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Central nervous system tumours in adolescents

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Abstract

Adolescents with brain tumours have been, and in most cases still are, haphazardly assigned, on referral, to either 'paediatric' or 'adult'-based treatment centres. In this age group, there is therefore a history of inconsistent treatment, delivery of inappropriate 'maturity-related' care and a reduced chance of gathering vital biological, clinical and treatment-related information germane to this group of patients and their tumours. These days, adolescents with brain tumours should be actively targeted for recruitment into clinical trials and admission into dedicated neuro-oncology centres or programmes that can deliver the necessary and age appropriate multidisciplinary management.

Keywords: Adolescents; Brain tumours; Treatment; Multidisciplinary management

The distinction between paediatric and adult brain tumours is arbitrary. This point is especially relevant to the management of adolescents whose brain tumour treatment will differ if they are referred to a paediatric centre, an adult unit, or a facility which manages patients of all age groups.

The term 'paediatric brain tumours' may alternatively delineate a group of histologically-distinct tumours or encompass patients within a certain age range. For example, atypical rhabdoid teratoid tumours and choroid plexus carcinoma occur predominantly in young children and are exceptional in adults. In contrast, both medulloblastoma and ependymoma occur in a wider range of ages. When defined by age, the upper limit of the 'paediatric' range varies arbitrarily. Surveillance, Epidemiology and End Results (SEER) data includes patients between either 0 or 14 years or between 0 and 19 years of age [1] and most North American trials enrol patients up to the age of 21 years. By contrast, entry into European brain tumour treatment trials such as Société Internationale d'Oncologie Pédiatrique (SIOP) 1, SIOP 2 and primitive neuroectodermal tumour (PNET) 3 was restricted to patients below the age of 15 years [2–4]. Such seemingly random age cut-offs lead to inconsistencies in the treatment of adolescents with central nervous system (CNS) tumours primarily related to the unit to which the patient is referred. When a low upper age limit is a criterion for accessing paediatric oncology services, adolescents tend to be cared for by adult physicians. The relevance of this division by age is questionable, especially for this group of patients which probably shares many medical and social characteristics with younger children than most adults. This review emphasises that adolescents with CNS tumours are a distinct group that will benefit from medical care sensitive to the physical and social challenges that they face. At the same time, access to clinical trials must be encouraged at every opportunity to facilitate and improve the acquisition of essential data relevant to this age group.

1. Epidemiology

The annual incidence of brain tumours in adolescents 15–19 years of age varies according to the registry reporting the data. After Hodgkin's disease, brain tumours and gonadal germ cell tumours compete for the second most common group of cancers in adolescents [5]. The lowest recorded incidence rates for brain

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tumours are in Puerto Rico, Costa Rica and New Zealand (10, 12 and 12 cases/million/year, respectively), whereas the published incidences in Australia and the US are well over 20 per million per year [5]. These differences have not yet been explained, but some registries may have incomplete data. The incidence of brain tumours in the 15–19-year-old age group is lower than in younger children. SEER data reveals a decrease in the incidence of brain tumours with increasing age: the proportion of brain tumours in the 0–4-year-old age group is nearly 50% higher than in the 15–19-year-old age group [6]. This discrepancy is largely explained by the much lower incidence of ependymomas and PNETs in the adolescent population (see Table 1).

Medulloblastomas and other so-called 'embryonal' tumours, which account for nearly 20% of all brain tumours in the younger group, represent only 7.3% of all CNS tumours in adolescents [7].

2. Pattern of care and participation in protocols

Adolescence is increasingly identified as an age group with specific medical and psychosocial needs. The problem in excluding adolescents and young adults from various paediatric and adult trials is that we have missed, and are continuing to miss, collecting valuable outcome data for this group of patients. Treatment considerations, therefore, cannot be based on survival data for this specific age group, but have to be based on information extrapolated from studies conducted in younger or older patients. The absence of an available clinical trial increases the potential, even in the same institution, of discrepant management. There are numerous barriers to participation in clinical trials. Many paediatric protocols are limited to patients aged less than 18 years old—in some cases, even to those aged less than 15 years old. However, most adult protocols prohibit the inclusion of patients aged less than 18 or 21 years old. In contrast, when protocols have no age limit, institutions may have strict admission policies that deny adolescents access to paediatric care. Other barriers may be physician- or patient-related. It is probable that the fears of having to cope with an adolescent or young adult, who may be less compliant and more time-consuming may contribute, in an 'adult' unit, to limiting their participation in clinical trials. The issue of consent in this age group also poses challenges and therefore may be a limiting factor. In the event of the adolescent patient being a minor, yet able to give consent, so-called 'Gillick competence', that consent must be obtained in addition to the consent of the parents or legal guardian. Specific information on adolescent participation in paediatric or adult brain tumour clinical trials is sparse. In 1993, the Commission on Cancer of the American College of Surgeons conducted a survey and examined clinical trial participation according to various factors, including the type of cancer [8]. Two hundred and twenty-six hospitals participated, representing an estimate of nearly 30% of childhood cancers in the US during the previous year. Patients, stratified into specific diagnostic groups and for whom there was an appropriate clinical trial, were analysed by trial participation. Patients with brain tumours treated in paediatric centres were more likely to be treated 'on trial' than patients treated in other types of facilities. However, only 25% of patients aged between 15 and 21 years receiving care in paediatric centres were registered on trials—yet this figure was almost twice as high as the 13.5% of similar patients treated in adult facilities. Although trial participation for adolescents was far superior to the estimated 2% participation by adult cancer patients, the overall figures for this age group are significantly worse than those for younger children. Statistics from national cancer registration from England for the period of 1995–1997 show that less than 30% of CNS tumour patients diagnosed in the 15–19-year-old age group are referred to paediatric oncology centres and registered with the United Kingdom's Children Cancer Study Group (UKCCSG) [9]. This poor registration of adolescents has negative implications, as it precludes a meaningful analysis of specific main determinants of outcome such as tumour biology, treatment specifics (such as the extent of surgery, and quality of postoperative management) and pattern of relapse. Sadly, there has been no study to date examining outcomes for adolescents with brain tumours in relation to patterns of organised care so the impact of centralised treatment on this patient group is still unknown.

Table 1
Age-specific CNS tumour incidence rates, per million per year, in the United States of America (USA), 1986–1995 [6]

CNS tumours	<5 years	15–19 years
Total	36.0	20.2
Astrocytoma	15.0	12.3
Medulloblastoma	9.6	2.5
Ependymoma	5.6	1.1

CNS, central nervous system.

3. Management of specific tumours in adolescents

During the past 20 years, studies performed by several cooperative groups have evaluated the correlation between the extent of tumour resection and outcome in the treatment of several types of paediatric brain tumours. It is now well established that the degree of surgical resection is one of the main determinants of survival in paediatric medulloblastoma, ependymoma

and glioma [10–12]. In contrast, the degree of resection in germinoma has no prognostic value so attempts at aggressive surgical management should be discouraged. In an analysis of children entered into three Children's Cancer Group (CCG) studies for high-grade glioma and medulloblastoma/PNETs, Albright and colleagues reported a greater extent of surgical resection when tumour surgery is performed by dedicated paediatric neurosurgeons [13]. This suggests different practice patterns between paediatric neurosurgeons and general neurosurgeons. The approach of the general neurosurgeon may well be influenced by the common treatment practice of adults for malignant glioma, in whom the usually poor outcome is not significantly altered by the degree of resection.

Particular issues regarding the management of medulloblastoma, high-grade glioma, germ cell tumours, craniopharyngioma and other pituitary tumours in the adolescent age group are now discussed in more detail.

3.1. Medulloblastoma

There is no study specifically reporting upon the features and the outcome of medulloblastoma in adolescents. Age has been a limiting factor for inclusion of adolescents in the SIOP cooperative trials (SIOP 1 and 2, PNET 3) which were only open to children aged less than 15 years old [2–4]. By contrast, the German and the French groups, Gesellschaft fur Padiatrische Onkologie und Hamatologie (GPOH) and Société Française d'Oncologie Pédiatrique (SFOP), respectively, have traditionally included adolescents and young adults in their studies [14,15]. The first clinical trial for medulloblastoma conducted by the United States Children Cancer Study Group included patients up to the age of 16 years [16]. Most of the subsequent CCG and Pediatric Oncology Group (POG) trials included adolescent and young adults up to 21 years of age. However, the true proportion of adolescents in these clinical trials, although believed to be low, is uncertain, because the results are invariably reported after patient stratification into $<$or $\geqslant$10-year-old groupings.

Three main factors seem to explain the poor accrual of adolescents into medulloblastoma trials, as follows: (1) the belief that differences in doses of prophylactic craniospinal radiation have little, if any, impact on the neuro-intellectual outcome of adolescents [17], (2) data from retrospective series which show that treatment with surgery and standard dose craniospinal radiation alone is associated with an 'acceptable' 5-year survival rate, of around 60% [18], and (3) some evidence that tolerance to postradiation chemotherapy is poorer in the adolescent and young adult than in the young child [18,19]. These points are not a cause for complacency in this group of patients (40% of whom still die from their disease) in view of the fact that the management of paediatric medulloblastoma has evolved considerably over the last two decades. Whilst adults are usually treated with higher doses of craniospinal radiation and no chemotherapy, the practice in younger children is aimed at decreasing late toxicities by reducing the dose of craniospinal radiation and introducing what paediatric oncologists hope is more effective chemotherapy. In some cases, tumour biology is now incorporated into the treatment stratification.

Three-year event-free survival (EFS) rates in young children with 'average-risk' medulloblastoma (defined as those with a postoperative primary tumour residue of less than 1.5 cm^2 and no evidence of seeding), treated with reduced dose craniospinal radiation and chemotherapy, can be as high as 86% [20]. Aiming at reducing long-term sequelae, current and planned paediatric studies are assessing further reductions of craniospinal radiation dose and new techniques of radiation. However, it is possible that adolescents with medulloblastoma will not benefit from advances in radiation techniques and chemotherapy protocols anticipated in younger children. Several paediatric studies have also highlighted the role of quality control in radiation treatment of medulloblastoma and cooperative trials are now incorporating quality control in their treatment design [21]. By contrast, reports on the treatment of medulloblastoma in adults reveal considerable diversity in the radiation techniques used, either in terms of dose or field or both [18]. Interestingly, relatively high survival rates have been reported in adolescent and adult medulloblastomas by oncology teams experienced in treating paediatric brain tumours [22–24].

3.2. High-grade gliomas

The general outlook for patients with high-grade gliomas (HGG) is poor, regardless of their age, and most oncologists consider radiation as a standard palliation for this tumour type. Although the advantage of aggressive surgical 'debulking' is still a matter of debate in 'adult' practice, it has proven to be of benefit in the paediatric age group. Chemotherapy may also play a role in improving survival in childhood HGG. An overall survival of 33% at 5 years was obtained with postoperative radiation followed by chemotherapy in the CCG 945 trial [25] which is significantly better than the approximately 10% 5-year overall survival rate in adult clinical trials [19]. The CCG 945 trial, enrolling 172 patients between 18 months and 21 years of age, demonstrated no difference between the two randomised chemotherapy regimens—'8 drugs in 1 day' compared with the much simpler two-drug regimen comprising vincristine and lomustine (CCNU). 88 patients (51%) were older than 10 years, but, as in many other trials, no specific information is given about the

adolescent group. Studies performed on tumours from this cohort have shown that the prognosis in children with malignant gliomas can be influenced by molecular changes in tumour cells. In analysing over 100 specimens from this study, Pollack and colleagues reported an increased expression of p53 in 36% of HGG in children between the ages of 10 and 18 years [26]. A strong inverse association between p53 overexpression and outcome has been found in HGG in childhood [27]. This contrasts with adult series, in which overexpression occurs with a similar incidence of 40%, but with no prognostic association [28]. It is likely, therefore, that childhood and adult HGG do not share the same biology and children and adolescents with HGG are more likely to benefit from aggressive management. In the presence of now recognised favourable features (a) complete resection and (b) no overexpression of p53, survival rates of up to 70% have been documented in this age group [27].

3.3. Germ cell tumours (GCT)

Malignant intracranial germ cell tumours (MGCT) tend to occur in adolescents and young adults, with a median age of 12–15 years. In 'pure' germinoma patients, high survival can be obtained with craniospinal irradiation alone, but the management of non-germinomatous MGCTs requires intensive chemotherapy followed by focal or craniospinal radiation [29] (Fig. 1). The combination of chemotherapy and focal radiation has now also been proposed as an alternative in germinoma, with the aim of decreasing the harmful 'late effects' of extensive whole brain and spinal radiation [30]. Survival rates of >90% have been reported in several germinoma series, while survival in non-germinomatous MGCT series is in the range of 70% [31]. These encouraging results have been consolidated through the development of cooperative studies, originally initiated in Germany and in France by national paediatric oncology groups (GPOH and SFOP), but extended by SIOP, and have always included adolescents and young adults. SIOP is currently conducting a large international cooperative trial that has so far enrolled over 300 patients with intracranial GCT since 1996 [32]. The challenges of chemotherapy management in this group of patients, especially those with complex endocrine disorders, including diabetes insipidus, has been highlighted by a study conducted by SFOP [30]. The safest way to guarantee the most appropriate management when chemotherapy is part of the treatment regimen is for the patient to be included in a cooperative trial, thereby facilitating access to specific chemotherapy guidelines, data centres and/or trial investigators.

In view of the high cure rate, especially for patients with germinoma, 'quality of cure' is now a main focus of interest in CNS-MGCT treatment. Short- and long-term side-effects are influenced by the type of treatment, particularly the specific chemotherapy agents used, and the technique and dose of radiation therapy. Large cooperative trials conducted by SIOP and Children's Oncology Group (COG) now include neuro-psychological testing and quality of life assessments amongst their objectives in order to define the range of late effects arising from variation in factors such as age, tumour type and location and treatment modalities.

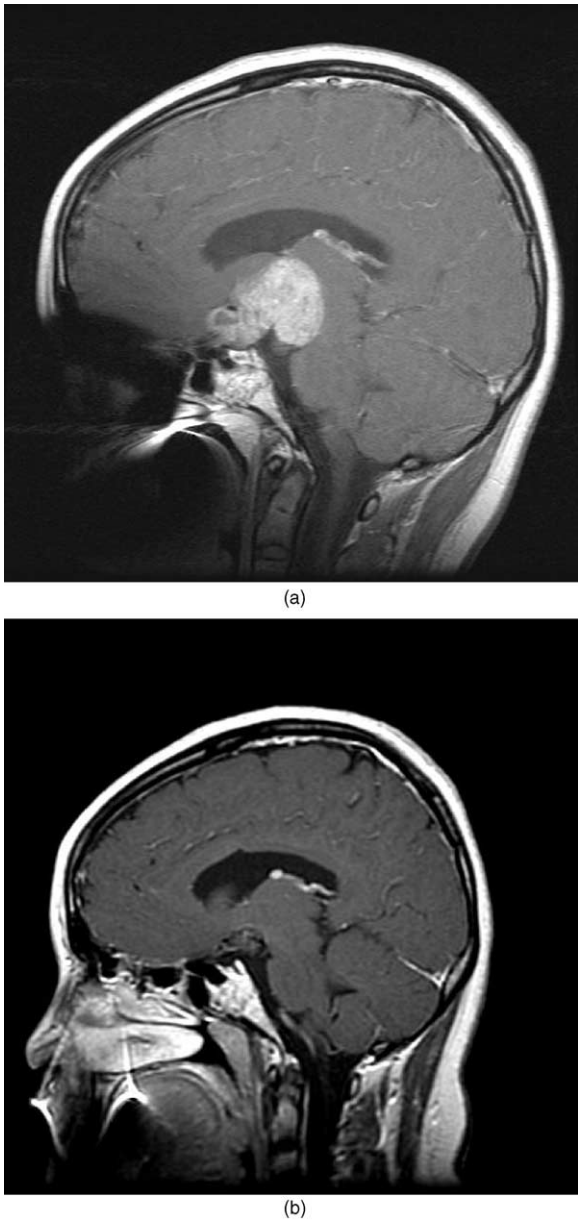

Fig. 1. Sagital postgadolinium enhanced magnetic resonance imaging (MRI) images of an adolescent with a suprasellar secreting germ cell tumour at presentation (a) and 2 years following successful treatment with chemotherapy and focal radiation (b). Severe fluid and electrolyte abnormalities, encountered following the administration of cisplatin, ifosfamide and etoposide-containing chemotherapy, on the background of diabetes insipidus, resolved with appropriate management.

3.4. Craniopharyngioma and pituitary tumours

These neoplasms arise in the sellar or suprasellar region and are the most common tumours causing hypopituitarism. Craniopharyngioma and pituitary tumours are histologically benign and therefore they do not metastasise. Craniopharyngiomas are nevertheless amongst the most complex tumours of childhood and adolescence, yet patients are often not seen by neuro-oncologists. The main challenge in managing the patient with a craniopharyngioma is to minimise the treatment-related morbidity which is, in turn, dependent upon the site, size and invasiveness of the tumour, the surgical approach and, in some cases, the postoperative treatment. Craniopharyngiomas in adolescents do not differ from craniopharyngiomas in younger children. Surgery aiming for a complete tumour resection is the treatment of choice advocated by some authors but, because of the risk of hypothalamic damage, others recommend limited resection followed by focal irradiation [33]. Results of treatment in patients with craniopharyngioma should not only provide resection rate and survival data, but also information on co-morbidity, such as endocrine dysfunction, obesity and neuro-behavioural and cognitive outcome. Because there are no randomised cooperative studies, possible improvements in the management of craniopharyngioma are not yet assessable and formal comparison between treatment options is not possible. Follow-up of patients with craniopharyngioma is often complex and, reflecting the multiple system morbidity, may involve and require care by many different disciplines such as endocrinology (endocrine dysfunction), neurology (seizures, neurological deficit), ophthalmology (visual deficit), dietician (obesity), psychiatry (behavioural issues), and respiratory medicine (sleep apnoea). Some morbidities, particularly behavioural and memory problems, affect social and learning capacities so specific attention also needs to be directed to educational reintegration. The '*sine qua non*' of a good paediatric neuro-oncology programme is the provision of this pattern of multidisciplinary support, coordinated by the neuro-oncologist, which is highly appropriate and essential for the 'best outcome'. However, there is generally a reluctance to transfer these patients, who have a 'benign' tumour and often do not need postoperative irradiation or chemotherapy, to such comprehensive care programmes. A better understanding of the complex follow-up needs of the craniopharyngioma patients may persuade neurosurgeons and radiotherapists that there is a genuine benefit from their integration into these programmes.

The prolactinoma is the most common pituitary adenoma in adolescents, followed by corticotropinoma and somatotropinoma [34]. Compared with adults, non-functioning adenomas are rare in adolescents. Consequently, children and adolescents with pituitary tumours are often not seen in paediatric neuro-oncology programmes. Their management is either medical (with dopamine agonists and somatostatin analogues for prolactinomas, somatotropinomas and thyrotropinomas) or surgical (corticotropinoma and non-secreting adenoma). If medical management fails, surgery and radiation treatment may be necessary. Because of their rarity, there are few published studies of pituitary adenoma in children and adolescents, and these patients are often included in 'adult' reports. Disappointingly, there is currently no cooperative study focusing on pituitary tumours in children and adolescents. The management of these tumours has certainly benefited from advances in the diagnosis and treatment of these tumours in adults, but the benefit of most pituitary adenoma treatments for children and adolescents still needs to be proven.

4. The adolescent and the neuro-oncology team

The diagnosis of a CNS tumour has an impact over and above that of other types of cancer in this age group. Particular to the adolescent with a CNS tumour is the risk of developing physical and intellectual handicap as a result of the disease or its management. Therefore, the threat to independence and normality is even more pronounced in this population. The patient, their family and the medical team develop 'triangular' interaction. Depending upon the social situation, the patient's partner may also be involved since the consequences of the tumour and its treatment often affect the relationship of the patient with friends, particularly their partner. Specific attention should be directed to communicating directly with the patient and, sometimes, their friends and partner too. Parents tend to underestimate their son's or daughter's maturity and may express the wish to exclude the patient from the initial disclosure and important follow-up meetings. Defining the appropriate relationship may be a challenging business, but oncologists should not exclude the adolescent from any decision-making. This is even more important when the patient has a neurological handicap, which may affect their self-esteem. Ultimately, the patient and their family have to face the diagnosis, comprehend all issues in relation to the treatment and understand the possible physical and psychological implications, as well as their social and economic consequences.

For many years, issues related to the diagnosis of a brain tumour have been restricted to their surgical and medical management. With improvements in survival, particularly for children with brain tumours, concerns have been raised regarding the social, academic and professional reintegration of long-term survivors. Adolescents, like children, benefit from multidisciplinary

support, which should include physical, social and cognitive rehabilitation teams incorporating physiotherapists, occupational therapists, speech therapists, social workers, neuropsychologists and psychologists. Brain tumour support groups for adolescents and young adults may provide the opportunity to socialise, reduce isolation and establish meaningful relationships (see Fig. 2). Many neuro-oncology programmes have integrated these support groups into their activities [35,36]. Although the health care team is, appropriately, still viewed as the primary source of information, adolescents are now becoming increasingly adept at accessing the web for further information. Recent work by our own team has demonstrated the variable quality of this information in the area of paediatric oncology, but this should not preclude the encouragement of using this format in patients' 'health information' packages [37]. Guidance on how to search for and judge the quality of the information should be given—Table 2 includes two websites that provide information on this subject, as well as other sites that an adolescent with a brain tumour may find useful.

5. Treatment failure and palliative care

Identification of tumour recurrence is one of the most challenging experiences for an oncologist dealing with adolescents. Various reactions, some of them directed towards the competence of the oncologist and their team, can be expected. Treatment refusal and non-compliance are not unusual at this stage of the illness. Sustenance of the patient's and family's confidence in

Fig. 2. Group of adolescents revelling in the challenges and camaraderie associated with an 'On the Tip of the Toes' winter expedition in James Bay, Canada. This Canadian-based charitable organisation works on improving self-esteem and confidence in the adolescent survivor of cancer, including brain tumours, by active participation in outdoor wildlife expeditions and other nature-oriented experiences [36].

Table 2
Recommended websites for adolescents/young adults with cancer, particularly brain tumours

Website address (URL)	Description
http://www.discern.org.uk/	UK site—tool to judge quality of health information
http://www.judgehealth.org.uk/	UK site—advice on searching for and judging the quality of health information on the Internet
http://www.cancerbacup.org.uk/	UK-based charity—good basic cancer information
http://www.cancerhelp.org.uk/	UK-based charity—good basic cancer information
http://www.acor.org/	US Association of Cancer Online resources
http://www.oncolink.com/	US well established cancer website
http://www.cancer.gov/	US NCI website—two levels of information for patients and for healthcare professionals (HCP's). Both are quite detailed.
http://www.emedicine.com/	US commercial site—two levels of information for patients and, if registered, detailed articles for HCPs
http://www.abta.org/	American Brain Tumor Association—charity site
http://www.braintumor.org	US National Brain Tumor Foundation—charity site
http://www.tbts.org	US 'The Brain Tumor Society'—charity site
http://www.childhoodbraintumor.org	US 'The Childhood Brain Tumor Organisation'—has some very good specific articles—detailed
http://www.teencancer.org/	UK-based charity—'Teenage Cancer Trust'—good teenager site
http://www.2bme.org/2bMe.html	Teenage Cancer site—description of hair loss, skin changes, etc.
http://www.cancersourcekids.com/	US site from cancer nurses—has teenager section
http://www.mskcc.org/mskcc/html/3335.cfm	MSK site with a teenage section
http://www.planetcancer.com/	US site for supporting teenagers with cancer
http://www.teenslivingwithcancer.org/	Good dedicated teenage cancer site
http://www.clic.uk.com/club/topsfr.htm	UK teenager cancer site—general information
http://www.ulmanfund.org/	US young adult cancer site—general support
http://www.youngwomenshealth.org/cancer.html	Boston Children's site—female fertility in cancer
http://www.fertilehope.org/	US site for cancer patients—fertility issues
http://www.gohear.org/	Good US site on hearing loss

UK, United Kingdom; US, United States; NCI, National Cancer Institute; MSK, Memorial Sloan Kettering.

the team, and clear agreement amongst all involved with respect to the goals of therapy, are paramount. Without these two important facets, the potential escalation of non-compliance may be the seed for subsequent difficult medical, ethical and even legal issues. Depending on the tumour type and the pattern of recurrence, the aim of the treatment may be either curative or palliative. Especially if the aim is to palliate, details of any relevant phase I and II studies should be discussed. The exclusion of patients less than 18 years of age, or sometimes even less than 21 years, from phase I or II 'adult' trials limits access to innovative treatments, particularly when the care is not provided by a paediatric team. By contrast, most institutional and cooperative phase I and II paediatric studies enrol patients up to the age of 21 years and may have strata for specific subgroups of brain tumours. It is therefore the responsibility of those in the position of managing these young patients in 'adult' units to ensure that patients and families are informed of these treatment opportunities, even if transfer to another centre is required.

Because of the paucity of available data in this field, palliative care for adolescents, particularly those with a brain tumour, is poorly developed. Such care needs to focus on the delivery of an effective home care programme as these young people, by and large, are not comfortable in an inpatient paediatric- nor adult-centred hospice or palliative care setting. In some cases, 'respite' care may be appropriate, so long as the setting is appropriate (see Ref [38]).

6. Conclusions

One of the aims of neuro-oncology programmes these days is to identify and focus upon adolescent patients in order to collect crucial data on tumour biology, efficacy of treatment and quality of life upon which future treatment-related trials will be based. Allowing adolescents to slip, by default, into the nebulous transition between the paediatric and adult services is no longer acceptable. Future clinical trials need to be designed so that adolescents can be offered participation. Paediatric treatment trials should extend their age eligibility criteria upwards and adult treatment trials downwards so that adolescents cannot be deemed ineligible simply because of their age. Analysis and reporting of data from these trials should address this specific adolescent age group. Finally, as for any age group, adolescents will benefit most from care coordinated by a robust multidisciplinary neuro-oncology team that has the expertise to deliver appropriate treatment, anticipate and deal with treatment-related morbidity, encourage rehabilitation and provide appropriate emotional support to the patient and their family.

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