Managing teenage/young adult (TYA) brain tumors: a UK perspective

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Practice points

- Brain tumors are rare cancers and patients should be managed in the context of appropriately trained multidisciplinary teams.
- Outcomes of teenage/young adult patients are likely to be better if treated in accordance with pediatric-designed protocols.
- Primitive neuroectodermal tumors are curable tumors that require maximal resection of the primary tumor, followed by craniospinal radiotherapy and chemotherapy as appropriate.
- CNS germ cell tumors are managed depending upon underlying primary pathology, with germinomas being highly radio-curable. Nongerminomatous germ cell tumors require intensive platinum-based chemotherapy followed by stage-adapted radiotherapy.
- Diffuse intrinsic pontine gliomas as a subgroup of primary malignant gliomas are invariably fatal with short survival times regardless of histological subtype if/when biopsied.
- Improvements in treatment outcomes has led to increased focus on the long-term sequelae of treatment, be it psychosocial, vocational or physical, and will require prolonged monitoring for this patient population.

SUMMARY Tumors of the CNS are among the commonest malignancies occurring in teenage/young adult patients (i.e., those aged between 15 and 24 years). The treatment of this patient population is challenging. Adolescence and young adulthood are a turbulent period of life, with physical, emotional, social and cognitive changes. Best practice advocates their treatment in dedicated teenage/young adult units, with multidisciplinary team input and access to clinical trials. Treatment of CNS malignancies is dependent upon histological subtype and staging, with varying combinations of surgery, radiotherapy and chemotherapy used. Clinical trials directly targeted at this patient population are rare; treatments are based on pediatric protocols as studies have demonstrated improved outcomes in patients (with other malignancies) treated as such. Scope for improvement lies in minimizing patient risk of recurrence and long-term sequelae of treatment. Molecular characterization of tumors may provide further information.

Tumors of the CNS are among the commonest malignancies occurring in teenage/young adult (TYA) patients (i.e., those aged between 15 and 24 years). According to the most recent statistics from Cancer Research UK, tumors of the CNS are the fourth most common cancer type in this

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age group [1]. However CNS tumors account for 60% of cancer deaths in the 15–24-year-old group and are disproportionately represented in cancer mortality statistics. A 2009 paper by Arora *et al.* reviewed data available from the national cancer register and found an incidence of 3.26 brain/CNS tumors per 100,000 person years in patients aged 15–24, which equates to a total of 196 cases annually, on average [2].

Tumors of the CNS are a diverse group arising from the various components of the brain structure, and also tumors more commonly seen outside the CNS, namely, germ cell tumors (GCTs). Using the measure of annual average number (AAN), 116 new cases of neuroepithelial tumors (gliomas of any grade), 12 embryonal tumors and seven GCTs can be expected each year [2]. In this review, we focus on three different tumors that are rarely seen in the adult setting, but represent a large proportion of TYA CNS malignancies: primitive neuroectodermal tumors (PNETs), GCTs of the CNS and diffuse intrinsic pontine glioma (DIPG).

Psychosocial challenges

The treatment of this patient population is challenging. Adolescence and young adulthood are a turbulent period of life, with changes in physical, emotional, social and cognitive aspects. This age group is expected to attain certain milestones, with increasing autonomy, independence from parents, increasing levels of responsibility and the development of a personal value system among others [3]. Hormonal changes lead to alteration in physical appearance, changing body image and sexual awakening. Socializing with peers becomes increasingly important. Young people may engage in risk taking behavior in an effort to test the limitations imposed by authority figures. For a young person experiencing such turbulence, a cancer diagnosis impacts upon all of these expected events. Such a diagnosis requires a premature confrontation of mortality, conflicting with the plans for educational attainment, social interaction and with the patient's body image. Cancer treatment can isolate patients from their peer group; the intense chemotherapy regimens and associated side effects require absences from school, college or work. Young adults who had recently gained independence can find they must relinquish this to parents, while parents in turn can find themselves imposing control and rules. Already a time of major body image change, cancer treatment,

be it surgery, chemotherapy or radiotherapy, can lead to dissatisfaction with body image and impact upon nascent sexual awareness. A tendency for risk taking may be reflected in poor compliance.

Once treatment has ended, TYA patients may find ambivalence is their main emotion – positive that treatment has ended but uncertainty over the future. Intense schedules of hospital attendances gives way to infrequent visits and an expectation of a return to normal life. Patients may find it difficult to identify with peer groups, having missed out on usually shared experiences: attending college, leaving home, dating, pursuing employment. The late effects of treatment, such as cognitive impairment, growth disturbance, endocrinopathy, infertility are also of concern. A combination of altered body image and self-esteem, changes in relationships and other social disturbances may also influence sexual activity and relationships. TYA cancer survivors have reported negative feelings about future relationships, uncertainty regarding their own attractiveness and sexuality and concerns regarding disclosure of their medical history to future partners/employers [3,4]. It is reassuring that for the majority of patients treated in this age group, a positive functional and psychological outcome can be expected although an impact from treatment as demonstrated in a number of studies. Nonetheless, there is a significant subgroup for whom increased supports are required. These patients report ongoing concerns, distant to their diagnosis, about the impact of their cancer upon future employment opportunities, finances and children. The importance of an experienced multidisciplinary team in this setting cannot be overstated in the efforts to reduce the proportion of patients with ongoing psychological concerns.

Choice of treatment protocols

TYA patients often have a better tolerance of high-dose/high-intensity chemotherapy than older patients due to an absence of comorbidities and good organ reserve. For example, the optimal treatment for PNETs in pediatric patients involves a complex regimen of high-intensity chemotherapy. In the TYA population, it is a delicate decision to decide which regimen should be followed. Studies have shown improved outcomes for teenagers and young adults with acute lymphoblastic leukemia when treated on regimens developed by pediatric oncologists. In a study by Ram *et al.*, TYA patients treated with

adult regimens had a statistically significant higher all-cause mortality at 3 years (response rate [RR]: 0.58; 95% CI: 0.51–0.67) [5]. The relapse rate was lower in patients given pediatric regimens. As a means of standardizing treatment and improving outcome, in 2005, NICE published the Improving Outcomes Guidance. The Improving Outcomes Guidance and its successor, the National Cancer Action Team Guidance for England, outlined several key factors required for the appropriate treatment of such patients. These factors relate to patients' choice of place of care, the need for multidisciplinary team input, agreed treatment protocols and encouraging and increasing patient enrollment on to clinical trials [6]. The implementation of national guidelines, with dedicated treatment centers for TYA patients has allowed streamlined care for such patients. A national network of centers facilitates collaboration in clinical trials and translational research. It also clusters the skill set needed to care for this complex group of patients. These factors allow the UK to continue to lead TYA cancer medicine development.

Primitive neuroectodermal tumors

PNETs are embryonal tumors within the small round blue cell tumor type. Medulloblastomas are also within this tumor type, as are pineoblastomas. Given the relative rarity of supratentorial PNETs, the discussion shall focus on the infratentorial group. There is almost a 1.5:1 male-to-female predominance and 70% of cases are diagnosed by the age of 20 years [7].

Recent work has focused on the molecular profiles of these tumors; distinct subtypes (SHH, WNT, group 3 and group 4) have been identified which have histopathological, molecular and clinical characteristics. Ellison *et al.* developed a novel diagnostic immunohistochemical method to distinguish tumor types, dividing them into three groups for this analysis [8]. WNT tumors are characterized by nuclear and cytoplasmic β -catenin staining, filamin A positivity and *YAPI* positivity. Over 80% demonstrated monosomy 6. Such tumors almost always present between the ages of 6 and 12 years and WNT are overwhelmingly associated with good prognosis. SHH tumors demonstrate positivity for *GAB1*, filamin A and *YAPI*. In total, 54% were desmoplastic tumors. Molecular analysis revealed an abnormality in the *PTCH1* locus in these patients, with loss detected in 38%. SHH tumors occur in infants and adults. Using this

method, the remaining tumors were termed non-SHH/WNT tumors. Such tumors demonstrate cytoplasmic staining for β -catenin only, weak filamin A staining and negative staining for both *GAB1* and *YAPI*. They demonstrate frequent *MYC* amplification and chromosome 17 copy number alterations. This last group is frequently separated into group 3 and group 4 [9]. Group 3 tumors demonstrate classic or large cell/anaplastic histology. They exhibit gains at chr 7, chr 1q, chr 17q and chr 18q with deletions at chr8, chr 11p, chr 5q, chr 10q and chr 16q [8,9]. *MYC* amplification is seen also. These tumors are driven by photoreceptor/GABAergic pathways and are associated with a poor prognosis. Group 4 tumors demonstrate the same histologic appearances as group 3 but have differing genetic aberrations. These tumors demonstrate gains at chr7, chr17q and chr18q with loss of chr8, chr X and chr11p [8,9]. They demonstrate *CDK6* and *MYCN* amplification. Such tumors are driven by neuronal/glutamatergic pathways. This subclassification provides the opportunity to stratify treatment further beyond the clinical (metastatic or not), histological (anaplastic or not) and *MYC* expression. Sonic hedgehog pathway inhibitors are already in clinical development and so offer another treatment option for these patients in selected circumstances.

PNETs become progressively rarer with increasing age with few cases beyond the age of 50. The presentation of patients with PNETs depends on age and tumor location. Midline tumors typically present with signs of raised intracranial pressure such as headaches, nausea and irritability. With progressive involvement of the cerebellar vermis, truncal ataxia may develop. Sixth nerve palsies are the most common cranial nerve palsies seen. Unilateral tumors more frequently present with unilateral dysmetria. MRI is the imaging modality of choice, with lesions appearing iso- to hypo-intense on T1-weighted images, of variable signal intensity on T2-weighted images and demonstrating heterogeneous enhancement. Restricted diffusion can help distinguish between PNETs and ependymomas. Diagnosis is based upon examination of the surgically resected tumor with staging completed by cranial axis imaging and cerebrospinal fluid (CSF) sampling.

Treatment of these patients depends on staging, (see [Table 1](#) for staging system) with the M stage the decisive factor in treatment planning, histological appearance and *myc*

Table 1. Chang staging system.

Stage	Definition of metastasis
M0	No evidence of gross subarachnoid or hematogenous metastasis
M1	Microscopic tumor cells found in cerebrospinal fluid
M2	Gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space or in the 3rd, or lateral ventricles
M3	Gross nodular seedings in the spinal subarachnoid space
M4	Extraneural metastasis

Data taken from [10].

expression. PNETs metastasize nearly exclusively via the CSF and only extremely rarely hematogenously. Surgical resection of the primary disease to a volume of less than 1.5 cm² as seen on imaging 48–72 h postoperatively, renders the patient ‘standard risk’ with a corresponding improvement in survival, hence good surgical resection is the first step in optimal management where feasible.

Craniospinal radiotherapy (i.e., radiation of the brain and entire spine) followed by a boost to the tumor bed is the cornerstone of curative management. The timing of radiotherapy in multimodal treatment was investigated in the POG 9031 trial [11]. In this study, patients were randomized to either chemotherapy (7 weeks of cisplatin and VP-16) followed by radiotherapy or craniospinal radiotherapy followed by chemotherapy (7 weeks of cisplatin and VP-16). All patients then received 28 weeks of maintenance chemotherapy with vincristine/cyclophosphamide. There was no difference in outcomes compared by treatment groups, with no excess morbidity. The multicenter HIT-SIOP PNET 4 Trial included patients aged 4–21 years [12]. It investigated if hyperfractionated radiotherapy was superior to conventional radiotherapy, both combined with standard radiotherapy, in patients with medulloblastoma. Hyperfractionation is thought to exploit the difference in repair capacity between tumor and late-responding normal tissue. This would potentially permit a dose escalation, improving local tumor control and increasing the biologic effective dose to the craniospinal axis without a concomitant increase in the biologically effective dose to the normal CNS. They found no benefit to hyperfractionation but did demonstrate a 5-year OS of 86% (85–87%), without any difference in those over 16 years old [12]. This excellent OS is likely a result of patient selection – less than 10% of patients had residual tumor >1.5 cm² postoperatively. A planned quality of life analysis found a possible benefit associated with radiotherapy to

executive function, with a more marked effect in patients less than 8 years. Overall, there was no significant benefit to health status, behavior or quality of life [13].

Currently in the UK, patients are treated according to the regime published by Packer *et al.* in 1994 [14]. This regime added cisplatin to the previously investigated CCNU and vincristine as outlined in Table 2, in effort to reduce patient toxicities and potentially improve outcome. Patients who were considered at highest risk for relapse after radiotherapy were eligible for inclusion into the study.

This study demonstrated a 90% progression-free survival at 3 years [14]. This compared favorably with a study by the Children’s Cancer Group and Pediatric Oncology Group, which demonstrated a 3-year disease-free survival of almost 80% [15].

Further investigations into the optimal chemotherapy for patients with metastatic PNET continue. Jakacki *et al.* examined the role of carboplatin as a radiosensitizer in these patients [16]. This study focused on patients with high-risk disease, including supratentorial PNET. All patients underwent surgical resection and craniospinal radiotherapy. The Goldie–Coldman model of therapeutic resistance states that the prompt elimination of tumor through the use of multiple concurrent drugs reduces the likelihood of emergence of resistance clones [17]. Hence it was postulated that combination chemotherapy targeting different aspects of the cell cycle would lead to more effective tumor control. Patients received daily carboplatin along with weekly vincristine. Carboplatin was given both for its role as a potent radiosensitizer and also an active agent in PNETs thought to be due to its creation of DNA strand breaks. This was followed by 6 months of maintenance therapy with cyclophosphamide and vincristine. Patients between the ages of 3 and 21 years were entered into the study, with a median age of 8.7 years; no data are available on the number of TYA patients

included. For the Phase II part of the trial, patients were randomized following craniospinal radiotherapy given with vincristine and carboplatin to differing regimens of maintenance treatment. In regimen A, patients received cyclophosphamide 1000 mg/m² on days 0/7 and vincristine 1.5 mg/m² on days 0/7 also. Regimen B added CDDP 75 mg/m² on day 0. Most patients required colony stimulating factors and/or transfusion support towards the end of radiotherapy; 10% of patients had an interruption in radiotherapy for medical reasons. The treatment appeared to translate across all risk groups. Four patients were excluded from the outcome analysis as it was felt there may be confounding factors in calculating their survival. For patients treated on the RP2D with M+ disease, the 5-year overall survival (OS) $\pm$ SE on regimen A was 82 $\pm$ 9% as compared with 68 $\pm$ 10% for those treated in arm B (p = 0.68) [16]. This study demonstrated the feasibility of daily carboplatin administration in this patient population.

Germ cell tumors

CNS GCTs are thought to arise from nests of embryonic cells that have been arrested in their journey along the primitive notochord during early fetal development occurring most commonly in teenagers and young adults with GCTs [7]. Thus they typically arise in a CNS midline location (suprasellar, pineal), with germinomas, embryonal carcinomas, choriocarcinomas and mixed GCTs. Peak incidence is during adolescence and early adulthood; this has led some authors to postulate that pubertal endocrine changes are implicated in the activation of these cells. Patients typically present with the signs and symptoms of obstructive hydrocephalus and ocular pathway involvement. Parinaud's syndrome of paralysis of upward conjugate gaze is the classic ophthalmological abnormality but pupillary and convergence abnormalities are seen also. Aside from ophthalmological abnormalities, patients may present with the signs

and symptoms of endocrine dysfunction such as diabetes insipidus or a failure to attain growth milestones due to growth hormone deficiency. The radiological investigation of choice is the MRI brain with lesions appearing hyperdense due to the high cellularity, with associated robust gadolinium enhancement. In mixed malignant tumors or teratomas, calcification and fat may be seen. CNS GCTs disseminate via leptomeningeal spread and hence gadolinium-enhanced neuraxis imaging is required at diagnosis.

Due to the heterogeneous nature of this tumor group, treatment is complex and requires input from all members of the multidisciplinary team. There is a high cure rate using a variable combination of chemotherapy, radiotherapy and surgery. Full staging involves sampling of serum and CSF to assess for tumor marker production, namely α -fetoprotein (aFP) and β -human chorionic gonadotrophin (bHCG). Tumors are broadly grouped into germinomas and nongerminomatous GCTs (NGGCTs) and treatment varies depending upon the primary tumor type and stage [18].

Germinomas account for approximately 60% of all intracranial GCTs and typically spread via the CSF. They are highly radiosensitive, with a disease-free survival of over 90–95% at 5 years with radiotherapy alone [19]. The current standard of care for patients with localized germinomas is whole ventricular radiotherapy with a conformal boost for patients with localized disease [20]. Craniospinal radiotherapy remains the gold standard for patients with disseminated M1 and M2/3 disease. In those whose disease is in an atypical location, for example, basal ganglia, craniospinal radiation is given. The role of chemotherapy in germinomas is controversial, these tumors have well documented radiosensitivity and chemotherapy may add to toxicity rather than survival. The SIOP CNS GCT 96 trial evaluated the possibility of reduced radiation volume in combination with radiotherapy in patients with germinoma [21]. Patients with

Table 2. The Packer chemotherapy regimen.

Chemotherapeutic agent	Schedule of administration
Vincristine 1.5 mg/m ² (max 2 mg)	Weekly alongside radiotherapy
	6-week break
Vincristine 1.5 mg/m ² (max 2 mg)	Weekly for 3 consecutive weeks of every 6 weeks
CCNU 75 mg/m ²	Every 6 weeks
Cisplatin 68 mg/m ²	Every 6 weeks
	Eight 6-weekly cycles

localized disease were randomized to receive either craniospinal radiotherapy (CSI) or two courses of carboplatin and etoposide alternating with etoposide and ifosfamide, followed by local radiotherapy [21]. Those with metastatic disease received CSI with focal boost to primary and metastases, with optional preceding chemotherapy. The overall survival for the treatment groups was similar and exceeded 95%. There was no difference in outcome when analyzed by age. There was an excess of ventricular relapses in patients treated with induction chemotherapy followed by focal radiotherapy. Chemotherapy alone is inadequate for the treatment of germinomas due to reported high relapse rates [21,22]. However, it may be used to reduce the treatment volume prior to radiotherapy providing the ventricles are included in the final radiotherapy volume.

NGGCTs are less sensitive to radiation, with a 5-year survival rate between 20 and 76% with radiotherapy (with or without adjuvant chemotherapy). Several studies have looked at the role of primary chemotherapy given the chemosensitivity demonstrated by their systemic counterparts. There have been three international CNS germ cell tumor studies, the most recent in 2010 [22,23]. In this series, 57 patients with NGGCTs were included [24]. These studies concluded that chemotherapy alone is less effective for these patients. The MAKEI 89 trial of trimodality treatment demonstrated a benefit in event-free survival in those treated according to protocol, with craniospinal irradiation and cumulative cisplatin dose significant for outcome [25].

Diffuse intrinsic pontine glioma

Gliomas are the most frequent malignant CNS tumor in adulthood with approximately 70% occurring in a supratentorial location. DIPG is a subtype of glioma arising within the pons. It is an expansile, diffusely infiltrating lesion involving the pons and accounts for approximately 10% of malignant pediatric brain tumors. Patients typically present with a history of progressive neurological deficits, ranging from visual defects, cranial nerve palsies, limb weakness and ataxia, with a history of less than 6 months [26]. Diagnosis is usually made on radiological grounds. An MRI characteristically shows an abnormal, enlarged pons, with minimal or no contrast enhancement and high signal on FLAIR/T2-weighted images. Envelopment and deviation of the basilar artery is frequently seen. Historically, it has been rarely

biopsied given its location and the inherent perceived risks but when biopsied, histology demonstrates an astrocytic tumor, of varying grades from II–IV. A recent series by Buczkowicz *et al.* documented the histological and postmortem findings of 72 patients over a 28-year period [27]. They demonstrated a wide range of histology from grade II astrocytoma to glioblastoma and PNET. As has been reflected in previous series, including a UK series by Cartmill and Punt, there was no correlation between histology and survival [27,28]. The issue of intratumoral heterogeneity was demonstrated by the differing grades within the same tumor from anaplastic astrocytoma to glioblastoma depending upon the tumor location. *TP53* was found to be mutated in between 40 and 77% of tumor samples. K27M-H3.3 mutation was found in 70% of patients; those with wild type H3.3 had an improved prognosis when compared with their mutated counterparts [27]. This may be used as a stratifying factor in future clinical trials given the risk of histological undergrading. Survival for DIPG in virtually all studies show a median survival time of less than 1 year and outcome has remained static over past decades.

Aggressive surgical resection with an aim for macroscopic complete resection is known to improve outcomes in adult patients with gliomas [29]. However, given the tumor location, there is no role in the current treatment paradigm for radical resection for patients with DIPG. A consensus statement following CPN Paris 2011 stated biopsy in a typical DIPG is justified when the patient is part of an appropriate trial and the biopsy will be used to either investigate or inform treatment selection. They also supported biopsy in atypical cases [30]. Radiotherapy remains the gold standard treatment for these patients and is usually given at a dose of 54 Gray (Gy) in 30 daily fractions of 1.8 Gy over 6 weeks. Radiotherapy offers no chance of cure but modifies the disease course slightly, prolonging survival by several months. Many studies since the 1990s have attempted to improve the outcome for such patients; hyperfractionation (using multiple fractions per day) and dose escalation have been examined. However neither technique has demonstrated an improvement in survival compared with conventionally fractionated RT [31]. A recent study by Janssens *et al.* examined hypofractionation compared with conventional radiotherapy. It demonstrated an equal overall survival in each treatment group

(mOS 9.0 months vs 9.4 months; $p = 0.84$) with a diminished treatment burden for these patients [32].

With static outcomes from treatment with radiotherapy alone, chemotherapy has been extensively explored. Temozolomide is an orally bioavailable alkylating agent which has shown improvement in overall survival in adult patients with glioblastoma and which, in combination with conventional fractionated radiotherapy, represents the current UK standard of care in such patients [33]. There have been several studies of temozolomide in patients with DIPGs, both in combination with radiotherapy and in combination with other cytotoxic agents. Their results are summarized below in Table 3. None of these have demonstrated a meaningful improvement with respect to outcome unlike that seen in adults with classical high-grade gliomas.

Given the overall poor prognosis for patients with DIPG, and the disappointing results with radiotherapy as the sole treatment modality, other chemotherapeutic options have been explored. These include conventional cytotoxic chemotherapies such as vincristine, immune-based therapies such as nimotuzumab and newer, targeted agents such as vandetanib (VEGFR-2 inhibitor) and dasatinib (PDGFR inhibitor) [39–41]. Tamoxifen, best known as treatment for estrogen receptor positive breast cancer, also acts as a protein kinase C modulator. It has been trialled in DIPG without a clinical benefit [42]. The HIT-GBM-C protocol combined radiotherapy with intensive chemotherapy using multiple agents; cisplatin, etoposide, vincristine and ifosfamide were all given with

further maintenance therapy post radiotherapy followed by valproic acid as a cell differentiating agent [43]. Thirty seven patients with DIPG were included in the study. Despite the intensive treatment, there was no improvement in outcomes for these patients with a median overall survival of 1.13 years, compared with the published data of radiotherapy alone [43]. They did however, demonstrate a 5-year overall survival of 63% in those patients where a macroscopic complete resection was achieved. Similar disappointing results have been found with other chemotherapy combinations [44,45]. It has been demonstrated *in vitro* that DIPG cells are not technically chemotherapy resistant, but rather express drug efflux transporters extracellularly [46]. This may provide a focus for further research and a potential treatment paradigm. There has been some preclinical work attempting to overcome drug efflux transporters; one such method conjugates the efflux susceptible drug to a cell-penetrating peptide. This causes rapid cellular entry and controlled drug release and may provide a therapeutic option in DIPG [47].

A recent Phase II study has shown some potential meaningful response to nimotuzumab, a monoclonal antibody against EGF receptor (EGFR) and it may be that there is a subset of patients for whom anti-EGFR treatment is a valid paradigm [40]. Current research focuses on other cellular mediators of vascular proliferation, such as VEGF and PDGF, which have been found to be critical in adult classical high-grade gliomas. The increasing role of immune therapy in the wider oncology field may find DIPG as an area of promise. A study

Table 3. Temozolomide trials in diffuse intrinsic pontine glioma.

Study/trial (year)	Patients (n)	TMZ dose/schedule	RT dose	Other drug	Median EFS/PFS (months)	Median OS (months)	Ref.
Müller <i>et al.</i> (2014)	6	75 mg/m ² /day	35.2–36 Gy [†]	–	4.0	7.6	[34]
Chassot <i>et al.</i> (2012)	21	75 mg/m ² /day followed by 200 mg/m ² days 1–5	54 Gy	–	7.5	11.7	[35]
ACNS0126 (2011)	63	90 mg/m ² /day followed by 200 mg/m ² /day on days 1–5	59.4 Gy	–	6.1	9.6	[36]
Kim <i>et al.</i> (2010)	17	75 mg/m ² /day followed by 150–200 mg/m ² /day on days 1–5	54 Gy	Thalidomide 150 mg/m ² /day then increased to 600 mg/m ² /day	7.2	12.7	[37]
Sirachainan <i>et al.</i> (2008)	12	75 mg/m ² /day followed by 200 mg/m ² /day on days 1–5	55.8–59.4 Gy	Cis-retinoic acid 100 mg/m ² /day after radiotherapy	10.2	13.5	[38]

[†]Craniospinal radiotherapy.
EFS: Event-free survival; OS: Overall survival; PFS: Progression-free survival; TMZ: Temozolomide.

of pegylated interferon α -2b did not improve 2-year survival although it did appear to delay time to progression [48]. It remains to be seen the role of immune checkpoint modulation, if any.

Clinical trials

There are currently 12 clinical trials of investigational medicinal products listed on the Cancer Research UK enrolling TYA brain tumor patients. Adult studies which permit patients from the age of 18 include the DCVax study (dendritic cell vaccine study in GBM), the OPARATIC study (a second line GBM study of temozolomide in combination with olaparib), the REO 13 BRAIN study (a study of reovirus), the BR14 study (examining schedules of chemotherapy in the first line setting in grade III tumors) and the TAVAREC study (a second line study of bevacizumab/temozolomide in grade II/III tumors). There are two studies looking specifically at the TYA group – SIOP CNS GCT II in patients with GCTs and the HERBY study, examining bevacizumab and temozolomide, which includes patients up to the age of 17 years with high-grade glioma.

It is recognized that while pediatric patients with cancer are commonly enrolled on clinical trials during treatment (with rates approaching 70%), the TYA population has not shown similar recruitment [49]. The exact reason for this is unclear. Such patients may transition from a pediatric unit to an adult unit, if treated in a center without a defined TYA unit. They may also be treated in an adult environment where access to pediatric driven research protocols is not readily available or may require the transfer of the patient to another unit. In such instances, referral to a center with a potential clinical trial should be discussed with the patient and their family.

The discovery of various cellular pathways implicated in tumorigenesis has led to the investigation of targeted therapies. The PI3K pathway has been implicated in gliomas; it is targeted in one of the studies currently in the CRUK portfolio [50]. The *WEE1* pathway is implicated in DIPG; it may represent a therapeutic target [51]. The Aurora kinase pathway is also upregulated and drugs targeting this pathway entered early stages of drug development [52]. The Sonic Hedgehog pathway (SHh) has been shown to be activated in medulloblastoma tumors and also in gliomas [53]. The role of targeting this pathway is under investigation; it has already shown impressive results in dermatology.

The potential of immune checkpoint therapy is gaining interest in neuro oncology. Approximately 70–80% of patients with glioma express PD-L1 on the tumor cell surface; this has been a target of anticancer therapy in other malignancies with positive results [54,55]. Several early studies are ongoing into the targeting of this part of the immune pathway, along with the role of CTLA4. Progress in CNS GCTs centers on minimizing long-term effects as effective treatments for disease control are available.

Future challenges/opportunities

The challenges and opportunities in treating this patient cohort are many. With improving event-free survival and overall survival in tumors such as PNET and CNS GCTs, the long-term effects of treatment become increasingly apparent. The long-term endocrine follow-up and potential derangement in such patients requires ongoing input from local teams in order to minimize morbidity.

It has been demonstrated in studies of leukemia regimens that cranial irradiation impacts upon cognitive functioning. Longitudinal studies have shown an impairment of cognitive functioning in patients treated with craniospinal irradiation [56–58]. These data are primarily in children with neuro oncological diagnoses or TYA patients treated with high-dose leukemia regimens and may not be directly applicable to the TYA population. However, it remains an area of concern for the community and efforts have been made to reduce the total dose of radiotherapy delivered. Raggi *et al.* demonstrated a seven field conformal technique with a modest reduction in the dose administered to normal brain tissue but this has not been widely adopted as the reduction was not thought to be clinically meaningful [19]. A 113-patient retrospective review of medulloblastoma patients treated with reduced volume radiotherapy (radiotherapy to tumor bed rather than entire posterior fossa), did show a stabilization of intellectual trajectories in those receiving less radiotherapy [59]. However, this was primarily a pediatric population and hence is not directly applicable to TYA patients.

With improving survival, longer term side effects gain importance. One such significant effect is the risk of development of subsequent malignant neoplasms (SMNs). A recent publication derived from the SEER database reported on the causes of mortality in 5-year survivors of a

CNS tumor diagnosed before the age of 20 years. The cumulative incidence of SMN at 30 years was 6.4% (95% CI: 4.8–7.7) [60]. An increased risk of death due to cardiovascular and cerebrovascular disease was also noted. This patient population had an almost 13-fold increased risk of death compared with their peers due to the increased risk of late effects but also of recurrent disease. A large retrospective Danish cohort series had similar results, demonstrating a 3.6% cumulative risk of cerebrovascular disease by age 20 years in those patients treated for a primary brain tumor as compared with 0.0% risk in the comparison population [61]. Cardiovascular disease presented primarily as cardiomyopathy and arrhythmia, with risks of 3.6 versus 0.1%.

Fertility can be a difficult issue to raise with a TYA patient. Already in a period of great psychosocial flux, a potentially fatal diagnosis and often urgent need to commence treatment may suppress the discussion. Long-term fertility sequelae vary depending upon treatment administered; platinum and etoposide are most implicated in long-term low/infertility. Patients may have long-term endocrinopathies, which will also impact upon future fertility. Recent NCCN guidelines state sperm cryopreservation should be offered to all patients. Fertility preservation is more complex in young women. Oocyte preservation, whilst no longer considered experimental, remains challenging. They suggest oophorectomy consideration for those receiving radiotherapy and consideration of embryo cryopreservation for those patients that can delay the initiation of treatment [62]. Formal referral pathways to a fertility specialist with routine referral at diagnosis will allow for early discussion of potential problems.

In DIPG, a knowledge gap exists on tumor biology which has perhaps hindered efforts to develop targeted therapies. Consideration should be given to biopsy where it is felt to be safe; especially in a center where molecular characterization is possible. Stereotactic biopsy has been demonstrated to be safe in retrospective series [27,28,63]. Biopsy may allow the initiation of targeted therapy, thus becoming therapeutic; inherent risk may be more acceptable for patient and treating physician alike. While in other tumor types focus has turned to patient selection and minimizing long-term effects, in DIPG improving survival remains the primary goal. Circulating tumor cells and circulating tumor DNA may provide an alternative to tumor

biopsy; further work is needed to evaluate the role of this technique in DIPG.

There is undoubtedly a great impact on the families of TYA patients diagnosed with a CNS tumor. BRIGHTLIGHT, a nationwide study, is open to patients with all tumor types aged between 13 and 24 diagnosed in England within the last 4 months. It aims to assess the impact upon patients' quality of life and the costs, financial and otherwise, to patients and their family. It will provide invaluable information to those who treat this patient population in years to come.

These patients are diagnosed at a time where they are beginning of their educational or vocational development. A Dutch study examined the impact of a cancer diagnosis and survival on survivors of childhood cancer and compared their psychosocial outcomes to a control group of young people without a cancer diagnosis [64]. The median age at diagnosis of the population was 8 (range: 0–19 years). They found several differences between survivors and the control group, with survivors more likely to have lower educational attainments, and less likely to be in full time employment. Survivors were more likely to be single and less likely to have biological children. Those with a CNS tumor were more likely to have lower educational attainments than other cancers that may relate to treatment induced cognitive impairment (80% lower educational attainment versus 59% for leukemia/non-Hodgkin's not treated with craniospinal RT, $p = 0.01$) [64].

Conclusion & future perspective

Teenagers and young adults remain a challenging population for treating physicians. Complex psychosocial needs, alongside often complex treatment pathways, must be considered. Progress has been made in the treatment of intracranial GCTs over the past decades, with similar improvements in medulloblastoma treatment but this has not been the case for DIPG. Stratification of tumors based upon molecular markers may, over the next decade, allow us to tailor treatments sparing some patients prolonged courses of treatment. This will minimize disruption to the patient's life and also minimize toxicities, both short- and longer term. Increasing use of biopsy in DIPG will add to the currently available data and allow further tailored treatments. Advances in the management of GCTs is likely to focus on two things: minimizing long-term side effects for

survivors and creating more treatments in those resistant to currently available therapies. In order to see such advances, a collaborative approach between oncologists, basic science researchers, specialists in adolescent/young adult medicine and patients and their families is required. The under-representation of these patients in clinical trials will need to be improved to assist this effort. This progress toward a personalized medicine approach for these patients will need to be coupled with long-term follow-up to monitor for treatment related effects. Implementation of treatment pathways, in particular clustering of TYA treatment in defined TYA centers, will aid

these efforts. This will allow the UK to continue to lead the treatment of TYA patients over the coming decade.

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