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Embryonal tumours of the central nervous system

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1. Introduction

Embryonal tumours are the most frequent brain cancers in children. Most occur before 15 years of age, with a peak between ages 5 and 10 years, but their incidence in infants is proportionally higher, accounting for 20–30% of all brain tumours in this age group. Other terms used to describe these tumours include small round blue tumours and primitive neuro-ectodermal tumours (PNETs). Five principal histological diagnoses are recognised: medulloblastoma, ependymoblastoma, supratentorial primitive neuro-ectodermal tumour (PNET), medulloepithelioma and atypical teratoid/rhabdoid tumour (ATRT) (Table 1), but medulloblastoma accounts for 70–80% of the total. Survival for patients with embryonal central nervous system (CNS) tumours has improved over the past 40–50 years. Advances in diagnostic imaging, neuro-anaesthesia, surgical techniques, improved delivery of radiation therapy and chemotherapy have each contributed and chemotherapy is now regarded as a standard treatment in most cases.

2. Epidemiology

Infants and children are most often affected, but these tumours also occur in adults. The annual incidence is estimated at 0.2–0.6 per 100 000 children per year [2–4]. Incidence rates and detailed distribution of histological subtypes are poorly documented, as most epidemiological studies report on medulloblastoma/PNET without subclassification. In a Sweden population-based study, the ratio of cerebellar medulloblastoma/PNET to other CNS sites was 4/1 [5], which differs significantly from the general statement of 10 to 30/1. The Surveillance, Epidemiology, and End Result (SEER) data suggest that, though the incidence of medulloblastoma is declining, the incidence of non-cerebellar PNET is increasing [6]. Geographical and temporal incidences may be variable [3,7]. The median age at diagnosis for medulloblastoma patients is 9 years (range 0–88 years), with two age peaks at 2–4 and 6–8 years [8]. There is a (65%) male predominance for medulloblastoma and supratentorial PNET.

Familial cases of medulloblastomas in twins or siblings have been reported [9,10]. Embryonal tumours of the CNS are observed in familial cancer syndromes such as Li–Fraumeni syndrome, Turcot syndrome and Gorlin's syndrome and in children with constitutional mutations of the *hSNF5/INI1* gene [11–14]. Pineoblastomas may arise in 5–10% of patients with bilateral retinoblastoma [15]. Finally, embryonal tumours of the CNS may arise in association with rhabdoid tumours of the kidney [16].

3. Natural history

All embryonal tumours of the CNS share in common their propensity to seed through the cerebrospinal fluid (CSF) pathways. The extent of disease at the time of diagnosis affects both the survival rate and survival time. Prognosis varies according to the histological diagnosis ranging from $<10\%$ for patients with rhabdoid tumours up to 70–80% for patients with non-metastatic medulloblastoma. So far as treatment is concerned, surgery and cranio-spinal irradiation are the main determinants of prolonged survival, regardless of the histological subtype [17,18].

4. Management

Because of the risk of seeding, initial investigations at the time of diagnosis include a search for leptomeningeal disease. Gadolinium-enhanced magnetic

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Table 1
Histological characteristics of embryonal tumours of the CNS [1]

	Medulloblastoma	PNET	Medulloepithelioma	Ependymblastoma	Rhabdoid tumours
Incidence	70–80%	10–20%	Rare	Rare	1–2%
Site	Cerebellum, fourth ventricle	Supratentorial spinal	Supratentorial and infratentorial	Supratentorial + +	Infratentorial and supratentorial
Histopathology	High density of small round/oval shaped cells with scanty cytoplasm and hyperchromatic nuclei	Similar to medulloblastoma	Mimics the embryonic neural tube with a neuroepithelium and usually multiple lines of differentiation	Features of PNET with ependymoblastomatous rosettes	Tumours containing rhabdoid cells with often variable component of mesenchymal, epithelial or primitive neuro-ectodermal cells
Rosettes	Homer–Wright (neuroblastic) rosettes	• Homer–Wright • Flexner–Wintersteiner (indicating retinoblastic differentiation)	• Ependymoblastoma • Ependymal	Multilayered concentric (ependymoblastomatous) rosettes	Homer–Wright and Flexner–Wintersteiner rosettes may be present in the PNET component
Immunoreactivity	Synaptophysin, NSE, neurofilament	Synaptophysin, NSE, neurofilament	Neuroepithelium, NSE, vimentin Tumour cells reflect the cell lineage	S 100, vimentin, cytokeratin, GFAP	• EMA, vimentin (rhabdoid component) • Variable expression in other areas
Variants	• Desmoplastic • With extensive nodularity • Large cell				

NSE, neuron-specific enolase; EMA, epithelial membrane antigen; GFAP, glial fibrillary acidic protein; PNET, primitive neuro-ectodermal tumour.

resonance imaging (MRI) scan of the brain and spine is the method of choice for detecting gross leptomeningeal seeding. CSF collection allows microscopic cytological examination, but the significance of positive CSF cytology is a constant matter for debate. Neither MRI scan nor CSF cytology alone is sufficient to detect seeding and the recommendation is to consider both investigations in every patient [19]. The staging system used in most reports is the 30-year-old Chang staging system, which was based on a review of surgical notes and autopsy cases [20]. With advances in imaging and management, this classification should now be obsolete and there is an urgent need to establish a new classification with clinical relevance. This is particularly evident for the T system, as there is no evidence that the tumour size influences survival. The distinction between M2 (seeding in the cerebellum and supratentorial compartment) and M3 (seeding in the spine) has no prognostic and therapeutic relevance either. New classifications have been proposed [21,22], but none has yet been agreed, so most cooperative groups still use the outdated Chang classification in their reports.

4.1. Surgery

Resection of the primary tumour is an essential component in initial management. However, the exact contribution of surgery to survival has been unclear until recently, partly because of the lack of systematic postoperative imaging studies. The first cooperative studies conducted by the Société Internationale d'Oncologie Pédiatrique (SIOP) and the North American Children's Oncology Group (CCSG) did not report any effect of the extent of resection on survival. By contrast, the more recent Children's Cancer Group (CCG)-921 study for medulloblastoma and PNET reported a $>20\%$ reduction in survival for medulloblastoma patients with >1.5 cm^2 residual tumour following surgery [23]. Although the survival rate for patients with complete resection was 40% compared with 13% for children with postoperative residue, the same study also showed no statistically significant benefit for surgical resection in patients with supratentorial PNET, possibly because of the small size of this subgroup [24].

4.2. Irradiation

Embryonal tumours of the CNS have a propensity to invade adjacent structures and to spread through CSF pathways. The understanding of these patterns and the disappointing results of focal radiotherapy in the first half of the 20th century led to the use of radiotherapy directed to the entire cranio-spinal axis [25]. In standard radiotherapy, the cranio-spinal axis dose is 23–36 Gy with an additional boost, to a total dose of 50–55 Gray, to the primary tumour site. Variations in the dose and

irradiation technique include (1) attempts to reduce the cranio-spinal dose in patients with no evidence of dissemination at diagnosis, (2) attempts at increasing the dose to the cranio-spinal axis in patients with high-risk features and (3) delivery of higher doses of radiotherapy using hyperfractionation, (4) attempts at delaying radiotherapy in infants and young children, (5) attempts to limit the extent of radiotherapy to the posterior fossa or the tumour bed in young children diagnosed with medulloblastoma, who are especially prone to its unwanted late effects.

4.3. Chemotherapy

The use of chemotherapy is controversial, especially in patients > 3 years old. Evidence that chemotherapy is effective in this group of tumours relies on *in vitro* and xenograft experiments and on phase II data [26]. Information from randomised phase III studies is sparse and the evidence that chemotherapy adds to the benefit of surgery and radiotherapy is weak. Nevertheless, most patients nowadays receive chemotherapy. Besides the possibility of a survival benefit, chemotherapy may be part of a strategy, in young children, to avoid or delay the use of cranio-spinal irradiation or, in average-risk patients, may be used as part of an investigational protocol aimed at decreasing the dose of cranio-spinal irradiation. On an experimental basis, intensive (high-dose) chemotherapy may be used in high-risk patients. However, despite promising response rates, particularly in medulloblastomas, the role of chemotherapy is still unclear.

Several agents have shown to be active in embryonal tumours of the CNS [26]. Most of the information on chemotherapy comes from phase II studies or infant protocols. However, it is important to recognise that response rates obtained after two courses of chemotherapy, the usual duration of this type of study, do not always predict the efficacy of a single agent or a combination of drugs and its contribution to improved survival. For instance, despite an excellent response rate in relapsed patients [27], the 'eight drugs in 1 day' protocol when combined with cranio-spinal irradiation gave disappointing survival rates in a randomised study [23]. The timing of chemotherapy is currently changing; in particular pre-irradiation chemotherapy is being abandoned and substituted by postirradiation chemotherapy.

4.4. Results of radiotherapy-based treatments in medulloblastoma

Both non-randomised and randomised trials have contributed to the definition of 'standard management' for medulloblastoma patients. However, there may be considerable differences between institutions and national groups, particularly with regard to the dose of cranio-spinal irradiation and the use of chemotherapy.

4.4.1. Randomised trials

The first cooperative trials in medulloblastoma patients were developed in the late 1970s when the CCG in North America and the SIOP set up separate randomised trials with a similar design. No risk groups were identified in these early trials and all patients were eligible for randomisation. The CCG-942 and the SIOP 1 studies both compared standard cranio-spinal radiotherapy with or without the addition of vincristine and CCNU (and prednisone in the CCG study). SIOP 1 was closed early after 4 years because of a 'significant' difference in survival, favouring the chemotherapy arm. This 'difference' disappeared with more follow-up, but the subset of children with partial or sub-total resection or brainstem involvement still showed a 'significant' survival benefit with chemotherapy [28][1]. The CCG study reached similar conclusions and identified a group of high-risk patients with large tumours and/or metastatic disease who apparently benefited from chemotherapy [29].[1] Although flawed because of (a) incomplete staging information in most patients and (b) the absence of a central pathology review, these early trials provided substantial information. More randomised trials were conducted in the mid-1980s by SIOP and CCG. The SIOP 2 trial divided patients into low-risk and high-risk groups, according to the extent of surgical resection, the presence of brainstem involvement and/or metastatic disease. The aim of SIOP 2 was to assess the value of preradiotherapy chemotherapy and a secondary aim was to assess two different doses of irradiation for 'low-risk' patients. Only two-thirds of the eligible patients in the 'low-risk' group were randomised in the radiotherapy dose and the number of patients per arm was $\leqslant 40$, so the trial was inconclusive [30]. The subgroup of 'low-risk' patients treated with preradiotherapy chemotherapy and reduced-dose radiotherapy fared poorly. The authors concluded that, overall, chemotherapy provided no survival advantage. They speculated that this was because the particular combination of drugs chosen and their doses were not optimal. There were two other conclusions. First, and based on their review of the operation imaging, they concluded that brainstem involvement and the extent of surgical resection were not prognostic and, second, they considered that reduced dose cranio-spinal irradiation was not better than the standard dose.

[1] Editor's footnote: Of course, this kind of retrospective subset analysis may not be valid; it can only define a point of interest for future prospective investigations.

The PNET III study, which followed SIOP 2, compared craniospinal irradiation with preradiotherapy chemotherapy followed by the same dose and technique of irradiation. Accrual rate in this study has been lower than expected, and the final conclusions of this trial, opened in 1992, have little relevance in 2002. This study reports a significant difference in the event-free survival in favour of the chemotherapy arm. The inclusion of patients without CSF cytology documentation, disparity in the timing and the method of assessment of surgical resection, the grouping of patients with total and sub-total resection in the same trial, the use of high-dose prophylactic craniospinal radiotherapy are major weaknesses which lessen the power of this randomised study [31]. In the meantime, the CCG conducted a randomised trial comparing the 'eight drugs in 1 day' [27] to a regimen containing CCNU, vincristine and prednisone (CVP) in high risk medulloblastoma, defined according to the conclusions of the CCG 942 study. In the former arm, radiotherapy was given after two cycles of chemotherapy. In the latter arm, chemotherapy was given after irradiation. This trial showed a significant benefit in event-free and overall survival for patients allocated to the CVP arm [23]. This difference was attributed to one, two or all of the three possible factors—the chemotherapy regimen, the delay in radiotherapy administration, and the vincristine dose intensity. This trial also highlighted the major influence of resection on outcome and confirmed the unfavourable impact of neuraxis dissemination at diagnosis on survival in both medulloblastoma and supratentorial PNET. Another randomised trial, conducted by the German Society of Pediatric Hematology and Oncology (GPOH), compared preradiation chemotherapy with 'maintenance' chemotherapy (after irradiation). Their conclusions were that delaying cranio-spinal irradiation has a negative impact on outcome [32].

Successful attempts in pilot studies suggesting that the dose of cranio-spinal irradiation for non-metastatic medulloblastoma patients could be safely reduced has prompted the CCG to conduct a randomised study comparing a neuraxis dose of 36 versus 23.4 Gy, with an identical dose (54 Gy) to the posterior fossa. No chemotherapy was given in either arm. This study was closed before completion, because of an excess of spinal recurrences in the reduced dose radiotherapy arm [33]. However, among the 126 patients randomised in this study, only 71 were considered assessable after central review, so limiting its credibility. A subsequent randomised trial designed to compare 'standard' cranio-spinal irradiation (36 Gy) to reduced dose plus chemotherapy failed to recruit, leaving unresolved the dilemma between low-dose and high-dose neuraxis irradiation. The randomised trial conducted by CCG and the Pediatric Oncology Group (POG), comparing two different regimens of chemotherapy (vincristine–CCNU–cisplatin versus vincristine–cyclophosphamide–cisplatin) given after reduced dose cranio-spinal irradiation in low-risk patients, has recently closed and preliminary results are awaited.

4.4.2. Single-arm studies

Improvements in neuro-imaging techniques have made it possible to stratify patients according to the extent of disease at diagnosis and the postoperative assessment of surgical resection. Using this criteria, an 'average risk' patient has been defined. Such children especially those <9 years old, may benefit from reduced dose irradiation to the cranio-spinal axis, thereby reducing the long-term neuropsychological consequences of high dose irradiation [34,35]. Experience with reduced dose cranio-spinal irradiation was first reported from single or limited centre studies with small numbers [36–38]. Most of these patients had non-metastatic medulloblastoma, and the doses of radiotherapy given to the neuraxis were between 18 and 26 Gy. The French group M7 reported a 72% 7-year event-free survival in non-metastatic patients using preirradiation chemotherapy and a 27 Gy dose of cranio-spinal irradiation [39]. The CCG conducted a pilot study using a reduced dose of cranio-spinal irradiation and a combination of vincristine, CCNU and cisplatin given after radiotherapy in children with non-metastatic medulloblastoma. Progression-free survival was 86% at 3 years and 79% at 5 years in this experience [40]. Despite concerns over the hearing toxicity of cisplatin given after irradiation, this schedule has been adopted as the standard treatment arm for the recently closed randomised CCG/POG trial and the future SIOP PNET4 trial for average-risk medulloblastoma patients.

Alternative techniques of irradiation have been proposed in order to improve outcome and/or to reduce long-term toxicity. The aim of hyperfractionated radiotherapy is to deliver a higher dose of radiation to the tumour with equivalent toxicity to the surrounding normal structures. Several limited studies have evaluated the feasibility of this technique in the setting of cranio-spinal irradiation [41–43]. In the PNET4 trial of SIOP, the effect of hyperfractionation will be compared with standard 'reduced dose' neuraxis irradiation in average-risk patients. Patients in both arms will receive postirradiation chemotherapy with vincristine–CCNU and cisplatin. Conformal irradiation to the tumour bed is also under evaluation, with the objective of determining whether the standard 54 Gy dose to the posterior fossa can be replaced by a more focused 54 Gy to the tumour bed and a lower dose to the surrounding posterior fossa. Quality of irradiation is important for optimal results [44–46]. Better survival may be achieved in large centres with better radiotherapy resources [28,47].

4.5. Is there a standard treatment for patients with high-risk medulloblastoma?

The management of patients with high-risk medulloblastomas varies, but overall survival for patients with metastatic disease shows little difference between series and is in the range of 40% [28–30,48]. The CCG 921 study has suggested that delayed irradiation may be detrimental in high-risk patients and the current recommendation is to use standard dose cranio-spinal irradiation immediately after surgery, then chemotherapy. In the POG 9031 cooperative study, doses of irradiation up to 40 Gy to the cranio-spinal axis were used for children with M2-M3 disease. Preliminary results suggest a substantial improvement in survival for metastatic patients [49]. However, follow-up data on neuro-intellectual and endocrine outcome are essential before accepting this option as 'standard treatment'. Several single arm institutional or cooperative studies are in progress, aiming to evaluate the role of either chemotherapy during irradiation or more intensive chemotherapy after cranio-spinal radiotherapy [50]. The optimal management of patients with incomplete resection and of those with M1 disease are still uncertain, but these patients are currently treated along the lines of protocols for metastatic patients.

4.5.1. Is there a role in surveillance scanning follow-up for patients with medulloblastoma?

Routine neuraxis scanning is standard practice in the management of patients with medulloblastoma. Surveillance schedules vary from an interval of 3–6 months for the first 2 years. CSF cytology may be included. The value of surveillance is uncertain because in some studies, the outcome of patients who develop clinically silent recurrence is dismal, which suggests that there may be no benefit in detecting recurrent disease before the onset of symptoms [51,52]. However, other reports have suggested longer survival when relapses are discovered asymptomatically [53–55]. These studies may have more frequent surveillance and therefore may detect recurrences earlier, before they become clinically symptomatic.

4.5.2. What is the role of high dose chemotherapy in recurrent medulloblastoma?

Recurrences occur in 30–50% of patients and may be local in the posterior fossa, distant or combined. Relapses outside the CNS are very rare. Treatment options are limited and 5-year survival is $<10\%$ in children previously treated with cranio-spinal irradiation [23,51]. Pilot studies have suggested that some patients may benefit from salvage strategies including high dose chemotherapy and stem cell rescue [56]. Such patients seem to be those who have a relatively late recurrence, those with a focal relapse and those who, at the time of high-dose chemotherapy, have minimal residual disease [57]. Criteria for management at the time of recurrence are poorly defined and may benefit from a better understanding of the factors influencing the length of survival [51].

5. Results of treatment for supratentorial PNET (sPNET)

Information on the best management of sPNET is sparse and the literature is limited to retrospective reviews of small numbers of patients, treated in variable ways [58–61]. Although sPNET and medulloblastoma share the same histological features, children with sPNET, especially those who present with dissemination at diagnosis, have a poorer survival. There has been only one prospective study, conducted alongside the CCG 921-randomised trial for medulloblastoma, that has included sPNET patients [62]. For children $>$ 18 months of age and treated with postoperative irradiation and chemotherapy in this study, the 3-year progression-free survival was 45%. In this subset of 57 patients, there was no difference between the 2 chemotherapy arms in progression-free or overall survival. Analysis of prognostic factors in this study and others are limited by low statistical power, because of the small number of patients. This protocol reported a better outcome for patients with primary pineal tumour (pineoblastoma) and a trend towards better survival for patients with completely or near completely resected tumours [24,63]. Dissemination at diagnosis is associated with a very poor outcome. Most cooperative groups treat patients with sPNET along the lines of high-risk medulloblastomas protocols. In the PNET3 study, patients with non-metastatic sPNET were randomised to either cranio-spinal irradiation or chemotherapy followed by cranio-spinal irradiation, but the small number of randomised patients precludes any statistically valid conclusions.

6. Treatment of infants with embryonal tumours

Over the last 20 years, postsurgery chemotherapy has been used in young children in order to delay or avoid the use of irradiation. Following encouraging reports from single centres using this policy [64–66], cooperative groups have conducted larger studies. POG used a cyclophosphamide, vincristine, etoposide and cisplatin combination administered for 1 year in children 24–36 months of age at diagnosis and for 2 years in younger children [67]. Patients were scheduled to receive cranio-spinal irradiation at the completion of chemotherapy. The CCG used a similar approach, but a different chemotherapy regimen [68]. The 2-year survival rates

for patients with posterior fossa medulloblastoma/PNET in these studies were 34 and 22%, respectively. In the POG study, the outcome was better for non-metastatic patients who had a complete resection. The Société Française d'Oncologie Pédiatrique (SFOP) and the GPOH have identified a subset of patients with non-metastatic disease who seem to do well without irradiation [69,70], but the United Kingdom Children's Cancer Study Group (UKCCSG) did not reproduce these results [71]. Is this strategy valid in 2002? Most patients develop progressive disease while on chemotherapy and the average time to relapse is short [72]. SFOP has used high dose chemotherapy followed by posterior fossa irradiation for young children with relapse at the primary site [73]. Because of encouraging results, several cooperative groups are investigating high-dose chemotherapy as a first-line option [74], or conformal radiotherapy to the primary tumour for those with non-metastatic medulloblastoma. Strategies that avoid or delay irradiation in supratentorial PNET are disappointing. Most children fail during chemotherapy and very few are salvaged by cranio-spinal irradiation [63,75]. More intensive chemotherapy is under investigation for this group of patients. A recent study of high-dose chemotherapy with stem cell transplant without irradiation in young children with brain tumours resulted in a 43% event-free survival in a cohort of 14 patients with sPNET, suggesting a possible benefit of increased dose intensity [74].

7. Results of treatment in pineoblastoma

Pineoblastomas are classified amongst the supratentorial PNET, but there are specific reports on this anatomical entity. In very young children, results of treatments aiming to avoid or delay radiotherapy are disappointing. Most children treated in this way have a rapidly progressive course and die within 2 years of diagnosis [63,75]. By contrast, older children treated with cranio-spinal irradiation with or without chemotherapy have a similar prognosis to those with posterior fossa medulloblastoma [63].

8. Results of treatment in ependymoblastomas

Ependymoblastoma usually develops above the tentorium, in the cerebral hemispheres, in relatively young children and is usually massive at the time of diagnosis. It is very rare. In a review of the literature, Cervoni and colleagues collected 28 cases of ependymoblastoma reported between 1970 and 1994 [76]. None of the children was alive at the time of the publication and the average survival time was 8 months. Some ependymoblastomas arise in the sacrococcygeal region [77]. The prognosis is better than for those arising in the CNS.

9. Is there a standard treatment for atypical teratoid/rhabdoid tumours?

These tumours are extremely aggressive and occur in young children, which limits the use of radiotherapy. The median survival from diagnosis is generally only 6–12 months [78], with the length of survival primarily related to the extent of resection. Although no prospective study has been conducted, rhabdoid tumours rarely respond to chemotherapy. Treatment programmes are often derived from rhabdomyosarcoma protocols because of reported possible effects [79]. Most authors include intrathecal chemotherapy. The number of reports on high-dose chemotherapy is too small to draw definite conclusions about its value. The role of radiotherapy, and the dose and extent of the field are still poorly defined.

10. Future directions

The management of embryonal tumours of the CNS is based on the historical experience of the moderately successful management of medulloblastoma patients. However, many aspects of the current management are not satisfactory. Its neuropsychological and cognitive consequences for the immature and/or growing brain mean that radiotherapy, as currently delivered, is a compromise rather than a popular therapeutic option. Currently, clinical trials are designed to determine whether, for non-metastatic patients, the dose of cranio-spinal radiotherapy can be safely reduced. High-dose radiotherapy is still required for patients with metastatic medulloblastoma. The paucity of biological markers with prognostic significance is one of the main limiting factors for the development of new treatment strategies. Identification of such markers might allow the development of a new and accurate 'staging' system and so that treatment can be tailored to the behaviour of the tumour. In this regard, *TrkC* or *HER-2* and *HER-4* or *MYC* mRNA [80–82] are promising. Perhaps a new era in the management of these tumours—a 'molecular prognostic era', now central to the management of patients with another neural tumour '*neuroblastoma*'—is about to begin.

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