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Relapsed intracranial ependymoma in children in the UK: Patterns of relapse, survival and therapeutic outcome

B. Messahel[a], S. Ashley[a], F. Saran[a], D. Ellison[b], J. Ironside[c], K. Phipps[d], T. Cox[d], W.K. Chong[d], K. Robinson[e], S. Picton[f], C.R. Pinkerton[g], C. Mallucci[h], D. Macarthur[i], T. Jaspan[i], A. Michalski[d], R.G. Grundy[i,], On behalf of the Children's Cancer Leukaemia Group Brain Tumour Committee*

[a]*Department of Paediatrics, Royal Marsden Hospital, Sutton, Surrey SM2 5PT, UK*
[b]*Department of Pathology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA*
[c]*Western General Hospital NHS Trust, Edinburgh, EH4 2XU, UK*
[d]*Great Ormond Street Children's Hospital, Great Ormond Street, London WC1N 3JN, UK*
[e]*Data Centre, UKCCSG, 9 Princess Road West, Leicester LE1, UK*
[f]*Regional Paediatric Oncology Unit, St. James University Hospital, Leeds LS9 7TF, UK*
[g]*Director of Cancer Services, Mater Hospitals, Raymond Terrace, Brisbane OLD 4101, UK*
[h]*The Walton Centre for Neurosurgery, Liverpool L9 7LJ, UK*
[i]*The Children's Brain Tumour Research Centre, University of Nottingham, The Medical School, Queen's Medical Centre, Nottingham NG7 2UH, UK*

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ABSTRACT

Relapsed ependymoma in children poses difficult dilemmas in management. Clinico-pathological and treatment data of 108 children with relapsed ependymoma in the United Kingdom (UK) treated between 1985 and 2002 were reviewed to identify prognostic factors affecting survival. The primary site was the most common site of relapse (84%). Overall 25% had metastatic relapse. Surgery at relapse was attempted in only 55%. Radiotherapy was delivered at relapse in 66% infants and 50% of older children were re-irradiated. Overall 5-year survival was 24% and 27% for children less than 3 years of age at initial diagnosis and older children, respectively. Multivariate analysis showed that, for infants, surgery ($p = 0.01$) and radiotherapy ($p = 0.001$) at relapse were independent predictors of survival. For older children regardless of the previous radiotherapy, repeat irradiation was associated with better outcome ($p = 0.05$).

Relapse was associated with poor outcome in both age groups. A survival advantage conferred by both radiotherapy and surgery at relapse is independently significant.

1. Introduction

There are few published data on the outcome of children with relapsed ependymoma and little evidence for the efficacy of salvage treatments.[1–5] Furthermore, the outcome of relapsed patients who did not receive radiotherapy as part of their primary treatment strategy is largely unknown.

The primary management of childhood ependymoma has changed with time, as has the increased use of chemotherapy as an adjunct to surgery and radiotherapy. An age specific

* *Corresponding author:* Tel.: +44 (0)115 823 0620; fax: +44 (0)115 823 0696.
E-mail address: richard.grundy@nottingham.ac.uk (R.G. Grundy).
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strategy for the treatment of ependymoma in the United Kingdom (UK) was in operation between the study dates.[6,7] From 1992 onwards children 3 years of age or younger at diagnosis with ependymoma in the UK were treated on the UKCCSG Baby Brain trial (CNS 9204) with chemotherapy following surgery in an attempt to avoid or delay RT,[8] based on concerns over late toxicity from radiotherapy in this very young patient group.[9] For older children treatment was offered in the context of the SIOP ependymoma study [CNS 9901] based on the degree of surgical resection obtained at initial surgery; patients with an incomplete resection received chemotherapy and if possible second look surgery prior to radiotherapy compared to radiotherapy alone for patients with a macroscopic and radiological complete resection.

The most widely accepted prognostic factor for outcome in ependymoma is the degree of surgical resection at first diagnosis. Complete surgical resection and gross tumour reduction (GTR) is associated with a better prognosis in most,[10–15] but not in all published series.[1,16,17] The relationship between histological grading and tumour outcome remains controversial, with no clear relationship between grade and outcome.[10,14,18–21] This is in part due to the lack of a clear consensus on the criteria for assigning histological grade.[22]

Unfortunately, over 50% of children still relapse, often despite initial complete resection. Treatment options at the time of relapse are often limited particularly if initial therapy included radiotherapy.

Factors affecting prognosis for relapse are reported in two studies. These are similar but not identical to those at primary diagnosis, for example the extent of surgical resection and progression to a more malignant phenotype based on histological grading.[1,23] These studies are limited in their conclusions due to the small patient numbers and heterogeneity of primary treatment.

We reviewed the treatment given to children enrolled in the prospective UKCCSG studies between 1985 and 2002[8] at the time of relapse and to determine prognostic factors influencing their outcome.

2. Materials and methods

Patients aged 18 years and under with a proven diagnosis of ependymoma that relapsed between January 1985 and October 2002 were identified from the UKCCSG (now CCLG) database. The database accrued patients treated on the National UKCCSG trial CNS 9204[8] and SIOP ependymoma trial (CNS 9901). Information on initial presentation included age, site of disease, histology, primary treatment and length of response to initial therapy. Data were collected at first and any subsequent relapse for children under and over 3 years of age at diagnosis and included site of relapse, therapy and outcome.

Based on differences in treatment strategy in the UK, patients were divided into two groups according to their age at initial diagnosis: Group A: very young children aged 3 years or younger at diagnosis and Group B: children older than 3 years at diagnosis. These two groups were analysed separately. Survival after relapse was measured from the date of diagnosis of relapse until date of death or last follow-up. A univariate analysis of survival was carried out by means of the Kaplan Meier method and comparison between groups was done by the log rank test. Variables investigated in this analysis included demographics, histological grade, surgical resection, non-surgical treatment, duration of response to initial therapy and site of and treatment at relapse. Variables that were significant under univariate analysis were then entered into a multivariate analysis using the proportional hazards model in order to test for the independent significance of prognostic factors. A step-up method was employed and variables were added at the 0.05 level of significance.

2.1. Pathology

Histological slides from all patients treated on UKCCSG/SIOP ependymoma clinical trials at diagnosis and relapse had central review of pathology (DE and JI). Tumours were classified as grade II or III according to World Health Organisation (WHO) criteria.[24] Ependymoblastomas were excluded. Histology for central pathological review was available in 92 of 107 cases (86%).

2.2. Assessment

2.2.1. Imaging and surgery

Patients were staged by full neuraxial imaging; post-operative scans (<48 h) were recommended. 50% of patients had central review of pre-operative and post-operative scans from primary diagnosis predominantly those on the CNS 9204 trial. All patients underwent primary surgery with the aim of achieving maximal surgical resection. A complete resection was recorded when there was no visible tumour documented by the surgeon at the end of operation, a subtotal resection when visible tumour remained and a biopsy when minimal tumour was removed. All patients treated on UKCCSG/SIOP clinical trial had central review of imaging and surgical reports.

2.3. Patient characteristics at initial diagnosis

A total of 108 patients with relapsed ependymoma met the criteria for inclusion into the review. There was a slight male predominance with 58/108 (54%) male and 49/108 (46%) female patients. Fifty-four patients (50%) were under the age of 3 years at initial diagnosis (Group A) and the remaining half were 3 years and older (Group B). The majority of patients had disease arising from the floor of the 4th ventricle (78%). Seven patients (6.5%) had evidence of metastatic disease on initial presentation based on imaging studies (91% had spinal imaging at diagnosis) (Table 1). At initial presentation 45% of Group A cases had WHO Grade III tumours compared to 41% of Group B cases.

2.4. Primary therapy prior to relapse

2.4.1. Group A (3 years of age or under n = 54)

After surgery, 43 children (81%) received chemotherapy; most (35/54) were treated according to the UK/SIOP baby brain CNS 9294 protocol and a further three were treated on the babé SFOP strategy.[6] Complete surgical resection at presentation

Table 1 – Demographics and details of primary tumour.

	Group A <3 years at diagnosis	Group B >3 years at diagnosis	Total
Patients	54	54	107
Gender			
Male: female	35:18	23:31	58:49
Age			
Median (range)	20 m 6 m–35 m	6 y10 m 3 y–15 y	3 y 6 m–15 y
Histology			
Low grade	21	25	46
High grade	25	22	46
Not known	8	7	15
Site of primary disease			
Infratentorial	**49**	**41**	**89**
Post fossa	45	33	77
Spine	1	4	5
Posterior fossa + spine	2	4	6
Cerebral + spine	1		1
Supratentorial	**5**	**13**	**18**
Frontal		2	2
Temporal		1	1
Parietal	1	9	10
Cerebral	3		3
Third ventricle	1	1	2

was obtained in 45% of patients. Of the 10 infants (19%) that did not receive chemotherapy following surgery, 4 were irradiated and 6 received no further post-operative treatment. The latter group consisted of 4 patients with a complete surgical resection and 2 with incomplete resection. A total of 10 patients were treated with radiotherapy, either alone or in combination with chemotherapy (1 focal with a primary tumour dose ⩽45 Gy, 3 focal with a dose of >45 Gy and 6 craniospinal with a total primary tumour dose of more than 45 Gy).

The median duration of response to initial therapy for Group A was 17 months (range 3 months–8.5 years) (Fig. 1).

2.4.2. *Group B (>3 years; n = 54)*

Surgical resection was performed at diagnosis in all patients in this group with 26 (48%) achieving a complete resection. The main modality of post-operative treatment in older children was radiotherapy, with 41% receiving focal and 33% receiving craniospinal irradiation (6 focal with a dose of ⩽45 Gy, 11 focal at a dose of >45 Gy and all those who received craniospinal radiotherapy were treated to a total tumour dose of >45 Gy). Eleven children (age 3–13 years, median 5 years) had no post-operative treatment with 8/11 having achieved a complete macroscopic resection. In these patients the disease was confined to the posterior fossa in 5 cases, posterior fossa and spine in 1 case and parietal lobe in 2 cases. The median duration of response to the initial therapy in this group being 19 months (range: 3 months–5 years) (Fig. 1).

Compared to the infant group there was no difference in time to relapse ($p = 0.6$).

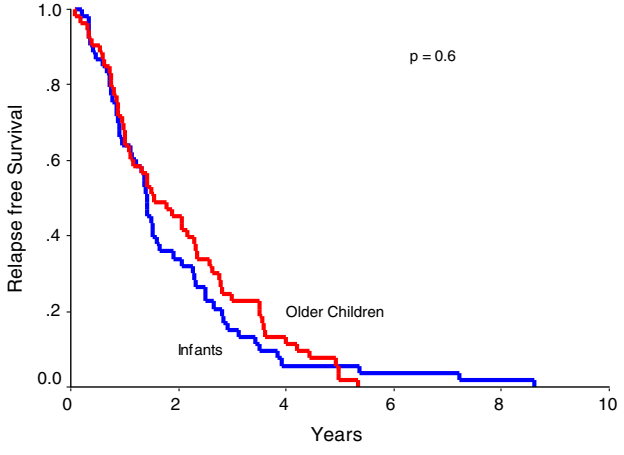


Fig. 1 – Duration of initial response for Group A (children <3 years) and Group B (older children >3 years).

3. Results

3.1. *Site of relapse*

Seventy five percent ($n = 80$) of all registered patients relapsed at the primary site alone; in 9% of cases relapse was both at the primary site and at metastatic sites; 5% suffered relapse only within the spine and 11% had a supratentorial relapse. In total, 25% of patients had a metastatic relapse either as the sole site of relapse or in combination with a local failure (Table 2).

Primary craniospinal radiotherapy was delivered to 6 of 54 patients in Group A [<3 years of age at diagnosis] and to 16 of 54 patients in Group B [>3 years of age at diagnosis]. Two cases in Group B received adjuvant chemotherapy. All six cases had disease localised to the posterior fossa. Subsequently five of six irradiated patients in Group A relapsed locally within the radiotherapy field. Four of these patients received additional chemotherapy. In Group B, 16 patients were treated

Table 2 – Site of relapse in Groups A and B.

	Group A	Group B	Total
Local	44	37	81 (75%)
Local + other sites in CNS	3	7	10 (9%)
Spine with no local relapse	2	3	5 (5%)
Other CNS site–no local relapse	5	7	12 (11%)

with primary craniospinal radiotherapy alone following surgery. In this group 14 patients experienced combined local and spinal relapses, two of whom had received craniospinal radiotherapy as part of their initial treatment.

Of 17 patients (6 in Group A and 11 in Group B) who had no primary post-operative treatment, 13 relapsed locally, 1 had a metastatic relapse and the remaining 3 had combined local and metastatic relapse.

3.2. *Histology*

There was no difference in the time to first relapse for grade II versus grade III tumours in either Group A (17 months versus 16 months; $p = 0.8$) or Group B (21 months versus 18 months; $p = 0.4$). Of note is that 15% of cases ($n = 14$) had a higher grade at recurrence compared to initial diagnosis. No patient with an ependymoma grade III at diagnosis recurred as grade II.

3.3. *Treatment of first relapse*

An attempt at surgical resection at first relapse was made in 54% of children. If we select out those patients who had surgery at relapse, then the extent of surgery was not a significant factor for survival after relapse in either Group A ($p = 0.9$) or Group B ($p = 0.3$). Sixty-six percent of infants were irradiated at relapse compared to 50% of older children. Etoposide was the main chemotherapeutic agent used in both age groups, the majority in both groups receiving this orally at either first or subsequent relapses (Group A; 4/7, Group B 9/10). Eight patients from Group A and six from Group B received no treatment at first relapse and subsequently died (Table 3).

3.3.1. *Group A (children 3 years of age or younger)*

No attempt at surgical resection at relapse was made in 25 of 54 patients (46%). All but one of these patients had relapsed in the posterior fossa (one in the spine). Sixty-one percent of patients who underwent surgery achieved a complete resection. Radiotherapy was the main stay of non-surgical oncological treatment for the infants in this group (66%). Focal radiotherapy was delivered to 57% (80% receiving a tumour dose of >45 Gy) and 43% received craniospinal radiotherapy followed by a focal boost (93% receiving a primary tumour dose of >45 Gy). There was no difference in survival between patients receiving focal radiotherapy and those who received craniospinal RT ($p = 0.5$). All patients diagnosed between 1985 and 1992 received craniospinal RT as part of their RT treatment strategy for localised ependymoma. Eighteen children did not receive radiotherapy at relapse, eight of whom had already been irradiated at first diagnosis. Four of the remaining ten patients who did not receive radiotherapy were less than 15 months of age at relapse whilst for the remaining six children no defining reason was given. For the 12 infants in whom a complete resection was achieved and who received adjuvant radiotherapy (Table 3), 5 are alive at 3–5 years post recurrence. Six infants received chemotherapy at relapse, two of whom had already received chemotherapy as part of the primary treatment.

3.3.2. *Group B*

Surgical resection was attempted in 58% (31/54) of patients of which 55% (17/31) achieved complete resection. Nineteen children received systemic chemotherapy at first relapse, 10 received combination chemotherapy containing Etoposide, 5 received single agent Etoposide and 3 children received other single agent drugs (Temozolamide, CCNU, Carboplatin).

Re-irradiation was undertaken in 14 children (26%) of whom 9 (64%) had focal fractionated radiotherapy (6 at $\leqslant$45 Gy and 3 at doses >45 Gy), 3 (21%) had stereotactic single fraction or hypofractionated RT (dose >45 Gy) and 2 (14%) craniospinal RT (with a primary tumour dose >45 Gy) (Table 3).

Table 3 – Non-surgical treatment of first relapse in Groups A and B (RTX = radiotherapy and CTX = chemotherapy).

	None	RTX	CTX	RTX + CTX
Group A				
All	14 (26%)	33 (62%)	4 (8%)	2 (4%)
Complete resection	5	12	0	0
Incomplete	1	9	0	1
No surgery at relapse	8	12	4	1
Group B				
All	16 (30%)	19 (35%)	11 (20%)	8 (15%)
Complete resection	9	5	2	1
Incomplete resection	1	8	3	2
No surgery at relapse	6	6	6	5

3.4. *Outcome after first and subsequent relapse*

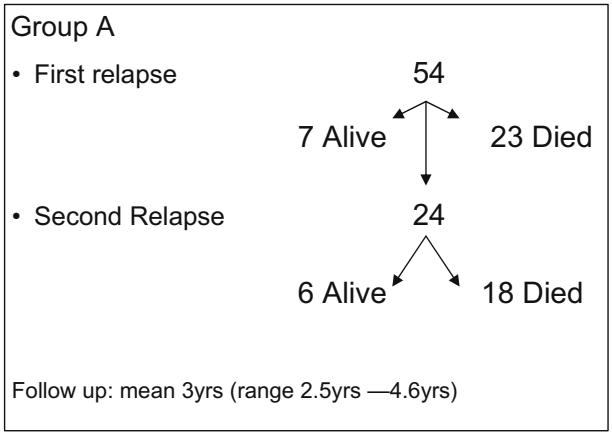
There was no significant difference in the survival after relapse between children in Group A and Group B (12 months – 95% CI 4–21 months versus 14 months – 95% CI 3–25 months; $p = 0.3$) (Fig. 2).

3.4.1. *Group A*

Twenty-two patients died at first relapse. Twenty four suffered a second relapse with only 6 of these still alive. The mainstay of treatment was further surgery with 5 of the 6 survivors having complete re-resections. In total only 13/53 patients survived first and subsequent relapses with a 5-year overall survival rate of 24% at a median follow-up of surviving infants of 4 years 4 months (range 1 year 11 months–11 years 10 months).

3.4.2. *Group B*

With a median follow-up of 6 years (range 1 year 8 months–15 years 9 months), the 5-year overall survival rate was 27%. Twenty children died after first relapse and 24 went on to have a second relapse of whom 20 have subsequently died. Six patients had more than 2 relapses, four of whom died following 3–6 relapses. Two of the four patients who were still alive following a second relapse had supratentorial disease (and had local relapses). One patient who relapsed with spinal disease was treated and subsequently relapsed again in this area and one had a primary infratentorial ependymoma, which relapsed locally. One child, who had suffered multiple relapses, died 10 years after initial relapse. Again, surgery was the mainstay of treatment and for those patients with chronic relapses repeated resections were performed at each relapse (Fig. 3).



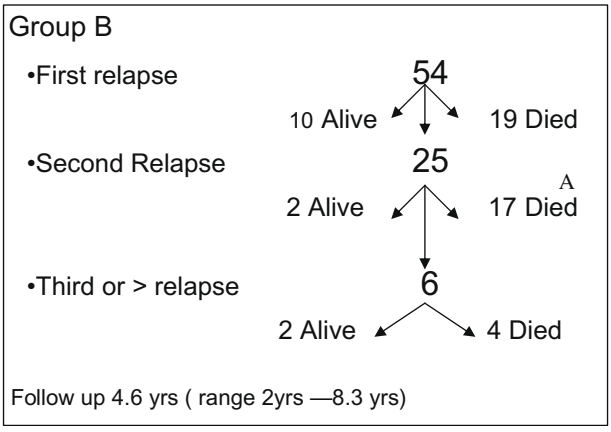


Fig. 3 – Flow chart A and B represent Groups A and B patients first and subsequent relapses.

3.5. *Factors affecting survival after relapse*

3.5.1. *Group A*

Multivariate analysis showed that factors relating to the primary tumour and its resection have no effect on survival after first relapse (sex $p = 0.3$, histological grade $p = 1.0$, initial site of disease $p = 0.5$, primary complete resection $p = 0.2$, primary chemotherapy $p = 0.3$) (Table 2). The small group of infants ($n = 10$) who received primary radiotherapy had a longer duration of initial response compared to those receiving chemotherapy (median 23 months versus 16 months; $p = 0.04$). However, this group of patients had a poorer survival after relapse ($p = 0.02$) compared to those who had delayed radiotherapy. At this time re-irradiation was not routinely considered feasible or appropriate. There was no significant difference in the overall survival from diagnosis based on the timing of radiotherapy ($p = 0.4$). Unirradiated infants who received radiotherapy at relapse (either focal $n = 20$ or craniospinal $n = 15$) had a significantly better survival after relapse than those in whom radiotherapy was given at the time of first diagnosis ($p = 0.001$) (Fig. 4).

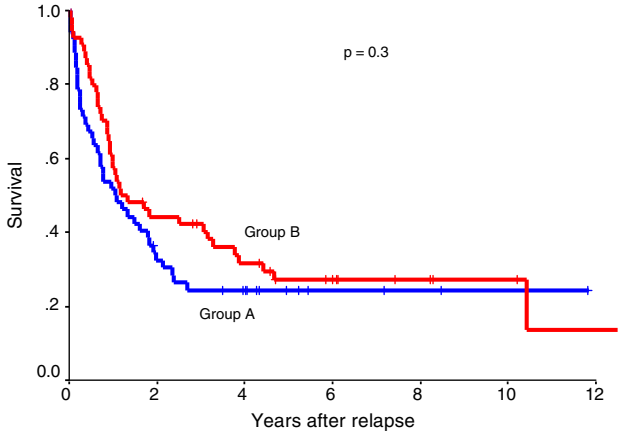


Fig. 2 – Overall survival of children <3 years (Group A) and older children (Group B). Median survival Group A 12 months (95% CI: 4–21 months). Group B 14 months (95% CI: 3–25 months). Difference is not significant; $p = 0.3$.

Surgical resection was performed at relapse in 53% of infants. The 4-year overall survival rate of those undergoing surgery was 34% compared to those in whom no surgery was performed (13%, $p = 0.01$) (Fig. 5).

There was no effect on survival after first relapse in relation to the duration of initial response ($p = 0.9$), relapse site (local versus other; $p = 0.7$) or chemotherapy at relapse ($p = 1.0$).

Under multivariate analysis, the survival advantage conferred by both surgery and radiotherapy at relapse retained independent significance.

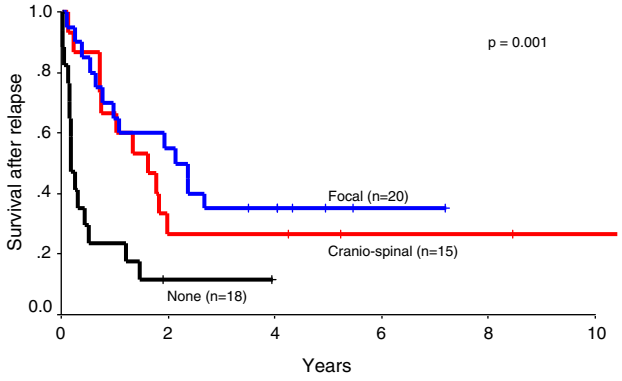


Fig. 4 – Comparison of children <3 years (Group A) survival after relapse by radiotherapy received at relapse.

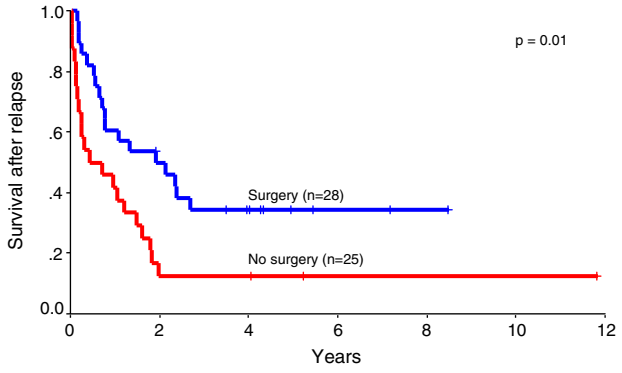


Fig. 5 – Comparison of children <3 years (Group A) survival after relapse by whether they received surgery or not.

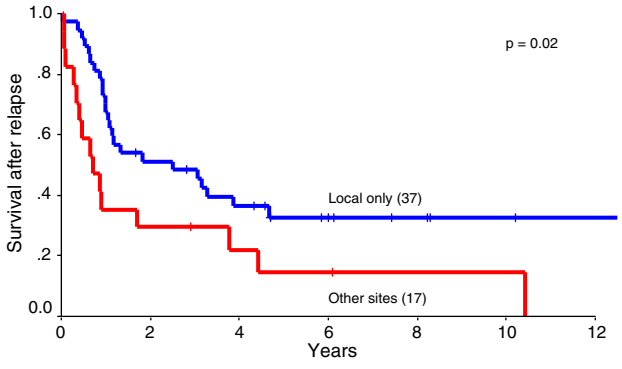


Fig. 6 – Comparison of older children's survival (Group B) after relapse by site of relapse.

3.5.2. *Group B*

At first relapse, children whose recurrence was limited to the primary site fared better than those relapsing with distant leptomeningeal metastatic disease (median survival 30 months versus 13 months; $p = 0.02$) (Fig. 6). Older children who received radiotherapy as part of their primary treatment had significantly poorer survival after relapse than those who did not (11 months versus 6 years; $p = 0.007$). But, for this age group, this was not balanced by a better initial duration of response compared to patients from Group A who did not routinely receive upfront radiotherapy. Older children who received craniospinal radiotherapy at relapse, had a better outcome than those who received either focal rediotherapy or none at all (P = 0.05) (Fig. 7). Although the numbers are small, the four children who received a primary tumour dose of less than 45 Gy at diagnosis did particularly poorly; all relapsed within 1 year and died within a year of their relapse. No other primary disease or treatment characteristics have an effect on survival.

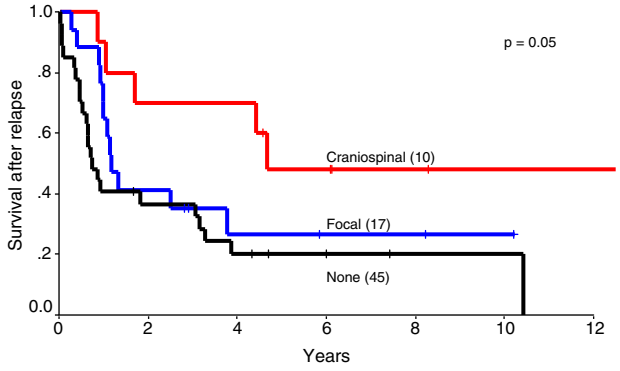


Fig. 7 – Comparison of older children's survival (Group B) after relapse by radiotherapy received at relapse.

In summary, under multivariate analysis, metastatic disease and radiotherapy at relapse were independently significant factors for survival.

3.6. *Timing of first and second relapse*

Overall the time interval to first relapse was 18 months; for Younger Group A children the median was 17 months (95% CI 15–19 months) and for older Group B children the median was 19 months (95% CI 15–19 months). The time interval between first relapse and second relapse was slightly longer in children under 3 years of age, who mainly received radiotherapy as salvage treatment, at 21 months compared to 19 months, but the difference was not significant (Group A: median 21 months [95% CI 16–27]; Group B: median 19 months [95% CI 5–33 months]). There was no difference in the timing of relapse based on whether chemotherapy or radiotherapy was given as the initial treatment.

4. Discussion

Patients with recurrent ependymomas have a poor survival (25% at 5 years) regardless of age at recurrence and subsequent treatment received. Based on our data the subgroup of infants and older children in whom surgical resection and/or radiotherapy/re-irradiation was delivered at the time of first relapse fared significantly better.

In the past re-irradiation as part of the relapse strategy following the previous radical RT has not been routinely considered in this situation. This is due to the potential significant acute and late sequelae of re-treating significant portions of the central nervous system. This is particularly relevant in local recurrences in the posterior fossa where re-treatment

usually encompasses the brainstem in the high dose target volume with conventional planning and delivery methods. This study has demonstrated that re-irradiation does confer a significant survival advantage, which is independently significant on multivariate analysis. Thus with increasing experience and availability of highly conformal radiotherapy techniques consideration to re-irradiation should be given in those circumstances. Such an approach has been successfully reported by other groups.[2,5,25] Given the very small number of eligible patients per year this should be ideally limited to a small number of neuro-oncology units with expertise in paediatric and high precision irradiation treatments, based on a nationally agreed referral pathway. This should ensure consistency in the advice received as well the ability to prospectively evaluate these data. While there remain concerns with respect to the long-term toxicity of re-irradiation, the poor outcome following relapse highlighted in this paper, make consideration of re-irradiation a justifiable option.

Although ependymoma is widely considered to be a 'surgical' disease,[26] an attempt at surgical resection was seen in only half the patients at relapse regardless of age. This study confirms that surgical resection at relapse is associated with a significantly better outcome,[1,23] though interestingly the extent of surgical resection at relapse based on local neurosurgical and radiological review was not a significant factor for survival after relapse. This suggests that reducing tumour burden is an important positive predictor of favourable outcome. Although we could not assess the reasons for not undergoing further surgery at relapse, as this would have been made at an institutional level, the evidence presented here should encourage robust discussion of these cases at neuro-oncology MDTs. The possibility of concentrating the expertise in designated national centres merits debate. It is, however, difficult to tease out the impact of the selection criteria for further surgery in each centre. Whether centralised special surgical centres or vigorous training and multi-centre audit can help address this surgical issue needs to be determined.

For older children in the UK, second look surgery with the aim of achieving a macroscopic complete excision is recommended as part of the SIOP 99 primary treatment protocol, which opened to recruitment in 1999. For local disease this protocol advocates radical focal radiotherapy 54 Gy after a macroscopic complete resection. Following an incomplete resection, the protocol advises four courses of chemotherapy, second look surgery for residual disease if feasible, followed by definitive focal radiotherapy. Prior to this protocol starting the treatment varied from centre to centre. This may explain why we saw no association between the extent of surgery and outcome for older children in our study.

The UK's infant brain tumours protocol opened in 1992, treating children less than 3 years with surgery followed by chemotherapy. We have included a small number of patients in Group A treated before CNS 9204 opened. When radiotherapy was administered as part of primary treatment a better initial duration of response was seen. However, no infants survived if they relapsed following primary radiotherapy as management at recurrence appeared to be less aggressive and no patient was considered for re-irradiation.

In the majority of older patients re-irradiation was delivered using a focal volume, with three survivors having had stereotactic hypofractionated radiotherapy or single fraction radiosurgery. The overall survival from diagnosis in both groups [A and B] was similar whether they received radiotherapy as part of primary treatment or at relapse, suggesting that the timing of radiotherapy is not an important prognostic factor.

The latest recorded recurrence in this series was 5 years post treatment, supporting the rationale for prolonged screening post therapy for children.[27] Of note older children appeared to have multiple relapses and that for some children this becomes a multiply relapsing 'chronic' disease from which most eventually succumb.

In contrast to the series reported by Goldwein et al. we were unable to confirm that histological grade of tumour had an impact on time to relapse in either group (A or B). Nor did other factors such as time interval to relapse, age of patient at diagnosis and location of primary tumour (infratentorial versus supratentorial).

Most first and subsequent relapses in both age groups tended to occur locally, with the primary site involved in 86% of cases. However, 16% of relapses were metastatic alone and 9% local and metastatic (in total 25%). Site of relapse in older children had a significant relation to outcome, with locally recurring tumours having a better outcome than those with metastatic relapse ($p = 0.02$) (median months 30 versus 13 months). Overall the time interval to first relapse was similar for younger and older children (Group A and B) at a median of 18 months from initial treatment. The time interval between first relapse and second relapse was slightly longer in the younger children under 3 years of age (Group A), who mainly received radiotherapy as salvage treatment, at 21 months compared to 19 months, but the difference was not significant. There was no difference in the timing of relapse based on whether chemotherapy or radiotherapy was given as the initial treatment.

A number of different chemotherapy agents, either as a combination or single agent regime, were employed at relapse including Etoposide, Cyclophosphamide and Carboplatin. There was no clear benefit for chemotherapy with respect to overall survival at the time of relapse, though this may reflect inconsistency of practice. However we could not determine whether the use of systemic chemotherapy improved progression-free survival as the data were not available. While Cisplatin is reported as the most active agent in a retrospective review in which a variety of chemotherapeutic agents were used,[28] in other malignancies there is debate over the efficacy between Cisplatin and Carboplatin (e.g. germ cell tumours), however, there are no data to compare Cisplatin and Carboplatin in this setting. The better side-effects profile and ease of use made Carboplatin, in the UK paediatric oncology community, the clear preference in the relapse setting. However, a number of other studies have shown a modest effect of chemotherapy on relapse-free survival in the setting of recurrent ependymoma and that no chemotherapy regimen had clear superiority over another.[29,30] Oral Etoposide has been used as a single agent in recurrent ependymomas in two separate studies, showing response rates between 17% and 40%.[3,31] Other chemotherapeutic agents have been used in an attempt to document efficacy in ependymoma. These include Irinotecan (1/5 achieved a PR for 11 months), Paclitaxel

(response rate of 5.7%) and Idarubicin (no response documented).[32–34] A study of Temozolamide in resistant or relapsed paediatric solid tumours included two patients with ependymoma; neither of them demonstrated a convincing response.[35] Similarly a Children's Oncology Group study found no response to this drug.[36] A single case report however observed a partial response to this drug in an adult patient.[37] Response rates have also been observed for the anti oestrogenic agent Tamoxifen but again the numbers of patients being treated were very small.[38–40]

A number of phase II studies looking at high dose chemotherapy with stem cell rescue have been conducted. The SFOP group have evaluated the use of high dose Busulphan-Thiotepa in 16 children with relapsed ependymoma, with only three reported to be disease free at 15, 25 and 27 months.[41] The CCG also conducted a similar study using high dose Thiotepa, Etoposide and Carboplatin, with only 1 of 13 children surviving to 25 months; five died from toxicity.[42] In addition, other phase II studies using a combination of Thiotepa and Carboplatin as well as high dose Ifosphamide have been used with little benefit documented in the limited number of patients treated.[43] The benefits of treating relapsed ependymoma with high dose chemotherapy confers, at present, no demonstrable benefit over less intensive treatment strategies. This remains, therefore, at present experimental and should be restricted to prospectively designed clinical trials.

Novel therapeutic strategies have been slow to emerge for ependymoma as little is known about the genetic mechanisms underlying tumourigenesis in ependymoma. A number of 'biological' and genomic markers have now been identified and reported to be of prognostic significance. However many of the 'biological' studies to date have looked at a single biological marker in isolation and/or have conducted the studies on mixed cohorts of adult and paediatric ependymomas.[44] A recent study has shown that low Nucleolin expression was the single most important biological predictor of outcome in paediatric intracranial ependymoma.[45] However, these findings require corroboration in a clinical trial setting.

5. Conclusions

Patients with recurrent ependymomas have a poor outcome for all age groups and primary treatment strategies employed. Multivariate analysis of our data demonstrated that both surgery and radiotherapy, but not chemotherapy at relapse, were of independent prognostic significance for survival. Thus a strategy for relapsed ependymoma should be based on aggressive second surgery and radiotherapy including the consideration of repeat stereotactic re-irradiation/radiosurgery. Experimental new biological agents should be considered in the context of future national or international trials. Furthermore these studies should prospectively incorporate biological studies focusing on the identification of novel molecular markers that could be used for prognostic and therapeutic stratification.

Conflict of interest statement

None declared.

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