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Management of Ependymoma in Children, Adolescents and Young Adults

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Abstract

Paediatric ependymomas are rare, malignant tumours arising throughout the central nervous system, but most frequently (in children) the posterior fossa. The standard of care for localised disease is gross total resection and focal radiotherapy, resulting in overall survival rates of up to 85%. Despite improvements in survival, treatment remains challenging, with persistently high rates of (rarely curable) relapse alongside risks of significant tumour and treatment-related toxicity. Systemic therapy is currently used to delay radiotherapy in very young children and in the management of metastatic or recurrent disease. Its use in the adjuvant setting is the subject of ongoing studies. Current research efforts are aimed at eliciting a better understanding of molecular biology, correlating this with tumour behaviour and defining targets for potential new agents. Prognosis seems to be related to the extent of surgical resection and the age at presentation. This article reviews clinical aspects of ependymoma management in children and young people.

Key words: Adolescents; children; ependymoma; gross total resection; proton beam therapy; radiotherapy

Introduction

Ependymomas are malignant glial tumours of the central nervous system. Although they are recognised in all age groups, they are most frequent in children and comprise between 5 and 10% of all paediatric intracranial tumours. Around half occur in children under the age of 5 years. The incidence of ependymomas in the under 24 s is about 35 per year in the UK [1] and about 200 patients per year in the USA [2,3]. Neurofibromatosis type 2 is associated with a higher risk of spinal ependymomas [4] but generally the aetiology of ependymomas is not clear.

Pathology

Ependymomas arise from the ependymal linings of the ventricles and spinal canal. Recent studies suggest radial glial cells as the cell of origin [5].

In children, 80–90% of ependymomas have an intracranial origin; the remainder (a smaller proportion than in adults) arise in the spinal canal. Of the intracranial tumours, two-thirds are situated in the posterior fossa (associated with the fourth ventricle) and one-third supratentorially, Estimates of metastatic disease at presentation range from 10 to 30% [6].

Microscopically, the tumour cells resemble normal ependymal cells and are arranged in perivascular pseudorosettes, tubular structures and papillary formations.

The World Health Organization (WHO) 2007 classification of brain tumours assigned grades I (myxopapillary and subependymomas), II (classical) and III (anaplastic) [7].

Myxopapillary ependymoma arises most frequently in the lumbosacral spinal cord. Subpendymoma most commonly presents as an intraventricular (fourth ventricle) tumour of adults.

Grade III (anaplastic) tumours are described as having increased cellular density, mitoses, necrosis and microvascular proliferation compared with classical (grade II) tumours. However, it is recognised that grade (II and III) does not appear to confer the usual prognostic significance and

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this differentiation is of limited utility unless confirmed on central histology review [8].

DNA methylation profiling of ependymomas has now identified nine molecular subtypes in paediatric ependymoma, three in each anatomical compartment (posterior fossa, supratentorial and spinal), which appear genetically, demographically and clinically distinct (see Figure 1) [9].

The revised WHO 2016 classification only partially incorporates this molecular classification, describing the following five subtypes [10]:

- subependymoma (WHO grade I);
- myxopapillary ependymoma (WHO grade I);
- ependymoma (WHO grade II);
- ependymoma, RELA fusion-positive (WHO grade II or III);
- anaplastic ependymoma (WHO grade III).

It would be anticipated that future iterations of the WHO classification will more closely reflect the molecular classification as clinical correlations are confirmed from ongoing prospective studies.

Clinical Features

The mode of presentation depends on the site of origin. In very young children, symptoms are often non-specific and include failure to thrive, lethargy and irritability. Posterior fossa tumours may present with symptoms of raised intracranial pressure (secondary to obstructive hydrocephalus), cranial nerve palsies, ataxia or neck pain. Supratentorial ependymomas may present with headaches, seizures and focal neurological signs. Presenting features of spinal ependymomas include limb weakness, incontinence, abnormal sensation and progressive pain [11].

Initial Diagnostic and Staging Investigations

The primary imaging modality of choice for the initial investigation of intracranial and spinal ependymomas is a magnetic resonance imaging (MRI) scan [12]. Both spinal and intracranial ependymomas typically demonstrate T1 hypointensity, and T2 hyperintensity with heterogeneous enhancement on T1 sequences post-gadolinium (see Figure 2). A minority of tumours do not enhance. There may be cystic and calcified elements within a tumour, with cysts more commonly seen in supratentorial tumours probably related to their later presentation [13,14].

Spinal ependymomas tend to occupy a central location within the cord and often have a sharper margin of enhancement than astrocytomas.

An MRI spine is a mandatory part of the work-up for intracranial ependymomas to exclude leptomeningeal dissemination. This may be manifest on MRI as smooth enhancement along the surface of the spinal cord,

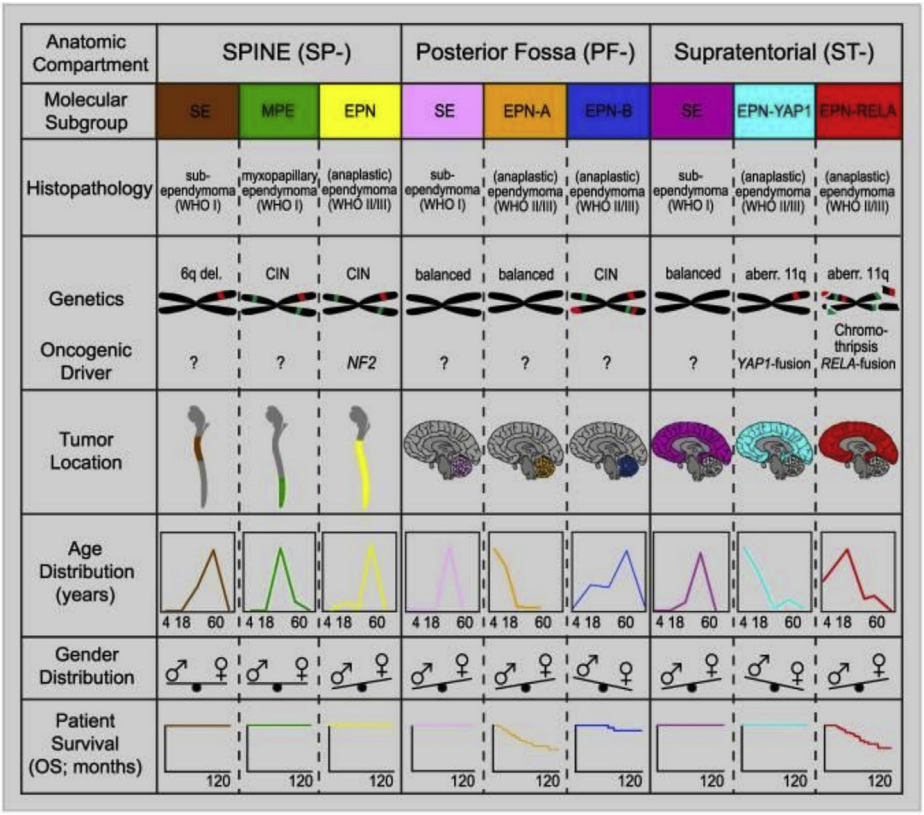

Fig 1. Schematic representation of key genetic and epigenetic findings in the nine molecular subgroups of ependymal tumors as identified by methylation profiling. CIN, Chromosomal instability. Reproduced with permission from [9].

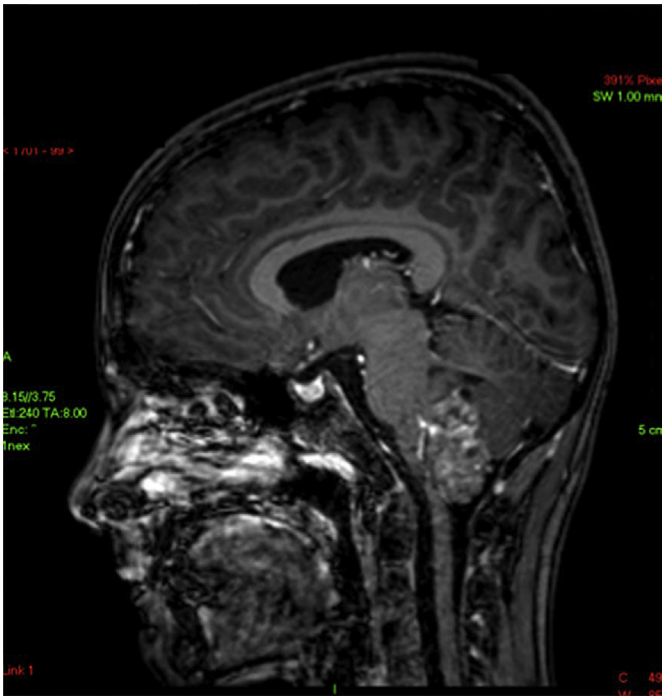

Fig 2. T1 + gadolinium coronal view of posterior fossa ependymoma.

enhancing foci in the extramedullary intradural or intramedullary spaces, nerve root thickening or thecal sac irregularity.

Lumbar puncture, for cytological examination of cerebrospinal fluid for tumour cells, should be carried out no earlier than 14 days postoperatively to reduce the risk of a false-positive result. Although a negative lumbar puncture within 2 weeks of surgery confirms M0 disease, a positive result within this time period will require a repeat sample.

Management of Newly Diagnosed Non-metastatic Ependymoma

Ependymoma must be managed within the setting of a multidisciplinary team experienced in the management of this disease. Where possible, patients with ependymoma should be enrolled on a clinical trial such as the currently recruiting SIOP Ependymoma II [15] and the ACNS 0831 studies [16]. The overarching design of SIOP Ependymoma 2 is illustrated in Figure 3.

Serial studies published over the past 20 years have confirmed the importance of gross total resection and focal radiotherapy in the management of non-metastatic ependymoma. Landmark studies are summarised in Table 1 [17–21].

Surgery

The extent of surgical resection (gross total resection versus near total versus subtotal) is consistently demonstrated to be the most important prognostic factor for this disease.

At initial diagnosis, operative intervention (e.g. insertion of a ventriculo-peritoneal shunt) may be required to manage hydrocephalus and stabilise the patient before definitive surgical management.

An early postoperative MRI is mandatory to assess the extent of surgical resection and, if present, the potential operability of any residuum. If this investigation is delayed beyond 72 h after surgery, it is difficult to distinguish between post-surgical changes (seen as a thin rim of enhancement along the cavity margins) and residuum.

Residual tumour may be defined using the R0-R4 five-point staging system as outlined in Table 2 [22].

As assessment of postoperative imaging can be extremely difficult, central radiological and surgical review is strongly recommended (for example, the Ependymoma Multidisciplinary Advisory Group in the UK) [22].

If postoperative residuum is confirmed, a second surgery should be considered, but any such decision must be taken in collaboration with the operating surgeon who will be aware of any difficulties encountered that may have led to the initial subtotal resection.

Radiotherapy

Standard postoperative management of completely resected intracranial ependymomas is with focal conformal radiotherapy, with excellent tumour outcomes and acceptable morbidity, even in children younger than 3 years [17–21].

The radiotherapy planning computed tomography scan is acquired in the treatment position and co-registered with the preoperative post-contrast T1 MRI images. Gross tumour volume (GTV) is based on the postoperative MRI and includes the tumour bed at the primary site modified to include any residuum. Reference to the initial preoperative imaging assists in the definition of the extent of the tumour bed and the anatomically involved tissues. The clinical target volume includes the GTV with a margin added to treat subclinical microscopic disease. Older protocols recommended an expansion of 1 cm from the GTV to the clinical target volume, but newer protocols use a margin of 0.5 cm [15,16,19,23].

The radiotherapy dose prescribed is 59.4 Gy in 33 daily fractions of 1.8 Gy per fraction, treating 5 days per week, with the dose to the optic chiasm and spinal cord limited to 54 Gy or less [19–21].

Very young patients or those undergoing multiple surgeries with tumours adjacent to the brainstem are considered at higher risk of developing brainstem toxicity and hence the total dose in these patients may be reduced to 54 Gy in 30 daily fractions.

For patients with a definable inoperable residuum following standard radiotherapy doses of 54–59.4 Gy, results from the second AEIOP study suggest that a highly conformal boost of 8 Gy in two consecutive daily fractions may lead to improved tumour control with acceptable toxicity [19]. This strategy is currently being tested in stratum 2 of the SIOP Ependymoma II Study [15].

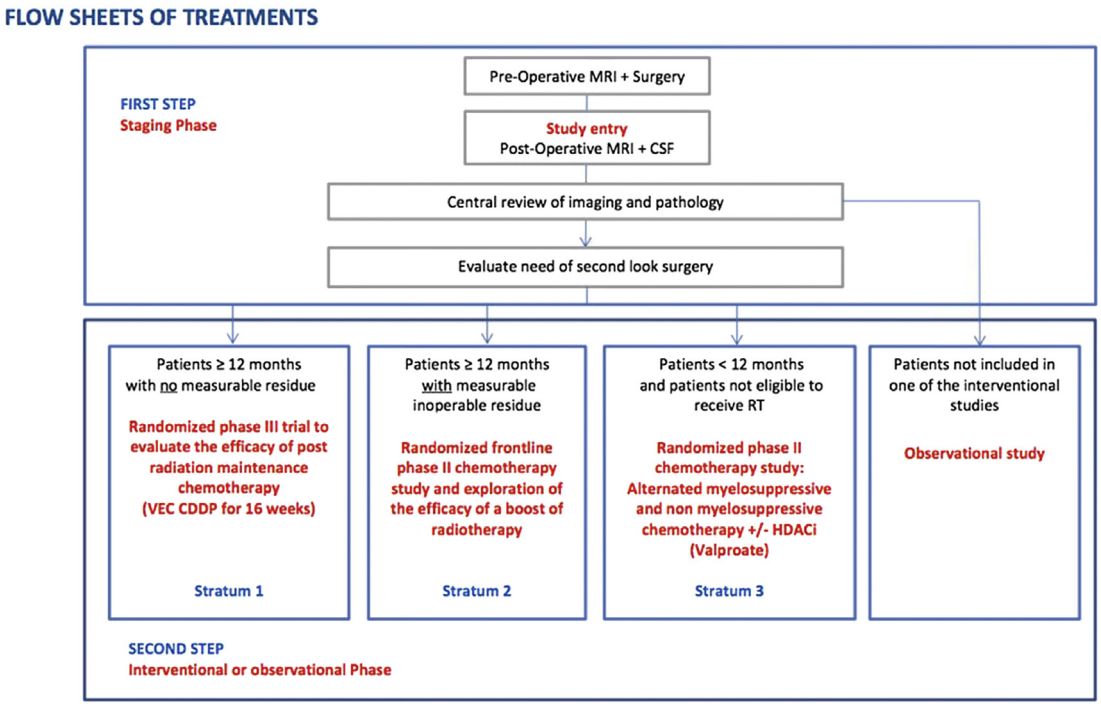

Fig 3. Schema for the SIOP Ependymoma II Study (courtesy of R. Grundy).

Role of Proton Beam Therapy

Ependymoma is one of the most common paediatric indications for proton beam therapy (PBT) [24]. PBT offers the potential to reduce side-effects, especially late toxicity, through reduced exposure of radiosensitive organs at risk adjacent to but not within the planning target volume [25,26]. An example of a proton beam dose distribution is illustrated in Figure 4. The dose distribution characteristics are particularly pertinent in very young children, who benefit from radiotherapy in terms of local control rates but are at greatest risk of quality of life-limiting normal tissue complications. Control rates are predicted to be equivalent and early outcome data support this proposition [27–31].

Table 1
Summary of surgery and radiotherapy studies

Name of study	*n*	Year of recruitment	Extent of surgery (GTR/NTR/STR)	Radiotherapy (fields/dose)	OS/PFS	Prognostic factors
HIT 88/89/91	55	1988–199?	28/55 - GTR	2/5 – no radiotherapy 40/55 CSI 13/55 focal	3-year OS 75.6% GTR 3-year PFS 83.3% STR 3-year PFS 38.5%	Extent of resection Metastatic disease
St Jude	153	1997–2000	81% GTR	Focal 59.4 Gy 54 Gy	7-year OS 85%	Extent of resection Tumour grade Age Race Pre-irradiation CTX
Second Prospective AIEOP Study	160	2002–2014	75% GTR	Focal 59.4 Gy + 8 Gy/2 fractions for residual	5-year OS 81.1% 5-year EFS 65.4%	Age <3 years (OS) Female gender Tumour grade GTR or NED post-radiotherapy boost
SFCE	202	2000–2014	85% GTR	Variable 62% > 54 Gy	5-year OS 71.4%	Tumour grade Age Extent of resection

OS, overall survival; PFS, progression-free survival; GTR, gross total resection; CSI, craniospinal irradiation; STR, subtotal resection; EFS, event-free survival; CTX, chemotherapy; NED, no evidence of disease.

Table 2
Definitions for the extent of surgical resection

	Extent of surgical resection
R0	No residual tumour on postoperative MRI in accordance with the neurosurgical report.
R1	No residual tumour on MRI but description of a small residual tumour by the neurosurgeon or if the neurosurgical result is unknown.
R2	Small residual tumour on MRI with the maximum diameter below 5 mm in any direction.
R3	Residual tumour that can be measured in three planes.
R4	Size of the residual tumour not differing from the preoperative status (e.g. after biopsy).
RX	Inadequate imaging or equivocal appearances of the surgical cavity. Every effort should be attempted to clarify the conclusion. Sometimes the presence of blood can be ruled out and distinguished from tumour if the MRI is repeated after some days. Repetition of MRI also may help to distinguish operative changes from residual tumour on T2/FLAIR.

MRI, magnetic resonance imaging.

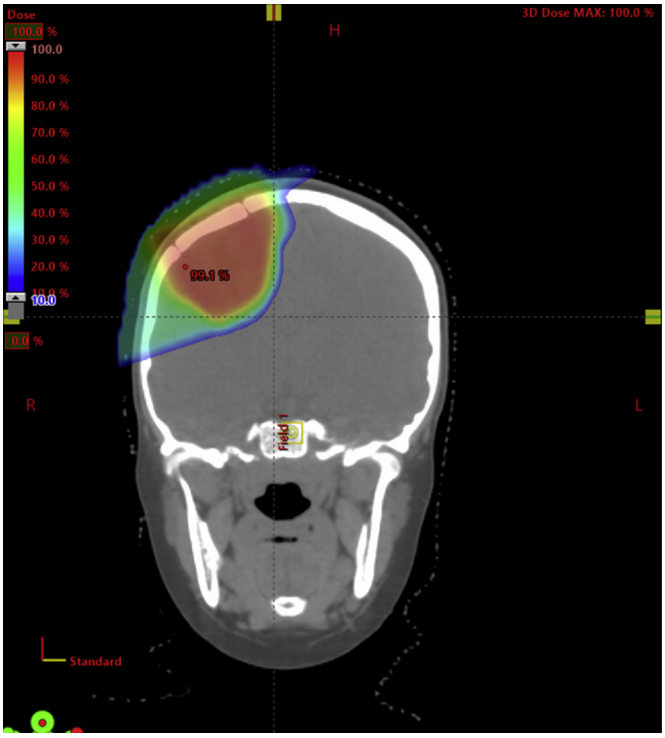

Fig 4. Proton dose distribution for right parietal ependymoma (prescribed 59.4 CGE in 33 daily fractions). Images courtesy of D. Indelicato.

Infant Ependymoma

Following the ground-breaking publication of Duffner *et al.* in 1993 [32] showing that postoperative chemotherapy may be used to delay or even avoid radiotherapy in children aged less than 3 years with malignant brain tumours, various multiagent chemotherapy regimens have been tested in ependymoma. The aim has been to reduce the potential serious morbidities associated with irradiation in the very young, while maintaining overall survival rates. This requires acceptance of inferior progression-free survival rates due to relapses, requiring radiotherapeutic intervention at a later date. The exact composition of regimens varies, but generally includes combinations of cis- or carboplatin, etoposide, cyclophosphamide and vincristine. Key trials are summarised in Table 3 [33–36]. They confirm that a proportion of very young children may receive postoperative chemotherapy and successfully avoid or delay radiotherapy, but tumour-related outcomes are consistently inferior.

A retrospective study of a sample of 804 children with intracranial ependymoma diagnosed between 1988 and 2005 taken from the SEER database compared outcomes for children receiving upfront radiotherapy and those receiving chemotherapy. Thirty-five per cent of patients aged less than 3 years received radiotherapy. For children aged less than 3 years, 3-year overall survival was 81% for those undergoing postoperative radiotherapy compared with 56% with no radiotherapy ($P = 0.005$) [37].

With a greater understanding of the contribution of other factors to long-term comorbidities and significant technical refinements in radiotherapy resulting in reduced late effects, even in the very young, more recently completed and current studies of radiotherapy have included children under the age of 3 years [15–21].

'Window' Chemotherapy

Interim chemotherapy to improve resectability of residual disease has been used with success in terms of second surgery rates and acceptable morbidity [20,38,39]. Such regimens include some combination of cyclophosphamide, etoposide and vincristine with the possible addition of carbo- or cisplatin. This strategy is the subject of ongoing study in the SIOP Ependymoma and ACNS 0831 protocols [15,16].

Adjuvant Chemotherapy

Most relapses occur at the primary site and, hence, focal radiotherapy is the standard of care for non-metastatic ependymoma. However, there are still significant numbers of metastatic relapses [40–42]. Craniospinal irradiation does not appear to have an impact when applied in the non-metastatic setting [17] and so there remains a requirement for alternative approaches with adjuvant systemic therapy.

An adjuvant chemotherapy strategy following surgery and radiotherapy in children with newly diagnosed intracranial ependymoma was initially piloted by Needle *et al.* [43]. Nineteen children aged from 3 to 14 years received systemic therapy comprising carboplatin, vincristine, ifosfamide and etoposide. The 5-year progression-free survival rate was 74%, which was superior to most reported contemporary series and suggested a role for adjuvant chemotherapy in improving tumour-related outcomes. Reported toxicity was restricted to myelosuppression. Adjuvant chemotherapy was also tested in the second AIEOP prospective study and in the ACNS 0121 study [20,39]. There

Table 3
Summary of infant ependymoma studies (studies including multiple histologies excluded)

Name of study	Number recruited	Year of recruitment	PFS (or EFS); OS
HIT-SKK 87 HIT-SKK 91 (as per 87 with IT MTX)	31 (9 had no radiotherapy)	1987–199?	3-year PFS 27.3% 3-year OS 55.9%
SFOP	73 (40% had no radiotherapy)	June 1990 – October 1998	4-year PFS 22% 4-year OS 59%
UKCCSG/SIOP	89 (42% had no radiotherapy)	December 1992 – April 2003	5-year OS 63.4%
HEADSTART III	19 (<10 years)	2004–2009	Supratentorial 3-year EFS 86% 3-year OS 100% Infratentorial 3-year EFS 27% 3-year OS 73%

PFS, progression-free survival; EFS, event-free survival; OS, overall survival.

is currently no established role for adjuvant systemic therapy outside trials, but it is being tested in currently recruiting, randomised studies [15,16].

Toxicity

In common with other paediatric brain tumours, long-term survivors of ependymoma will probably be affected by a constellation of late effects due to the effects of the tumour and its treatment. These include neurocognitive sequelae, endocrine abnormalities, second malignancies and adverse psychosocial effects [44–49]. Specific effects and their severity depend on the age of the patient, the treatment modalities received and the site and volume of radiotherapy treatment fields.

There is increasing recognition of imaging changes within the brainstem following radiotherapy in a proportion of patients [19,30,50–53]. These are most commonly asymptomatic and resolve spontaneously but can rarely progress to fatal brainstem necrosis. It is uncertain whether these changes are seen more commonly following PBT as the true incidence following treatment with X-rays is not defined. It is therefore a responsibility of the radiation oncology community to ensure long-term follow-up of patients receiving both X-rays and PBT to continue to gain a full understanding of the relative benefits and harms.

Management of Spinal Ependymoma

Spinal cord ependymomas are very rare in children. Gross total resection where feasible is the standard of care. Radiotherapy is generally recommended following incomplete excision, particularly for the less frequent grade II and III histologies. There is a lack of evidence regarding the utility of postoperative radiotherapy, with no consistent demonstration in tumour-related outcomes [54].

Management of Newly Diagnosed Metastatic Ependymoma

Disseminated disease is unusual at diagnosis and is more frequently encountered in relapsed disease. Variable management approaches are described and there is a paucity of evidence upon which to guide management decisions [55]. Resection of the primary tumour and any other areas of bulk disease should be attempted if possible. Adjuvant therapies depend on the age of the child. Craniospinal irradiation should be considered, depending on the age of the child. The optimum dose has not been established in a trial setting as these patients are relatively rare, but a dose of 36 Gy in 1.8 Gy fractions is standard with a boost to the primary tumour bed of 59.4 Gy and metastases. It is necessary to consider the tolerances of adjacent organs at risk, e.g. spinal cord metastases would generally be treated to around 50 Gy (conventionally fractionated). In younger children (for whom craniospinal irradiation results in unacceptable late toxicity), chemotherapy alone may be considered, or a combination of chemotherapy and focal radiotherapy.

Management of Recurrent Ependymoma following Focal Radiotherapy

Although recurrent ependymoma generally has a poor prognosis, a minority of children may be cured with a strategy of maximal tumour resection followed by radiotherapy. Re-irradiation of the primary site is described with apparent acceptable short-term toxicity, although doses described exceed normally accepted brainstem thresholds [56–62]. However, even where local control is achieved, patients may be subject to distant relapse.

For patients with distant relapses, surgical resection of the primary and maximal debulking of sites of metastatic disease should be considered, followed by craniospinal

irradiation and boost to the primary and sites of metastases [56], as described for newly diagnosed metastatic disease.

The role of re-irradiation with focal radiotherapy versus craniospinal irradiation upfront for patients with non-metastatic recurrences has not been established.

Various chemotherapy regimens have been tested in this setting with generally disappointing results [58,63].

The optimal management of recurrent ependymoma requires further evaluation and, where possible, patients should be enrolled in a clinical trial, such as the ongoing St Jude study [64].

Role of Novel Agents

Ependymoma response rates to conventional chemotherapy are modest. Effort is therefore being directed at evaluating the role of novel therapeutic agents based on targeting the increasingly recognised key molecular changes. A number of targeted agents have been tested in early phase trials, including the tyrosine kinase inhibitors erlotinib and gefitinib and the vascular endothelial growth factor inhibitor bevacizumab, but results so far have been disappointing [65–68]. The current SIOP Ependymoma II protocol adds the histone deacetylase inhibitor valproate to a cyclophosphamide, etoposide, methotrexate, carboplatin and vincristine combination in children under the age of 12 months or those for whom radiotherapy is otherwise contraindicated [15].

Follow-Up

A recent study confirmed the utility of scheduled radiological follow-up rather than imaging in response to symptoms only in terms of improved survival [69]. Standard follow-up regimens for intracranial ependymoma mandate MRI brain with gadolinium with a frequency of 3 monthly for around 1–2 years, then 4 monthly and then 6 monthly to 5 years. Beyond 5 years recommendations for MRI are variable. Some protocols advise stopping at 5 years with a low threshold for scanning in response to symptoms; others suggest continuing until aged 18 years. The spine should be imaged at least at suspected relapse and consideration may be given to annual spinal examinations according to trial or local protocols.

Age-appropriate neurocognitive testing should be carried out intermittently, e.g. at 2 and 5 years after the end of treatment and at age 18 years. Endocrinological assessment should be carried out at least annually to age 18 years. Ophthalmological assessments should be carried out where indicated and audiometry for those receiving platinum chemotherapy.

Outcomes

Five-year overall survival rates after gross total resection and focal radiotherapy are in the order of 75–85% [17–21]. These reduce significantly where there is subtotal resection, in very young patients and for those with metastatic disease at presentation.

Conclusion

Ependymoma in children and young people continues to present clinicians with challenges, both in terms of tumour outcomes and treatment toxicities. Surgery with gross total resection is the mainstay of treatment, followed by focal radiotherapy to doses up to 59.4 Gy. Although results for those with gross total resection are very encouraging, there is still a significant proportion for whom gross total resection is not possible, who present with metastatic disease or who relapse after standard therapy. Outcomes for these groups remain disappointing. Increasing understanding of the biological diversity and prognostic implications may enable more refined patient selection for standard treatments but may also provide targets for new agents, which may lead to improved outcomes in the future. Clinicians are to be encouraged to enter patients into clinical trials, where available, so that improvements in outcomes continue to accrue, with better understanding of this disease [70].

Conflicts of interest

The authors declare no conflicts of interest.

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