–100.0)	0.52 (0.20–1.32)	..	89.5 (76.8–100.0)	83.1 (59.4–100.0)	0.75 (0.25–2.22)	..
Ethnic origin									
White	126	75.5 (66.3–84.7)	70.4 (57.7–83.1)	1.0	0.26	87.7 (80.6–94.8)	84.5 (74.7–94.3)	1.0	0.017
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 (27.4–94.0)	2.84 (1.16–6.92)	..
Sex									
Female	58	84.7 (73.9–95.5)	81.0 (66.3–95.7)	1.0	0.018	91.8 (83.8–99.8)	88.6 (76.8–100.0)	1.0	0.091
Male	95	66.7 (53.4–80.0)	61.0 (43.4–78.6)	2.40 (1.13–5.06)	..	81.1 (70.1–92.1)	76.0 (61.1–90.9)	2.20 (0.86–5.61)	..
Age at CRT (years)									
≥3	75	79.0 (66.8–91.2)	69.4 (52.2–86.6)	1.0	0.37	90.1 (81.1–99.1)	81.7 (68.0–95.4)	1.0	0.46
<3	78	68.6 (55.7–81.5)	68.6 (52.1–85.1)	1.34 (0.71–2.52)	..	80.4 (69.8–91.0)	80.4 (66.1–94.7)	1.37 (0.60–3.12)	..
Total dose (Gy)									
54	22	80.7 (61.5–99.9)	70.6 (44.1–97.1)	1.0	0.67	85.4 (68.9–100.0)	77.7 (53.8–100.0)	1.0	0.82
59.4	131	72.4 (62.4–82.4)	68.8 (55.5–82.1)	1.04 (0.87–1.24)	..	85.0 (77.0–93.0)	81.6 (70.8–92.4)	0.98 (0.80–1.19)	..
Number of surgical procedures									
1	87	79.7 (69.3–90.1)	74.4 (60.3–88.5)	0.55 (0.29–1.02)	0.056	90.1 (82.7–97.5)	83.9 (72.3–95.5)	0.56 (0.24–1.26)	0.15
2–4	66	65.6 (49.5–81.7)	62.0 (41.2–82.8)	1.0	..	78.4 (64.5–92.3)	78.4 (60.6–96.2)	1.0	..
Surgical extent									
GTR	125	81.5 (72.7–90.3)	77.3 (65.0–89.6)	0.21 (0.11–0.40)	<0.0001	93.0 (87.3–98.7)	88.0 (78.8–97.2)	0.16 (0.07–0.36)	<0.0001
NTR or STR	28	41.0 (17.7–64.3)	34.2 (12.1–56.3)	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 (26.0–71.4)	1.0	0.008	73.6 (55.6–91.6)	66.9 (43.0–90.8)	1.0	0.038
No	118	78.1 (68.3–87.9)	75.9 (62.8–89.0)	0.43 (0.22–0.81)	..	88.6 (81.3–95.9)	85.3 (75.1–95.5)	0.42 (0.18–0.98)	..

HR=hazard ratio. CRT=conformal radiotherapy. GTR=gross-total resection. NTR=near-total resection. STR=subtotal resection.

Table 2: Univariate analysis of event-free survival and overall survival according to different variables

MRI, required tracheostomy, and had postoperative hypertension needing medication. Two of the three also had a history of a postoperative seizures. There were no other cases of necrosis and no other patients had a similar constellation of clinical signs and symptoms before or during radiotherapy. Including all three cases of necrosis, the cumulative incidence of brainstem necrosis at 7 years was 2.5% (95% CI 0.0–5.2); excluding the patient who died after a seizure, it was 1.6% (0.0–4.0).

Seizure disorders required chronic medication in five patients with supratentorial tumour location. Two needed surgery for epilepsy and were able to reduce or stop medication. There was one case of radiation-related cerebral vasculopathy in a patient with infratentorial tumour location that required revascularisation surgery. The patient was aged 12 months at the time of irradiation and the high-dose volume encompassed the Circle of Willis.

7-year estimates of local control, EFS, and overall survival were 87.3% (95% CI 77.5–97.1), 69.1% (56.9–81.3), and 81.0% (71.0–91.0), respectively (figure 2). Median time to

progression was 22.5 months (range 5.0–90.9) from diagnosis and 20.3 months (3.1–75.4) from the start of conformal radiotherapy.

Univariate analyses of overall survival by various clinical variables are presented in table 2. Multiple regression analysis showed overall survival was affected by tumour grade, extent of resection, and ethnic origin: gross-total resection was associated with a lower risk of death from any cause than was near-total or subtotal resection (HR 0.16 [95% CI 0.07–0.37]; $p < 0.0001$), while the risk of death was greater in patients with anaplastic tumours than in those with differentiated tumours (HR 3.98 [1.51–10.48]; $p = 0.0052$) and in non-white patients versus white patients (HR 3.0 [1.21–7.44]; $p = 0.018$). However, death from necrosis accounted for the lower overall survival in non-white patients, compared with white patients: when we excluded the two patients who died of necrosis, the comparison of ethnic origin was not significant for overall survival (HR 2.1 [0.8–5.7]; $p = 0.16$ by univariate analysis). The use of chemotherapy before conformal radiotherapy was associated with a lower overall survival than with no use of chemotherapy

in the univariate analysis (66.9% [95% CI 43.0–90.8] vs 85.3% [75.1–95.5]; $p=0.038$), but not in the multiple regression analysis, possibly because of a correlation between chemotherapy before conformal radiotherapy and extent of resection: a smaller proportion of patients had chemotherapy before conformal radiotherapy in the gross-total resection group than in the near-total or subtotal resection groups (24 of 125 patients vs 11 of 28; $p=0.022$).

Univariate statistics of EFS by clinical factor are presented in table 2. Multiple regression analysis showed that EFS was affected by tumour grade, extent of resection, and sex: gross-total resection was associated with a lower risk of death from any cause than near-total or subtotal resection (HR 0.20 [95% CI 0.11–0.39]; $p<0.0001$), while the risk of progression was greater in patients with anaplastic tumours than in those with differentiated tumours (HR 2.52 [1.27–5.01]; $p=0.008$) and in male patients versus female patients (HR 2.19 [1.03–4.66]; $p=0.042$). The use of chemotherapy before conformal radiotherapy was associated with a lower EFS than no use of chemotherapy in the univariate analysis (48.7% [95% CI 26.0–71.4] vs 75.9 [62.8–89.0]; $p=0.008$), but not in the multiple regression analysis. The latter might be explained, as before, by the correlation between chemotherapy before conformal radiotherapy and extent of resection. Although EFS was better in those patients with fewer surgical procedures before irradiation than in those who had more, this effect was not significant ($p=0.056$; table 2). There was no difference in 3-year EFS when comparing patients treated from July 11, 1997, to Feb 4, 2003, with those treated from Feb 5, 2003, to Nov 18, 2007 (79.0% [69.0–89.0] vs 81.0% [63.2–98.8]; respectively; $p=0.98$).

The cumulative incidence of local failure was 16.3% at 7 years. Multiple regression analysis showed that the cumulative incidence of local failure was affected by the extent of resection, sex, and age at the time of irradiation. Gross-total resection was associated with a lower risk of local failure (HR 0.16 [95% CI 0.067–0.38]; $p<0.0001$) compared with near-total or subtotal resection. The risk of local failure was greater in male patients than in female patients (HR 3.85 [1.10–13.52]; $p=0.035$). Patients under the age of 3 years at the time of conformal radiotherapy had a greater risk of local failure (HR 3.25 [1.30–8.16]; $p=0.012$) than older patients. Despite 18 of the 22 children treated with 54 Gy being 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 (11.5% [95% CI 5.9–17.1]) was affected by tumour grade (cumulative incidence at 7 years was 17.1% [8.1–26.1] for anaplastic tumours vs 5.2% [0–11.0] for differentiated tumours; HR 4.1 [1.2–14.0]; $p=0.017$), but not by tumour location, sex, ethnic origin, age, or extent of resection.

In view of the favourable prognostic factors of female sex and gross-total resection in the setting of 59.4 Gy,

restricting analyses to this population indicates an overall survival of 7 years of 90.3% (95% CI 77.8–100.0) with a cumulative incidence of any failure or local failure of 15.2% (3.8–26.6) and 5.1% (0.0–12.2), respectively. Excluding patients with anaplastic tumours and those who had previous treatment with chemotherapy results in even higher survival and disease control (data not shown).

In a separate analysis, we excluded patients who had been treated with any previous chemotherapy or who had incurred a delay from first surgery to irradiation. The resulting 107 patients treated with postoperative radiotherapy within a median time of 1.5 months (range 0.6–4.4) from first surgery. Within this group of patients, clinical factors presented in table 1 were independent of one another, except for infratentorial tumour location (associated with anaplastic ependymoma [$p=0.031$]) and age under 3 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) and 85.0% (74.2–95.8), respectively; EFS at 5 and 7 years was 79.2% (69.2–89.2) and 76.9% (63.4–90.4). Local control at 5 and 7 years was 91.4% (84.3–98.5) and 88.7% (77.9–99.5), respectively. Multiple regression analysis showed that overall survival and EFS were lower in patients with anaplastic ependymoma than in those with differentiated ependymoma (overall survival: HR 5.41 [1.39–21.15]; $p=0.015$; EFS: 4.28 [1.54–11.91]; $p=0.005$) and higher after gross-total resection than after near-total or subtotal resection (overall survival: 0.17 [0.05–0.56]; $p=0.004$; EFS: 0.15 [0.06–0.36]; $p<0.0001$); overall survival was lower in non-white patients than in white patients (3.70 [1.05–13.01]; $p=0.041$). By contrast with the overall population, sex was not significantly associated with overall survival, EFS, or local failure, and age was not associated with local failure.

In univariate analyses of the subpopulation of 107 patients, EFS was 88.2% [95% CI 73.3–100.0] in females compared with 69.2% [49.0–89.4] in males (HR 2.74 [95% CI 0.92–8.17]; $p=0.07$). The cumulative incidence of local recurrence was 12.6% (5.1–20.1) when measured at 7 years. This was affected by extent of resection (7.8% (0.5–15.0) for gross-total resection vs 40.0% (13.9–66.1) for near-total or subtotal resection; HR 0.11 [0.04–0.38]; $p=0.004$). The cumulative incidence of distant failure was 8.6% (2.8–14.3) when measured at 7 years, and was affected by tumour grade (2.2% [0.0–6.6] for differentiated ependymoma vs 14.6% [4.4–24.8] for anaplastic ependymoma; HR 6.2 [0.8–55.5]; $p=0.082$). The difference in tumour grade was significant using the log-rank test ($p=0.039$).

Discussion

This study highlights the long-term benefits—in terms of local tumour control, EFS, and overall survival—of gross-total resection (including undergoing second surgery as a requisite for patients with macroscopically incomplete resection after initial surgery) and high-dose postoperative radiotherapy for the treatment of children

with localised ependymoma, even for those who are younger than 3 years. Although it is important to understand the pitfalls that limit a 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 exclude patients with metastatic disease and increase the rate of gross-total resection, suggest the need to identify subclinical metastatic disease, develop new strategies to treat disseminated disease, and find ways to prevent adverse events including second tumours.

Our findings also show the highest rates of overall survival and EFS in childhood ependymoma depend on treatment with gross-total resection and lower tumour grade. A higher EFS was also noted in female patients than in male patients. Local tumour control was greatest in female patients treated with gross-total resection and those older than 3 years of age at the time of irradiation. These findings further support the known prognostic factors of extent of resection and tumour grade, and provide further evidence that the independent clinical factors of sex and age are prognostic for EFS and local tumour control. Indeed, the treatment protocol used here reduces the number of prognostic factors: age is no longer a prognostic factor for EFS and overall survival when chemotherapy is not given and treatment delays are not incurred. Although disease control for all patients remains the primary objective, treatment of paediatric patients places heavy emphasis on keeping therapy to a minimum whenever possible, and on the identification of favourable groups; the three prognostic factors of extent of resection, tumour grade, and sex identified here provide an opportunity for risk stratification and could help to identify such groups.

The improved EFS and overall survival in our study, compared with historical series, are probably due to increased local tumour control. While local control was improved with this treatment protocol, metastatic failures increased relative to local failures and accounted for nearly half of all failures. Patients with metastatic failure were treated with various treatment approaches. Because we have not noted sequential local failure in these patients, it could be concluded that the development of metastatic disease was not related to the inability of radiotherapy to achieve disease control at the primary site. The overall proportion of metastatic failures seemed to depend on the number of patients with anaplastic tumours. Although the potential benefit from craniospinal irradiation has been discounted in historical series due to the high rate of local failure, future treatment strategies should focus on identifying patients with subclinical metastatic disease or anaplastic tumours who might benefit from systemic therapy or craniospinal irradiation.

Available data on local tumour control for ependymoma are limited because most series have not differentiated between local and distant failure in their estimates of EFS. Local failure has been the greatest obstacle to im-

	Time period	Patients, n	5-year EFS	10-year EFS	5-year OS	10-year OS
Merchant (present)	1997–2007	153	74%	69%	85%	75%
Akyuz ¹⁸	1972–91	62	..	36%	..	50%
Perilongo ¹⁹	1977–93	92	..	35%	..	56%
Shu ²⁰	1980–2000	49	41%	31%	66%	56%
Oya ²¹	1961–99	48	42%	42%	62%	47%
Pollack ²²	1975–93	40	46%	36%	57%	45%
Jaing ²³	1985–2002	43	46%	..	54%	..
Van Veelan-Vincent ²⁴	1980–99	83	48%	46%	73%	51%
Robertson ²⁵	1986–92	32	50%	..	64%	..
Mansur ²⁶	1964–2000	60	58%	46%	71%	55%

EFS=event-free survival. OS=overall survival.

Table 3: Event-free survival and overall survival estimates from selected radiotherapy series reporting 5-year and 10-year outcomes

proving overall survival in ependymoma; previous reports show the proportion of patients with local failure to be between 59% and 97%.^{18–25} Isolated local failure accounted for 39% of failures in our series. Local failure might be attributed to various factors; our results show that the extent of resection is an important contributing factor. Our estimates of local tumour control exceed those expected from contemporary series using prescribed doses of 54 Gy or more, and with similar rates of gross-total resection.^{1–3} This is probably due to the prospective nature of this work, systematic targeting with conformal radiotherapy, our procedures (image registration, rigorous immobilisation, use of general anaesthesia, non-coplanar and multifield delivery, and small number of elapsed treatment days), and the relatively high prescribed radiation doses and healthy tissue tolerances that we allowed the spinal cord, brainstem, and optic chiasm to receive. Future efforts to increase local tumour control in ependymoma should prioritise increasing the rate of gross-total resection, using second surgery when needed, and avoiding treatment delays. Consideration should also be given to higher total doses of radiotherapy and combining synergistic agents with irradiation, since the cumulative incidence of local failure remains high at 16%. Future studies should also consider reducing the margin around the target volume from 10 mm to 5 mm to limit the dose to healthy 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 EFS after irradiation ranging from 41–58% when measured at 5 years to 31–46% at 10 years.^{4,18–26} Overall survival has ranged from 54–73% at 5 years to 45–56% at 10 years. Our EFS and overall survival estimates at 5 years were 74% and 85%, respectively. Although these differences might be attributable to treatment era and the distribution of major prognostic factors, the improved outcome persists when

considering the most favourable patients, including those treated with gross-total resection, early postoperative irradiation, and prescribed doses of 54 Gy or more: patients treated in our series with gross-total resection had 5-year EFS estimates of 82%, rising to almost 85% when patients treated with immediate postoperative irradiation, and without chemotherapy, were considered.

The benefits of improved disease control might be realised 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 assessment, we had the opportunity to document the incidence and time course of a broad range of treatment-related side-effects and to note various rare adverse events. We have reported separately the neurological, endocrine, and cognitive effects in this patient cohort.^{27–29} Our recent report assessing the academic abilities of these patients is contemporary with this paper, and highlights the vulnerability of reading ability compared with other academic skills.²⁸

A potential limitation to our study is the fact that some of the patients were initially treated elsewhere, before being referred to us. Referral from beyond the geographical region is nearly always associated with bias toward more difficult cases (initial subtotal resection), aggressive tumours (anaplastic ependymoma), and younger patients. However, with an annual US incidence of 0·76 cases per 100 000 individuals aged 0–19 years, and fewer than 274 000 individuals in this age group, the immediate locale of St Jude would be expected to yield less than one case of ependymoma or anaplastic ependymoma per calendar year. Patients were thus recruited for treatment on this protocol from 37 of the 50 States of the USA and from two countries other than the USA. Furthermore, although the absence of a required time interval from first surgery to irradiation aided recruitment, it might also have contributed to a referral bias and affected selection—ie, patients were selected with a more difficult to treat disease than normal. St Jude accepts regional patients for treatment irrespective of disease status; however, those from beyond the immediate geographical region were required to fulfil the enrolment criteria for our protocol to be accepted for treatment.

Although we have reported overall survival as a measured outcome, this endpoint might not be a suitable measure of success, because patients who fail radiotherapy 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;³⁰ the paucity of side-effects from limited-volume irradiation could provide new salvage options for these patients. Our data indicate that failure after 3 years

is infrequent; 3-year EFS could thus serve as a better measure of success. Of course, late failures are known to occur, and patients in our series have shown rare, but clinically significant, somatic effects and second malignancies. Nonetheless, the relatively low rate of local failure seen here, compared with historical 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.

Radiotherapy for childhood ependymoma will continue to evolve even as investigators search for means to reduce local and neuraxis treatment failure. Newer methods of delivering radiotherapy promise further reductions in the dose to healthy tissues and increased conformity of the highest doses to the target volume. New methods will also allow for modulation of toxicity based on improved understanding of the relation between dose, irradiation volume, and clinically significant side-effects. In the absence of objective information about healthy tissue dose constraints in this patient cohort, we applied dose limits only for irradiation of the optic chiasm and cervical spinal cord. With long-term follow-up, we are modelling dose, volume, and healthy tissue effects longitudinally with the hope to further optimise treatment.³¹

Contributors

TEM 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. LEK, FAB, and RAS participated in the provision of study materials, patients, and editing of the manuscript. All authors participated in the final approval of the manuscript.

Conflicts of interest

The authors declared no conflicts of interest.

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