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Central nervous system tumors in adolescents and young adults: A Society for Neuro-Oncology consensus review on diagnosis, management, and future directions

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Abstract

Adolescents and young adults (AYAs; ages 15–39 years) are a vulnerable population facing challenges in oncological care, including access to specialized care, transition of care, unique tumor biology, and poor representation in clinical trials. Brain tumors are the second most common tumor type in AYA, with malignant brain tumors being the most common cause of cancer-related death. The 2021 WHO Classification for central nervous system (CNS) Tumors highlights the importance of integrated molecular characterization with histologic diagnosis in several tumors relevant to the AYA population. In this position paper from the Society for Neuro-Oncology (SNO), the diagnosis and management of CNS tumors in AYA is reviewed, focusing on the most common tumor types in this population, namely glioma, medulloblastoma, ependymoma, and CNS germ cell tumor. Current challenges and future directions specific to AYA are also highlighted. Finally, possible solutions to address barriers in the care of AYA patients are discussed, emphasizing the need for multidisciplinary and collaborative approaches that span the pediatric and adult paradigms of care, and incorporating advanced molecular testing, targeted therapy, and AYA-centered care.

Keywords

adolescents and young adults | brain tumors | precision medicine | survivorship

Adolescents and young adults (AYAs) constitute a population with specialized needs facing multifaceted challenges in oncological care.[1] Defined by the National Cancer Institute (NCI) as individuals aged 15–39 years at the time of initial cancer diagnosis, AYA patients are particularly vulnerable as this age range spans important biological and social milestones, and the discordance between life plans and demands of a life-altering diagnosis can be difficult. AYA patients include pediatric (regionally defined as <18 [Canada and Europe], or <21 [USA]) patients who transition to adult care as well as adult

patients who receive a new diagnosis of cancer while in the AYA age range. Access to specialized care, transition of care from pediatric to adult institutions, unique tumor biology, and under-representation in clinical trials are challenges in the care of AYA oncology patients and contribute to relatively inferior survival outcomes.[2,3]

Central nervous system (CNS) tumors are the second most common tumor in AYAs[4] with an average annual age-adjusted incidence of 12 per 100 000. Malignant brain tumors in 15–29 have seen increasing mortality rates despite a decline in other cancers.[5,6]There are many barriers in the care of AYAs with CNS cancers, contributing to their poor prognosis compared to other cancers.[6] Within AYA, CNS cancers are the second highest cause of mortality after female-specific breast cancer, with the highest mortality seen in those 15–25 years.[5]

The 2021 WHO Classification for CNS Tumors (WHO CNS5) highlighted the importance of integrated molecular and histologic characterization in several AYA-relevant tumors, notably within the classification of glioma, medulloblastoma, and ependymoma.[7] There is an emphasis on molecular testing including DNA methylation profiling, which has revealed specific entities enriched in AYA and prognostic molecular markers that may carry therapeutic implications. In this era, access to timely and clinically relevant testing, neuropathology, and molecular pathology expertise, in addition to referral to oncologists who have robust experience in the unique tumor biology and treatment considerations, is critical. However, there is a lack of standardized molecular testing of CNS tumors in AYA and a paucity of data with regard to the ideal treatment approach for specific tumors. Adding to this, the care of AYAs is fragmented across institutions and significant variations in practice exist between adult and pediatric practitioners. Few clinical trials span the AYA years, and access to these trials is limited by restrictions on age at enrollment. Finally, additional supportive care and psychosocial aspects need consideration in the care of AYAs, including oncofertility, cancer survivorship, neurocognitive and physical rehabilitation, and psychosocial support (addressing loss of autonomy, finding work, and developing relationships, to name a few).[2,8,9]

In this review, we examine AYA-specific considerations and current challenges in the care of AYA neuro-oncology patients, specifically in the context of the most common diagnoses encountered in this population (**Figure 1**). We focus on the distinct diagnosis and management of these tumors, specifically glioma, medulloblastoma, ependymoma, and CNS germ cell tumors. Lastly, we provide some possible solutions to address barriers that complicate the care of AYA patients, focusing on treatment and clinical trial strategies.

Glioma

The WHO CNS5 recognizes pediatric and adult-type gliomas, both of which can arise in AYA patients. As the management of these glioma subtypes can differ, a rational approach to molecular testing is essential in identifying the subtype of glioma and possible molecular alterations, which can guide discussions on prognosis, treatment approaches, clinical trial options, and anticipatory care.[13] Specifically, Bennett et al. described that up to 82% of AYA gliomas harbor a potentially targetable molecular aberration (58% in genes encoding isocitrate dehydrogenase (IDH) enzymes, and 24% with RAS/MAPK alterations).[10]This is relevant given that precision therapies could help delay or avoid radiation therapy and cytotoxic chemotherapy, which may both have long-term deleterious effects.

Adult-Type Glioma

Adult-type diffuse gliomas are the most common type of glioma in AYA, representing 15.2% of all brain tumors.[6,10] The main defining molecular alteration in adult-type diffuse gliomas is the IDH mutation, giving rise to 3 main glioma subtypes: (1) diffuse astrocytoma, IDH-mutant; (2) oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and (3) glioblastoma, IDH-wild type (IDH-wt).[7] While the distinction between low-grade and high-grade glioma can help guide diagnostic and therapeutic approaches, molecular markers (including *CDKN2A/B* loss in IDH-mutant astrocytomas and oligodendrogliomas) are integral to prognostic stratification.

IDH-mutant gliomas in AYA.—IDH mutations are rare in pediatric populations, but slowly increase with age and peak in the fourth decade, highlighting the different biology and tumor drivers in adult versus pediatric-type gliomas.[14,15] Most (90%) IDH-mutant gliomas harbor a mutation in IDH1 R132H that can be identified via immunohistochemistry (IHC).[16] Recent data suggest the frequency of non-canonical mutations, including IDH2, is higher in AYA compared to older adults.[17] Sequencing for non-canonical pathogenic IDH mutations should be sought in AYA with diffuse glioma or oligodendroglioma by histology who do not harbor IDH1 R132H using IHC.

The management of IDH-mutant glioma in AYA is outlined in **Table 1** and more thoroughly reviewed in the previously published Society for Neuro-Oncology (SNO) consensus review on IDH-mutant glioma.[24] Pivotal results from the landmark INDIGO trial (NCT04164901) showed a significant progression-free survival (PFS) benefit of vorasidenib in IDH1 and IDH2 mutant non-enhancing grade 2 glioma compared to placebo.[20]This may effectively delay radiation or cytotoxic chemotherapy and unwanted toxicities and impact survivorship in AYA. The role of proton therapy for cognitive preservation in IDH-mutant glioma is currently being investigated in the NRG-BN005 study, which was closed to accrual earlier this year (NCT03180502) and may be of particular relevance to the AYA population.

The following aspects should be highlighted specifically for AYA with IDH-mutant glioma:

- Following maximal safe resection, select AYA patients with WHO grade 2 IDH-mutant gliomas with near gross total resection may be observed until progression.
- While age <40 was previously proposed as a prognostic factor guiding clinical decision-making with regards to

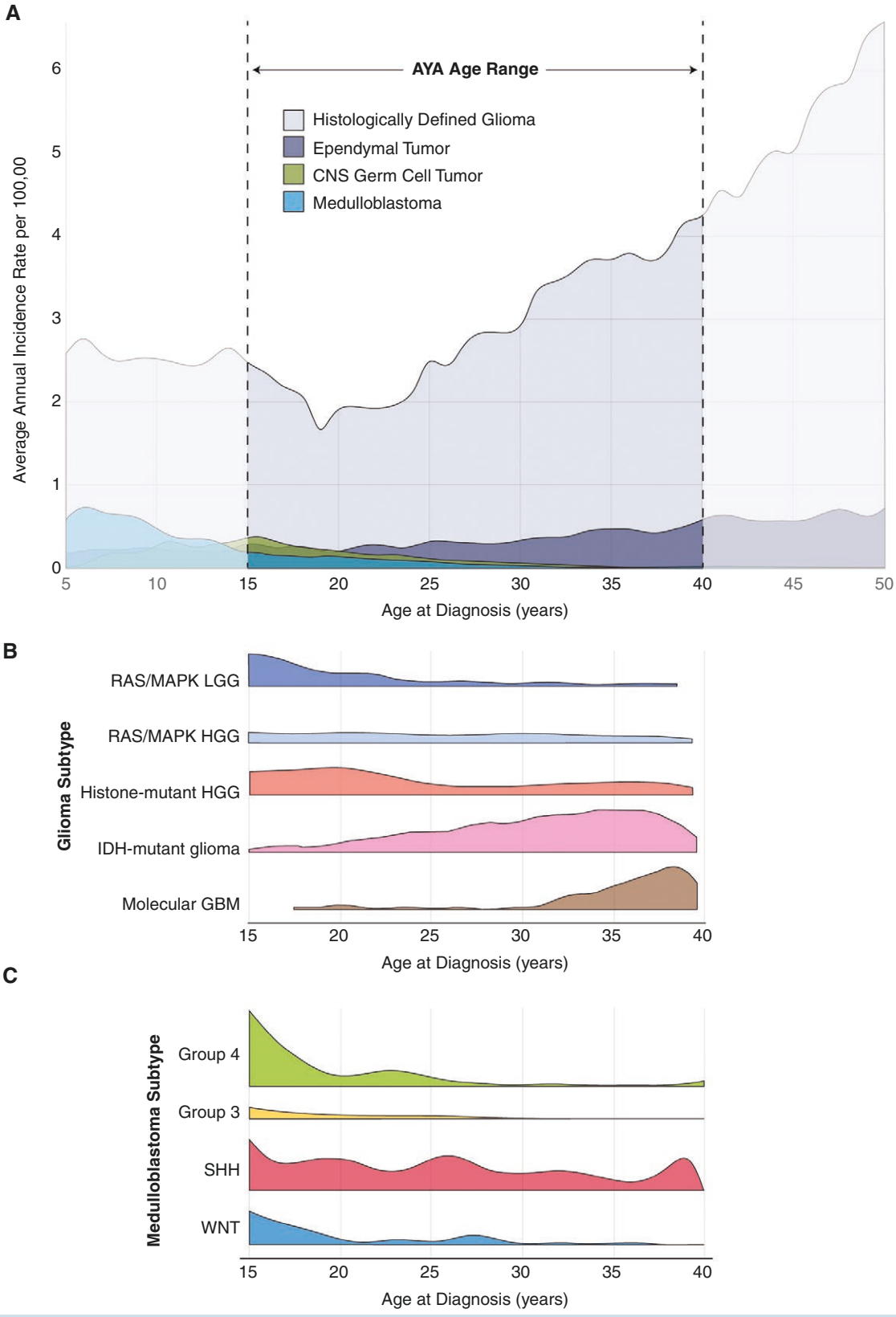

Figure 1. (A) Overview of the relative incidence of brain tumors in adolescents and young adults. The incidence of the different subtypes of glioma[10] and medulloblastoma[11] in this population are further defined in (B) and (C), respectively. Molecular GBM is defined per WHO 2021 criteria[7] *Figure generated using data from CBTRUS: Data provided by CDC's National Program of Cancer Registries and National Cancer Institute's Surveillance, Epidemiology and End Results Program, 2016–2020*[10–12]

Table 1. Current Management of Adult-Type Gliomas in AYA[18]

Glioma subtype	Current management	Ongoing Clinical Trials
Oligodendroglioma, IDH- mutant and 1p/19q-codeleted grade 2	Adjuvant treatment may be deferred until progression in select patients (eg, with gross total resection) Radiotherapy (50.4–54 Gy in 28–30 fractions) followed by adjuvant procarbazine, lomustine, and vincristine (PCV)[19] or temozolomide. *The current standard of care for IDH-mutant LGG is currently under revision following the results of the INDIGO trial*[20]	INDIGO trial (NCT04164901), CODEL trial (NCT00887146) POLO trial
Oligodendroglioma, IDH- mutant and 1p/19q-codeleted grade 3	Radiotherapy (57–60 Gy in 30–33 fractions) in combination with (PCV)[21] or TMZ	CODEL trial (NCT00887146)
Astrocytoma, IDH- mutant grade 2	Adjuvant treatment may be deferred until progression in select patients (eg, with gross total resection). Radiotherapy (50.4–54 Gy in 28–30 fractions) in combination with either adjuvant TMZ,[22] or PCV[19] *The current standard of care for IDH-mutant LGG is currently under revision following the seminal results of the INDIGO trial*[20]	
Astrocytoma, IDH- mutant grade 3	Radiotherapy (57–60 Gy in 30–33 fractions) in combination with adjuvant TMZ[22]	
Astrocytoma, IDH- mutant grade 4	Management according to grade 3 IDH-mutant astrocytoma or IDH-wt glioblastoma.	
Glioblastoma, IDH-wild type	Radiotherapy (60 Gy in 30 fractions) combined with concurrent TMZ followed by 6 months of adjuvant TMZ[23] NGS for targetable mutations is recommended	

Abbreviations: LGG, low-grade glioma; HGG, high-grade glioma; ORR, objective response rate; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival.

upfront postsurgical management (in addition to tumor size, the extent of resection, and neurological deficits),[25] these studies predate the molecular era. Currently, the impact of age on tumor biology in IDH-mutant tumors has not been fully elucidated.

- While the role of targeted IDH inhibition represents a particularly attractive strategy in AYA, these patients were underrepresented in the INDIGO trial (median age, 40.5 years). Many questions remain, including whether IDH inhibition would ultimately delay or prevent eventual malignant transformation to higher-grade glioma, the efficacy and long-term safety of IDH inhibition in younger patients, and the approach to family planning.
- Primary mismatch repair deficient IDH-mutant astrocytoma (PMMRDIA) are high-grade gliomas (HGGs) characterized by IDH mutations in addition to germline mutations in mismatch repair genes (*MLH1, PMS2, MSH6,* or *MSH2*). DNA methylation profiling, DNA-sequencing, or IHC-based identification of mismatch repair deficiency syndrome can help establish a diagnosis. The median age at diagnosis for PMMRDIA is 14 years and carries a poor prognosis with a median survival of only 15 months.[26] The role of immunotherapy in patients with PMMRDIA alone or in combination is an area of active research.

Glioblastoma.—Glioblastoma has an average annual age-adjusted incidence rate of 0.58 in AYA compared to 7.04 in those above 40 (based on 2016–2020 data).[4] However, this may not reflect the most recent WHO CNS5 classification which further distinguishes pediatric-type alterations (such as *FGFR* and *BRAF* mutations) within IDH-wt astrocytomas. AYA-specific data on the prognosis for glioblastoma is relatively sparse but recent SEER and CBTRUS data indicate that median overall survival is 24 months, with 5- and 10-year survival rates of 27.3% and 19%, respectively, highlighting that these tumors may behave biologically distinctly from GBM in those >40 years.[6] The approach to glioblastoma is reviewed more broadly in the SNO/EANO consensus review on glioblastoma in adults.[27]

The following aspects should be highlighted specific to AYA with glioblastoma:

- IDH-wt diffuse gliomas in AYA (including IDH-wt LGGs) should prompt further molecular testing including next-generation sequencing (NGS) of the *IDH1* and *IDH2* loci.
- The AYA population is enriched with rare subsets of glioblastoma carrying specific drivers such as MMR-deficiency (both somatic and constitutional), rare gene fusions, or RAS/MAPK mutations that are all potentially targetable. Therefore, both IHC and advanced molecular testing should be proposed, especially when other common drivers of this population (ie, IDH or histone mutations) are lacking.

Pediatric-Type Glioma

Pediatric-type gliomas account for approximately 30% of newly diagnosed gliomas found among AYAs[10] and are divided into LGG and HGG based on histology and molecular features. While pediatric-type alterations are enriched in midline locations, they are found throughout the CNS.

Pediatric LGGs are typically driven by single alterations in the RAS/MAPK pathway[28] and associated with an excellent long-term outcome,[10] with treatment focused on reducing morbidity and minimizing toxicity of therapy. Pediatric HGGs encompass many different entities and are divided into gliomas harboring histone mutations (diffuse hemispheric glioma [DHG], G34-mutant and diffuse midline glioma [DMG], H3-K27M-altered), diffuse pediatric-type HGG, H3- and IDH-wt and infant-type hemispheric glioma. While the latter occurs occasionally in AYA, this review focuses on the first 2 entities. In addition, several other tumors affecting AYAs also carry mutations in the RAS/MAPK pathway, including pilocytic astrocytoma, ganglioglioma, and pleomorphic xanthroastrocytoma, now regrouped under circumscribed astrocytic gliomas under the WHO CNS5 classification. While many studies on pediatric-type LGG have previously included pilocytic astrocytomas, these entities are not discussed specifically within this review. A summary of the current therapies for pediatric-type glioma is presented in Table 2.

Pediatric-type LGG.—Pediatric-type LGG (pLGG) accounts for 26% of newly diagnosed glioma in AYA.[10] It is typically driven by a single alteration in the RAS/MAPK pathway, with enrichment in AYAs for single nucleotide variations (SNVs) such as *BRAF* V600E and *FGFR* SNVs compared to the *BRAF* fusions more commonly seen in young children.[10,28] Notably, in IDH1 R132H-wt WHO grades 2 and 3 glioma, alterations in the RAS/MAPK pathway (including *BRAF*V600E and *KIAA1549-BRAF* fusion) are found in approximately equal numbers as non-canonical IDH mutations[10] suggesting that further sequencing for variants beyond IDH1 R132H should be routinely considered in IDH-wt LGG.

In pediatric patients, treatment is currently dictated by several factors including tumor location, symptomatology, molecular alterations, and growth pattern. Gross total resection is potentially curative, with the rate of success largely dependent on tumor location. Radiation therapy, while an effective treatment for pLGG,[42] has been associated with long-term toxicity in pediatric cohorts.[43] Long-term toxicities of radiation therapy in AYA, in the context of more precise methods of radiation delivery and proton therapy, have not been clearly established but remain a significant concern.[44,45,46] Given the anticipated excellent long-term survival in LGG, radiation is often reserved in the context of recurrent disease following targeted therapy or chemotherapy, even though these other treatment modalities can also carry unknown late toxicities. When radiation therapy is indicated, and when accessible, proton therapy is sometimes prescribed in the treatment of pLGG in AYA. While chemotherapy has been employed successfully in children and adolescents,[47,48] some approaches, especially those including vincristine, may be associated with greater neurotoxicity in adolescents and likely adults.[49] More recently, various small molecule inhibitors (targeted therapy) have been employed with improved outcomes compared to chemotherapy in specific pLGG populations. For patients with *BRAF* V600E LGG, a recent trial demonstrated superiority of dabrafenib, a BRAF inhibitor (BRAFi), in combination with trametinib, a MEK inhibitor (MEKi) to chemotherapy for newly diagnosed patients prompting an FDA approval for these specific patients in March 2023.[31] MEKi such as selumetinib[34] and trametinib[50] have also shown efficacy in recurrent BRAF-altered LGG and prospective, randomized studies that are open to those under 21 years are underway comparing them to chemotherapy for those newly diagnosed LGG with BRAF fusions. More recently, the second-generation BRAFi tovorafenib has shown high response rates and durable tumor control in pLGG with *BRAF* mutations or fusions in the phase 2 FIREFLY-1 trial.[36,51] *FGFR*-altered tumors have been included in some of these trials.[50] FGFR inhibitors have also been employed in small studies, with some efficacy in addition to significant toxicity; however, the role of these agents is unclear at this time.[52]

Unfortunately, these trials have been performed primarily in patients under 18–21 years old and there is a lack of data to broadly apply this paradigm in the AYA population. Many questions regarding targeted therapy remain, including optimal duration of therapy, safe strategies to stop therapy, impact on the natural history of tumor behavior, and long-term risks of prolonged use of these agents. Specifically, the frequency and severity of adverse effects in AYA compared to children or older adult patients is an important factor to consider and has not yet been fully described across the different targeted therapy options.

The following aspects should be highlighted specific to AYA patients with IDH-wt LGG:

- Molecular testing including sequencing for non-canonical IDH mutations and pediatric-type alterations including fusions is recommended.
- For patients with pLGGs who have undergone complete resection, observation and surveillance imaging are recommended given excellent curative rates and since transformation to higher grade gliomas is not typical.
- For those requiring adjuvant treatment postsurgery, we recommend a patient-centered approach outlining different treatment modalities and their short- and long-term toxicities, including targeted therapy, chemotherapy, and radiation. Associated toxicities may vary with age.
- Use of targeted therapy could be considered in subsets of LGGs harboring targetable alterations, particularly *BRAF*-altered tumors, despite a paucity of evidence in formal clinical trial settings, given the success of these agents, combined with the increased toxicity associated with chemotherapy and significant long-term risks of radiation.
- We would advocate for increased study of AYA patients treated with targeted therapy through clinical trial opportunities or registry studies to further understand outcomes in these populations.
- The above discussion should take into consideration patients' wishes for family planning given the unknown teratogenicity risk of newer targeted agents.

Pediatric-type HGG.—Pediatric-type HGG accounts for 7% of newly diagnosed gliomas in AYA. DMG accounts for the majority of these (60%), followed by diffuse pediatric-type HGG (30%), then H3- and IDH-wt, and DHG (10%). The treatment and prognosis of these different entities vary.

Table 2. Selected Targeted and Systemic Therapy in Pediatric-Type Glioma

Trial (phase)	Eligible age (years)	Population (*n*)	Outcome	Median time to response (months)
Dabrafenib (I/IIa)[29]	1–18	*BRAF* p.V600E LGG, recurrent/refractory (32)	ORR 44%	3.8
Trametinib +/– Dabrafenib (I/II)[30]	0–18	Refractory/recurrent malignancy (139–91) trametinib only (48 LGG), 48 trametinib and dabrafenib (34 LGG, 2 HGG)	*Trametinib only:* 15% PR 46% SD *Dabrafenib/ trametinib:* 25% PR 64% SD	3.8
Trametinib/ Dabrafenib (II)[31]	1–17	First-line therapy for *BRAF*V600E mutant LGG (73)	ORR 47% 12-month PFS 91%	
Dabrafenib/ Trametinib (II)[32]	1–18	Relapsed/refractory *BRAF*V600E mutant HGG (41)	ORR 56.1% 12-month PFS 44.1%	
Dabrafenib/ Trametinib (II)[33]	≥18	Recurrent/progressive *BRAF*V600E mutant glioma (58)	*HGG (n = 45):* ORR 15% *LGG (n = 13):* ORR 69%	
Selumetinib (II)[34,35]	3–21	Stratum 1: *BRAF* p.V600E, or *KIAA1549-BRAF* LGG, recurrent/ refractory (25)	36% PR 36% SD 2-year PFS 70%	7.54
		Stratum 3: NF-1 associated LGG, recurrent/refractory (25)	36% PR 64% SD 2-year PFS 96%	3.57
		Stratum 4: Recurrent/refractory optic pathway/hypothalamic LGG (25)	24% PR 56% SD 2-year PFS 78%	19.7
Tovorafenib (II)[36]	0–25	Relapsed/refractory *BRAF*-altered LGG (77)	ORR 67% Median PFS 19.4 months	3.0
Infragratinib (II)[37]	>18	Recurrent/progressive *FGFR*-altered glioma (26)	ORR 7.6% 6-month PFS 16%	
Everolimus (II)[38]	3–21	LGG, recurrent (23)	9% PR (2/23) 43% SD (10/23) 2-year PFS 39%	0.9
CPT-11,[39] bevacizumab and irinotecan (II)	<21	LGG, recurrent/refractory (35)	5.7% sustained PR 17.7% SD 2-year PFS 47.8%	
HERBY,[40] RT +TMZ followed by TMZ +/– bevacizumab (II)	3–18	HGG, treatment-naïve (62)	1-year PFS 38% (vs 48% in control arm) ORR 42% (5/12)	
Gefitinib + RT (II)[41]	3–21	Brainstem glioma, treatment-naïve (43)	1-year PFS 20.9% 1-year OS 56.4%	

Abbreviations: LGG, low-grade glioma; HGG, high-grade glioma; ORR, objective response rate; PR, partial response; SD, stable disease; PFS, progression-free survival; OS, overall survival.

DMG in AYA tends to be found more commonly outside of the pons (including the cerebral peduncles, thalamus, and spinal cord) compared to children.[53] The role of surgical resection is often limited given the midline location. However, where feasible, biopsy enables diagnostic confirmation and molecular characterization which may allow clinical trial enrollment. Treatment varies but typically involves focal radiation with or without concurrent/ adjuvant chemotherapy. The prognosis is very poor with median survival of 19 months.[53] Newer therapies are currently being studied in clinical trials including novel oral therapies (specifically the ACTION trial (NCT05580562) with ONC201),[54] low-intensity focused ultrasound, and immunotherapeutic approaches with a focus on vaccine therapy and chimeric antigen receptor-T cells.[55,56]

DHG, G34-mutant is a rare tumor that has an increased incidence in AYA,[57] with a median survival of 12–17 months.[57,58] Historically, treatment includes maximal safe

surgical resection followed by radiation with concurrent and adjuvant chemotherapy. Given the poor survival, new agents are needed and AYAs must be included in clinical trials for these tumors.

Diffuse pediatric-type HGG, H3- and IDH-wt is a recently described and understudied tumor type. While it shares the absence of histone alterations and IDH mutations with adult-type GBM, it is distinguished from adult-type GBM based on its distinct methylation profile.[59–61] These tumors can occur sporadically, or alternatively in the setting of constitutional mismatch repair deficiency syndrome (MMRD), where there is some evidence of response to immunotherapy.[61] Finally, this tumor type is observed in gliomas developing following therapeutic radiation.[62]

HGGs harboring BRAF V600E have prolonged survival compared to other molecular subgroups of HGG in AYA; however, this remains a fatal diagnosis.[10] Treatment with the combination of BRAFi with MEKi has shown radiographic response in patients after tumor progression.[33,63] Specifically, the Rare Oncology Agnostic Research basket trial evaluated the effectiveness of the combination of dabrafenib and trametinib in patients with solid tumors including recurrent/refractory LGG and HGG, and showed a 69% objective response rate in LGG and 33% in HGG, demonstrating clinically meaningful activity.[33]

While not discussed separately in this review, high-grade circumscribed glial tumors such as pleomorphic xanthoastrocytoma and gangliogliomas harboring *BRAF* V600E mutations can also arise in AYA. These tumors have been shown to respond to BRAF/MEK inhibition in pediatric patients at recurrence.[64]

The following aspects should be highlighted specific to AYA patients with pediatric-type HGG:

- Surgery or biopsy with molecular testing is recommended to identify targetable, driver alterations.
- For histone-altered tumors, patients should be enrolled in a clinical trial if possible, given the poor prognosis and lack of durable treatment options. In the absence of a clinical trial, the backbone of therapy remains radiation, with or without chemotherapy. Targeted therapy may be utilized following irradiation or at recurrence if a suitable alteration is identified.
- For HGG with *BRAF*V600E, maximal safe resection followed by radiation is currently the standard of care. Treatment with adjuvant BRAFi plus MEKi could be considered (especially in MGMT unmethylated patients) as this may prolong survival. Further treatment options are needed at the time of progression as resistance may develop.

Glioma in Cancer Predisposition

Cancer predisposition syndromes (CPS) occur due to germline mutations resulting in a predisposition to develop malignant disease, including CNS tumors. In AYA, CPS should be considered in patients diagnosed with glioma. Many CPS can lead to glioma, with neurofibromatosis type 1 (**NF-1**), **MMRD** (including Lynch syndrome and constitutional MMRD), and Li-Fraumeni syndrome (**LFS**) being the most common.

AYA patients with NF-1 are more likely to have a new tumor diagnosed outside of the optic pathway compared to younger patients, with an increased risk of HGG.[10] Many of these HGGs are transformed pilocytic astrocytomas (high-grade astrocytoma with piloid features; "HGAP"). They cluster on methylation profiling separately from other HGG and have *CDKN2A/B* or *ATRX* mutations.[65] Unfortunately, NF-1-associated HGGs have a particularly dismal prognosis and novel therapies are needed.[66] Children with NF-1 associated LGG have benefited from the use of MEKi at the time of recurrence, but such benefit has yet to be shown in HGAP.[34,65]

MMRD is found in 5%–10% of all newly diagnosed HGGs and rarely in LGGs in AYA.[67] Tumors encompass both IDH-mutant and IDH-wt glioma. If suspected, IHC can be done to evaluate for loss of relevant protein expression (*MSH2, MSH6, PMS2,* and/or *MLH1*). Molecular testing should also be considered as false negatives of IHC have been reported. This is crucial to recognize given the poor prognosis, ineffectiveness of temozolomide and opportunity for alternative treatment approaches using immune checkpoint inhibitors.[68,69]

While the proportion of gliomas among LFS cohorts has been described, the incidence in the AYA population with newly diagnosed gliomas has not been examined. Similar to MMRD, tumors may be IDH-wt or IDH-mutant with enrichment of non-canonical IDH mutations.[70] There are no specific therapies unique to LFS, but it has potential clinical implications for family planning, genetic counseling, and surveillance. While radiation therapy may result in subsequent tumors, options for therapy may be limited. As a result, radiation is often recommended and patients should be informed of the risks versus benefits.

The following aspects should be highlighted specific to AYA patients with a suspected CPS:

- Referral for genetic counseling and germline testing should be made in suspected cases.
- In confirmed cases of CPS, cascade testing must be performed on first-degree relatives given the survival benefit associated with implementing a surveillance screening protocol[71,72]
- For patients with new or progressive low-grade tumors in the setting of NF-1, use of MEKi should be considered, while patients with HGG may benefit from MEKi through a combinatorial strategy.
- For patients with MMRD, additional assessments for IDH status and tumor mutation burden should be performed. Treatment with immune checkpoint inhibitors should be discussed with a provider with expertise in this rare subgroup. Novel combination therapies are needed for non-responders.

Future directions for AYA with glioma.—

- The role of upfront targeted therapy in both LGGs and HGGs with targetable alterations (in conjunction with or in lieu of radiation therapy and temozolomide) needs to be further elucidated.
- Efforts are needed to implement clinical trials focused on relevant alterations and tumor biology with an expanded age of eligibility spanning the AYA population.

- Given the long survivorship of AYA patients with LGGs, clinical trials, and prospective studies should aim to capture the quality of life measures, neurocognitive status and functional outcomes.

Medulloblastoma

Medulloblastoma (WHO grade 4) is one of the most common malignant brain tumors in childhood.[4] Medulloblastoma is much rarer in the adult population, accounting for less than 1% of all adult CNS tumors[73]; however, it remains the most common embryonal tumor diagnosed in the AYA population. In the past decade, molecular profiling studies revealed heterogeneity among medulloblastoma resulting in molecular stratification into four main subgroups (Wingless (WNT), SHH-activated and *TP53*WT, SHH-activated and *TP53* mutant, groups 3 and 4), with further subclassification possible within each subgroup.[11,74] These advancements have allowed for improved prognostication, risk stratification, and development of molecularly driven clinical trials.[75,76] SHH medulloblastoma predominates in adults,[4] with WNT and group 4 medulloblastoma also seen.[77] Group 3 medulloblastoma is essentially absent in the adult population, with varied prognoses compared to children. Patients with SHH-activated medulloblastoma with either somatic or germline *TP53* mutation have a poorer prognosis, with significantly higher rates of relapse.[78] When compared to pediatric and adolescent SHH-activated medulloblastoma, young adults have a significantly lower incidence of germline *TP53* mutation and *MYCN* amplification.[77] Additionally, chromosome 10q loss was found to be predictive of worse PFS while chromosome 14q loss was not prognostic in adults with SHH-activated medulloblastoma,[77] divergent from pediatric data. WNT-activated medulloblastoma has been generally associated with excellent survival and pediatric trials in this population are currently aimed at therapy de-escalation. WNT-activated medulloblastomas in young adults, however, have been incompletely studied and may have a relatively less favorable prognosis; associated molecular aberrations in TP53 and OTX2 may predict a poorer outcome in this population.[79,80]

For diagnostic and therapeutic purposes, maximal safe resection is recommended for all patients with a suspected diagnosis of medulloblastoma as a residual of more than 1.5 cm^2 based on postoperative MRI is established as a high-risk feature in pediatric studies. Questions have been raised about whether this somewhat arbitrary residual amount remains prognostic when molecular features are considered. The prognostic significance of residual tumors in the adult population is less clear. This threshold of 1.5 cm^2 is often a consideration for second-look surgery and was considered a high-risk factor for the proposed (and subsequently suspended) Alliance AMBUSH trial[76,81] and an exclusion criterion for the initial version EORTC/NOA/COGNO PersoMed-I trial (NCT04402073).[82] On the other hand, aggressive surgical resections can lead to posterior fossa (PF) syndrome, with impaired mobility and speech, even mutism, affecting a significant portion of patients.[83] Surgical experience with pediatric infratentorial resections and multidisciplinary discussion may help arbitrate the judicious balance between maintaining an acceptable quality of life with prolongation of overall survival.

The modified Chang criteria are the most commonly used criteria for staging medulloblastoma.[84] MRI of the spine should be done preoperatively or 10–14 days postoperatively to evaluate for spinal metastasis. Cerebrospinal fluid (CSF) cytology (through lumbar puncture, if safe) is obtained 10–14 days after surgical resection to evaluate for microscopic disease. The postoperative MRI should precede the lumbar puncture in this situation to reduce the incidence of false positive reports of leptomeningeal disease. In general, any evidence of metastatic disease (M1–M4) currently is considered a high-risk feature.

For diagnostic classification, conventional histopathology, and immunohistochemistry should be paired with molecular testing in an integrated approach. Recently, DNA methylation profiling has become a standard part of the diagnostic work-up for medulloblastoma including identification of molecular subgroups and copy number changes.[85] Additionally, NGS can be performed to identify specific mutations/variants and copy number changes. For patients with SHH or WNT medulloblastoma, germline testing (eg, *TP53* mutation in SHH (especially for those <18 years of age), and APC in WNT medulloblastoma that do not have a -β-catenin mutation] is recommended.

For AYA patients with medulloblastoma, aggressive multimodal treatment with surgery, radiation therapy, and chemotherapy is recommended given the potential for cure. Following maximal safe surgical resection, craniospinal irradiation (CSI) therapy is recommended. While the neurocognitive impact of CSI is less in AYA when compared to younger children, proton therapy should be considered, when available, to reduce short- and long-term hematologic and visceral toxicities (specifically involving the neck, chest, abdominal, and pelvic organs). The standard radiation therapy plan for pediatric patients with average-risk disease includes CSI of 23.4 Gy with an additional boost to the tumor bed up to a total dose of 54 Gy. For patients with high-risk disease, the CSI dose is escalated to 36 Gy with a boost as above, and boosts to metastatic sites should be included if feasible. In adults, data supporting the use of 23.4 CSI for average-risk medulloblastoma is limited. Therefore, the use of this lower dose or the more conventional neuroaxis dose of 36 Gy depends on the treatment site and physician preference. Recent studies have looked to standardize this practice, with clinical trials in the US and Europe evaluating the effectiveness of 23.4 Gy CSI for adult patients with average-risk medulloblastoma.[76,82] The role of concomitant vincristine during radiation therapy in the AYA population is unknown given the lack of clear impact on survival. Given the significant neurotoxicity seen in these patients, the omission of vincristine should be considered as contemporary clinical risk-adapted treatment regimens have omitted concomitant vincristine with no impact on outcome.[86]

Chemotherapeutic regimens used in pediatrics have been well established through multi-institutional clinical trials (including large consortium trials in North America and Europe) for both average- and high-risk patients. The standard practice in adults is less clear.[87,88] The most common regimen in adults is the Packer A regimen, with eight cycles of vincristine, cisplatin, and lomustine. While there is no consensus on which regimen to use for AYA

patients, it is important to note that there is clear data in both pediatric and adult literature that the addition of maintenance chemotherapy after radiation improves outcomes when compared to radiation therapy alone.[89,90] It is imperative for treating oncologists to recognize that AYA patients have relatively poorer tolerance to chemotherapy and suffer from increased incidence and severity of peripheral neuropathy and myelosuppression compared to pediatric patients, and therefore often require dose/regimen modification during treatment.[88,91] It is this poorer tolerance and often inability to deliver adequate chemotherapy that has raised concerns over reducing the dose of CSI. Lastly, there is currently no standard chemotherapy regimen for recurrent medulloblastoma; various additional cytotoxic chemotherapy and antiangiogenic agents have been tested with varied success. SMO inhibitors can also be considered for SHH medulloblastoma in post-pubertal patients.

AYAs with SHH medulloblastoma are enriched for mutations in PTCH and SMO, which makes them excellent candidates for SMO inhibitors. In early phase studies, several SMO inhibitors showed impressive objective responses in patients with multiply progressive SHH-medulloblastoma.[92,93] Despite early response to treatment, one key issue with these inhibitors is the rapid development of drug resistance and escape mechanisms.[93] As such, several strategies have been proposed/trialed, including the use of these drugs as maintenance therapy, as well as in combination with other therapies such as with MEKi, PI3K inhibitors, or temozolomide.[94] The current approach to medulloblastoma is summarized in **Table 3**.

The following aspects should be highlighted specific to AYA patients with medulloblastoma:

- The most common molecular subgroup seen in the AYA population is the SHH subgroup, with most of these cases harboring sporadic mutations in the *SMO* or *PTCH* genes.
- Compared to childhood SHH-medulloblastoma, AYA, and adult medulloblastoma have a lower frequency of *TP53* mutations and are more commonly associated with *TERT* promoter mutations.[96]
- NGS and DNA methylation profiling should be integrated into the diagnosis of AYA patients with medulloblastoma, with germline testing where appropriate.

Table 3. Current Management of Medulloblastoma in AYA and Future Directions

Diagnostic work-up and treatment of AYA with medulloblastoma	Current practice	AYA considerations/uture directions and trials
Diagnosis and subgrouping	**Neuroradiology** - Brain MRI pre and post (within 48 hours) surgery (Including: Axial or 3DT1-weighted,T2-weighted, FLAIR, DWI, and postcontrastT1-weighted sequences) - Spinal MRI should be done preoperatively or 10–14 days postoperatively **Other diagnostics** - CSF cytology: 10–14 days after surgery, if safe **Pathology** Histopathological diagnosis: classic, desmoplastic or nodular, extensive nodular, or large cell/anaplastic Molecularly defined subgroups: WNT-activated, SHH-activated and *TP53*WT, SHH-activated and *TP53*mut, or non-WNT and non-SHH. DNA methylation can aid in molecular subgrouping	**Future directions:** • Metabolic imaging and radiomics to predict molecular subgrouping • Liquid biopsy on CSF for disease monitoring
Surgical therapy	Maximal safe resection (midline transvermian or telovelar approach)	
Radiation therapy	Craniospinal irradiation (within 28–42 days after surgery) 36 Gy in daily fractions of 1.8 Gy, or a dose of 35.2 Gy in daily fractions of 1.6 Gy, each five times weekly + a local dose escalation to the posterior fossa with a total dose up to 54–55.8 Gy A craniospinal irradiation dose reduction to 23.4 Gy might be used in AYA with standard/average-risk disease	**AYA considerations:** • Role of proton radiation therapy • De-escalation of radiotherapy in select patients • Currently trialed in EORTC-1643-BTG/NOA-23 trial[82]
Systemic therapy	Commonly used chemotherapy regimens include: 1. Packer chemotherapy regimen[95] 2. Cisplatin-etoposide-based combination[90]	Tolerance is worse in adolescents and adults than in children. • Consider age and risk-dependent modulation of treatment[91] • Consider decreased use of vincristine[91]
Targeted therapy	SMO inhibitors at recurrence	Upfront use of SMO inhibitors in combination with chemoradiation • Currently trialed in EORTC-1643-BTG/NOA-23 trial[82]

FLAIR, fluid-attenuated inversion recovery; DWI, diffusion-weighted imaging; CSF, cerebrospinal fluid.

- Multi-modal treatment with surgery, radiation therapy, and chemotherapy is recommended.
- Consideration for the use of a lower dose of 23.4 CSI in average-risk cases and discussion of proton therapy, whenever available, in all cases.
- Choice of chemotherapy regimen should be influenced by age, risk factors, and performance status and in conjunction with radiation dosing.

Future directions for AYA with medulloblastoma

- Further studies are required to evaluate dose reduction of CSI for certain subgroups (ie, average risk medulloblastoma, WNT medulloblastoma).
- The optimal chemotherapy regimen (concurrent and adjuvant) needs to be established.
- The role of targeted therapy upfront or at recurrence needs to be further investigated.
- Ongoing trials including EORTC 1634-BTG/NOA-23 (PersoMed-I; NCT04402073) which randomizes postpubertal patients between standard dose versus reduced dosed CSI and SHH-subgroup patients between utilization of an SMO inhibitor (with chemoradiation) versus chemoradiation alone will generate data which may translate into a change in practice for adults with medulloblastoma.[82] This trial has recently been paused due to low recruitment but is planned to be reopened with an adapted design and relaxed inclusion criteria.
- Clinical trial design in medulloblastoma should consider eligibility criteria spanning older pediatric to the AYA age range.

Prospective registries gathering real-world evidence on the efficacy of current treatment regimens, adverse effects, and long-term outcomes in AYAs with medulloblastoma are essential given the challenges and lack of industry support for clinical trials.

Ependymoma

Ependymal tumors can arise from childhood through adulthood and include ependymoma (EPN), myxopapillary ependymoma (MPE), and subependymoma (SE). The biology and location of these tumors differ significantly.[97,98] In AYA, they occur at a rate of 0.35 per 100 000,[4,6,99] with the spinal cord being the most common location for ependymal tumors, followed by PF with supratentorial (ST) tumors being the least common.[100] Spinal cord ependymal tumors accounts for close to 20% of all spinal tumors in adults.[101]

Ependymal tumors are subdivided into 10 distinct subgroups based on molecular features and tumor location, which have recently been incorporated into the 2021 WHO CNS classification.[7,97,102] SE is histologically classified as WHO grade 1 and occurs throughout the CNS. MPE was reclassified as a WHO grade 2 tumor and commonly arises in the conus medullaris and filus terminale, and can disseminate throughout the brain and spine at diagnosis or recurrence.[7] Both of these histological subtypes are significantly more common in adults compared to children and are typically associated with excellent outcomes, although relapses can occur for MPE.[103]

EPN can be classified as WHO grade 2 or 3 based on histological findings; however, this grading is subject to significant interobserver variability and its prognostic value is unclear.[100,104,105] In AYA, ST-EPN must be confirmed to have *ZFTA*-fusion for diagnosis, as *YAP1*-fused EPN is typically restricted to young children.[97,100,104] *ZFTA*-fused EPN in AYA have been associated with higher rates of recurrence compared to children, with *CDKN2A* being a negative prognostic marker.[104,106] PF ependymoma (PF-EPN) in AYAs are enriched with the PF-B subgroup and are associated with improved outcomes compared to the PF-A subgroup, which is most commonly seen in younger children.[97,100,104] In distinguishing PF-A vs PF-B, one cost-effective method has been the immunohistochemical evaluation of H3K27me3. The reduction of staining is highly specific to PF-A and can therefore help inform postsurgical management and prognosis.[107] Loss of 13q has been shown to be a negative prognostic marker for PF-B-EPN.[100,108] In adults, the outcome for ST-EPN-*ZFTA*-fused, PF-B-EPN, and PF-SE with ependymoma histology demonstrate a 5-year PFS of 60%, 64%, and 67%, respectively, and 10-year overall survival (OS) of 60%, 42%, and 45%, respectively.[100]

Spinal EPN (SP-EPN) typically has chromosome 22q loss associated with an *NF-2* inactivating mutation occurring either sporadically or with germline neurofibromatosis type 2.[105,109] Outcome is excellent with 5-year OS of 100%.[97] A distinct subgroup of SP-EPN harboring *MYCN* or rarely *MYC* amplification has been found in adults and is associated with poor prognosis with a median PFS of 17 months.[7,102,110]

Despite insights into tumor biology, treatment for ependymal tumors has not changed over the last few decades, with stratification generally based on histology and the extent of surgical resection.[111] For SE, which are often asymptomatic, maximal safe resection is sufficient, and patients are subsequently managed with serial observation. Treatment of MPE also includes maximal safe resection; however, radiation should be considered for patients with significant residual tumors or those with metastatic disease, taking the toxicity of radiation into account. Treatment of EPN includes maximal safe resection, potentially followed by focal irradiation, although prospective studies in AYAs and adults are limited. For localized WHO grade 2 ST-EPN with complete resection, there may be a role for close observation alone given the potential for salvage surgery at recurrence.[112,113] For PF-B-EPN, gross total resection and focal radiation should be considered given improved PFS; further prospective trials are needed to explore treatment de-escalation.[100] For grade 3 EPN, SP-EPN-*MYC,* or grade 2 EPN with incomplete resection, treatment generally includes maximal safe resection followed by focal radiation. Disseminated disease at the time of initial presentation is rare, but in such cases, CSI with boost treatment of metastatic sites should be considered after resection of the primary tumor and metastatic disease, the latter when feasible or to alleviate symptoms. Proton beam irradiation offers equivalent outcomes compared to photons, with reduced radiation exposure to normal tissue in young patients, and could be considered for AYAs.[114] Chemotherapy for newly diagnosed ependymomas may

have a role in some subgroups of pediatric patients (especially infants),[112,115] while it is not well-studied in adult patients.[111]

At recurrence, there is no standard-of-care approach that is universally accepted. For localized recurrence of EPN, data from pediatrics supports maximal repeat safe resection followed by focal re-irradiation. Re-irradiation has been shown to be safe and has prolonged survival outcomes.[116,117] The role of CSI at the time of localized recurrence remains controversial. CSI at the time of distant recurrence appears to benefit those with distant-only failure whereas those with combined local and distant failure have a high rate of subsequent progression and are unlikely to survive.[116] In adults, treatment with temozolomide with or without lapatinib has been shown to be safe with some radiologic response in various tumor locations; however, molecular subgrouping was notably not included in the analysis.[118,119] Novel treatment strategies are needed for recurrence.

The following aspects should be highlighted specific to AYA patients with ependymoma:

- The tumor specimen should undergo molecular analysis given the potential for misdiagnosis based on histology alone with consideration for methylation array testing. *ZFTA*-fusion is required for the diagnosis of ST-EPN in this age group.
- For MPE or EPN, staging including imaging of the craniospinal axis along with CSF examination should be performed.
- There is the potential role for observation for WHO grade 2 EPN that has undergone gross total resection; however, one must be cautious with this approach given the poor interobserver reliability of WHO grading. Focal radiation (54-60 Gy) should be considered in cases where there is a residual disease, in grade 2 PF-EPN, and offered for all grade 3 EPN. Future clinical trials incorporating molecular subgrouping (eg, *YAP1* vs. *ZFTA*) will be critical in evaluating this question.

Future directions for AYA with ependymoma:

- Novel treatments are needed for SP-EPN-*MYC* and recurrent EPN. As SP-EPN-*MYC* occurs in adulthood, clinical trials should be developed with novel therapies for this population.
- There are many molecularly informed clinical trials recruiting patients in pediatrics for recurrent EPN. Given the limited treatment options for these patients, consideration should be given to expanding the age eligibility to include AYA patients.

Germ Cell Tumors in AYA

Intracranial germ cell tumors (iGCT) are rare CNS tumors, occurring in 0.11 per 100 000 in the AYA population in the United States[6,101] with increased rates in males (approximately 5.5 times that of females) and Asian/Pacific Islanders (approximately 60% higher incidence rate).[120] Clinically, iGCT is subdivided into germinoma and non-germinomatous germ cell tumor (NGGCT). Germinoma represents two-thirds of all iGCT, with a peak incidence in adolescence.[120] iGCTs are typically seen in the suprasellar region, pineal region, or simultaneously in both (bifocal) and rarely in other locations such as the basal ganglia.[120]

Diagnosis of iGCT can be made with histopathology and/or tumor marker confirmation (β-hCG and/or α-fetoprotein) in the blood or CSF of the patient. Notably, diagnostic approaches for iGCT can differ across the globe, both in terms of the emphasis on surgical resection/biopsy as well as the cutoff value of β-hCG to differentiate germinoma and NGGCT. For a subset of patients with characteristic imaging findings and elevated tumor markers, a diagnostic biopsy may not be necessary.[121] Staging should be done to assess for CNS dissemination, including imaging of the craniospinal axis with lumbar CSF cytology evaluation. Imaging of the chest, abdomen, and pelvis should also be pursued when appropriate to assess for any extracranial involvement. At diagnosis, serum and CSF tumor markers should be evaluated in all patients when feasible. Novel biomarkers such as microRNA may support diagnosis and allow evaluation of treatment response but are currently not part of the standard of care.[122]

In general, pure germinomas are responsive to treatment and are associated with survival rates >90% in AYA.[123] Surgery should be limited to establishing a diagnosis unless decompression is required to reduce symptoms or restore CSF pathways. Current strategies in pediatric consortium trials are aimed at therapy reduction to reduce long-term sequelae of treatment, while treatment of AYAs remains heterogeneous.[124] Radiation therapy is important in maintaining excellent cure rates for germinoma.[125] CSI has been found to be an effective treatment irrespective of disease status; however, clinical trials have shown comparable outcomes for those with nonmetastatic disease using chemotherapy combined with reduced field of radiation using whole ventricular irradiation (WVI).[126] In AYAs, this approach has been associated with superior PFS compared to CSI,[123] though there is no international consensus on optimal chemotherapy regimen or radiation dose (**Table 4**). For metastatic disease, CSI is the standard treatment, with radiation boost augmented by the inclusion of induction chemotherapy. Notably, bifocal germinoma should be treated as a localized disease assuming no evidence of distant metastases.

Compared to germinomas, NGGCTs are more resistant to treatment and require multi-modal treatment (Table 5). Conventional treatment for NGGCT includes induction chemotherapy followed by CSI.[133,134] For localized disease, recent data from ACNS1123 suggests that reduced field radiotherapy using WVI maintains excellent PFS and OS as compared to ACNS0122 and SIOP96[135]; however, concerns were raised over the possibility of increased distant spinal recurrences.[135] The current Children's Oncology Group (COG) study, ACNS2021 (NCT04684368), utilizes a similar chemotherapy regimen with the addition of spinal irradiation to WVI, aiming to decrease spinal relapses. Similar to germinoma, there is no consensus on optimal chemotherapy regimen,[133–136] and the range of methodologies used makes comparison of radiotherapy approaches

Table 4. Treatment and Outcomes of Localized Germinoma in Different Studies

Study	Age inclusion (years)	Chemotherapy	Radiation	PFS (%)	OS (%)	Conclusion
SIOP 96[126] (*n* = 235)	4–42 Median 13	None	24 Gy CSI + 16 Gy boost	97 (5 y)	95 (5 y)	Increased relapse outside of focal radiation field. Led to the concept of WVI.[127]
		Carboplatin/ etoposide alternating with etoposide/ ifosfamide (4 cycles)	40 Gy IFRT	88 (5 y)	96 (5 y)	
CHLA[128] (*n* = 20)	7–21 Median 15.5	Carboplatin/ etoposide (4 cycles)	21.6–25.5 Gy WVI + boost to total 30–30.6 Gy pre-biopsy tumor volume	89.5 (3 y)	100 (3 y)	Demonstrated feasibility of alternative chemotherapy regimen.
POG9530[129] (*n* = 12)	9.5–17.7 Median 15.1	Cisplatin/ etoposide alternating with cyclophosphamide/ vincristine (4 cycles)	Response based (IFRT): CR—30.6 Gy <CR—50.4 Gy	92 (3 y)	100 (3 y)	Demonstrated efficacy of response-based reduction in radiation dose.
Brazil[130] (*n* = 43)	4.7–25.5 Median 13.2	Carboplatin/ etoposide (4 cycles)	Response based: CR—18 Gy WVI + boost 12 Gy PR—18 Gy WVI + boost 22 Gy (mature teratoma) or 36 Gy (immature teratoma) Metastatic—24 Gy CSI + boost 12 Gy	100 (5 y)	100 (5 y)	
COG ACNS1123[131] (*n* = 137)	4.9–21.5 Median 14.1	Carboplatin/ etoposide (4 cycles)	CR—18 Gy WVI + boost 12 Gy IFRT (*n* = 74)	94.5 (3 y)	100 (3 y)	Did not meet criteria for non-inferiority for reduced dose WVI, though patient follow-up limited sample size leading to this result.
		Carboplatin/ etoposide (4 cycles)	PR—24 Gy WVI + boost 12 Gy IFRT	93.8 (3 y)	93.8 (3 y)	
SIOP CNS GCT II[132]	14. 1 years (range 5,0–41,0 years).	Carboplatin/ etoposide/ Ifosfamide (4 cycles)	Response based: CR—24 Gy WVI PR—24 Gy + boost 12 Gy IFRT SD—(incomplete resection with germinoma + teratoma) 24 Gy WVI + boost 30 Gy IFRT	CR—97% (4 y) PR/ SD—95% (4 y)	Not available	Safe to omit boost for patients with CR after chemotherapy. WVI dose 24 Gy should be standard consolidation treatment.

Abbreviations: CSI, craniospinal irradiation; y, years; PFS, progression free survival; OS, overall survival; WVI, whole ventricular irradiation; IFRT, involved field radiation therapy; CR, complete response; PR, partial response; SD, stable disease.

difficult. For metastatic disease, induction chemotherapy followed by CSI is required.

For patients with residual disease following chemotherapy, second-look surgery should be considered.[135] For these cases, if there is the absence of residual malignant components and tumor markers are negative, an excellent outcome is maintained.[134,135] Second-look surgery should also be considered for patients with progressive radiographic disease in the absence of tumor marker elevation, given the possibility of growing teratoma syndrome.[137]

While there are no dedicated prospective trials for AYA patients, this age group has had representation in European consortium trials in iGCT as well as the current COG trial (in collaboration with the National Clinical Trial Network which includes AYA). Currently, for AYAs with GCT, there is limited data in the literature to support specific treatment approaches.[123]The excellent outcomes observed in pediatric studies for iGCT need to be confirmed in the AYA population.

The following aspects should be highlighted specifically for AYA patients with iGCT:

- In cases with characteristic imaging features with tumor markers suggestive of a particular entity, biopsy may not be necessary.
- Staging, including craniospinal imaging and lumbar puncture, should be performed to assess for tumor marker elevation and cytologic dissemination.
- β-hCG and α-fetoprotein should be evaluated in serum and CSF in all patients when feasible for diagnosis and assessment of treatment response.
- Treatment typically includes chemotherapy followed by radiation, although there is no international consensus on optimal chemotherapy or radiation regimen.
- Second-look surgery should be encouraged for patients with residual tumor or tumor progression, particularly in the absence of tumor marker elevation to assess for growing teratoma syndrome.

Table 5. Treatment and Outcomes of NGGCTs in Different Studies

Study	Age inclusion (years)	Chemotherapy	Radiation	PFS (%)	OS (%)	Conclusion
SIOP96[133]	4–30 Median 12 *18% >16 years old	Cisplatin/etoposide/Ifosfamide (4 cycles)	Localized—54 Gy IFRT (n = 116)	72 (5 y)	82 (5 y)	Identification of risk factors, including serum/CSF AFP > 1000 ng/mL and < CR after chemo/2nd look surgery as risk factors for recurrence.
			Metastatic—30 Gy CSI + boost 24 Gy (n = 33)	68 (5 y)	75 (5 y)	
POG9530[129] (n = 14)	6.5–18.1 Median 11.4	Cisplatin/etoposide alternating with cyclophosphamide/vincristine (4 cycles)		79 (3 y)	79 (3 y)	
ACNS0122[134] (n = 102)	3–23 Median 12	Carboplatin/etoposide alternating with cyclophosphamide/vincristine (6 cycles)	36 Gy CSI + boost 54 Gy	84 (5 y)	93 (5 y)	Neoadjuvant chemotherapy +/– 2nd look surgery resulted in improved outcomes. Therapy reduction may be feasible for good responders.
ACNS1123[135] (n = 107)	3.7–21.6 Median 11	Carboplatin/etoposide alternating with cyclophosphamide/vincristine (6 cycles)	CR—30.6 Gy + boost 54 Gy (n = 66)	88 (3 y)	92 (3 y)	Closed early with 8 recurrences (stopping rules), but in retrospect 2/8 participants were not eligible to receive reduced dose RT. All recurrences included distant (spinal) metastasis.
SIOP CNS GCT II[136] (n = 23, HR stratum only with AFP > 1000 ng/mL or age < 6 years)	13 years,(age range: 0,1 to 25,1 years)	Cisplatin/etoposide/Ifosfamide (2 cycles + 2 high-dose cycles)	Risk adapted as per SIOP96	60 (3 y)	Not available	This is a feasible regimen. High-risk patients may benefit from further dose intensification.

Abbreviations: PFS, progression-free survival; OS, overall survival; y, years; CSF, cerebrospinal fluid; AFP, alpha-fetoprotein; CR, complete response; CSI, craniospinal irradiation; HR, high risk.

- Given the excellent survival, an effort to minimize long-term therapy-associated toxicity should continue.

Future directions for AYA with iGCT.—

- AYA patients should continue to be included in multi-institutional consortium trials with a goal to maximize survival outcomes and minimize long-term toxicity.

Discussion

AYA patients represent a unique population where tumor biology and delivery of care span both adult and pediatric paradigms of care. The AYA Progress Review Group report published in 2006 described the deficiencies in oncological care and defined action items needed to improve the survival of AYAs with cancer.[138] This report spurred the development of many AYA cancer programs internationally, which raised awareness and began to address specific deficiencies in existing cancer care models. These programs led to a surge in AYA-specific research, which provided critical insight into various components of care. These efforts have by and large been championed by physicians specializing in solid (non-CNS) tumors and hematological malignancies, leading to a relative dearth of AYA neuro-oncology-specific programs and research publications.

Despite recent data suggesting that survival outcomes among AYAs have continued to improve across the board over the last decade, outcomes for AYA neuro-oncology patients have surprisingly worsened.[1] This emphasizes the urgent need for comprehensive efforts to increase research, promote clinical trial enrollment, and augment oncological care, to improve survival for patients. Recognizing the challenges unique to CNS oncology patients, we present some possible solutions around central themes, summarized in **Figure 2**.

Standardized Molecular Sequencing for Diagnosis and Therapy Selection

Robust clinical molecular testing is central to accurate diagnosis, prognostication, and informs therapeutic decisions.[139] There is significant variability across institutions regarding testing strategies, partly related to unequal access due to differences in the availability of NGS platforms and issues related to third-party coverage. Centralized testing and uniform access through partnerships with

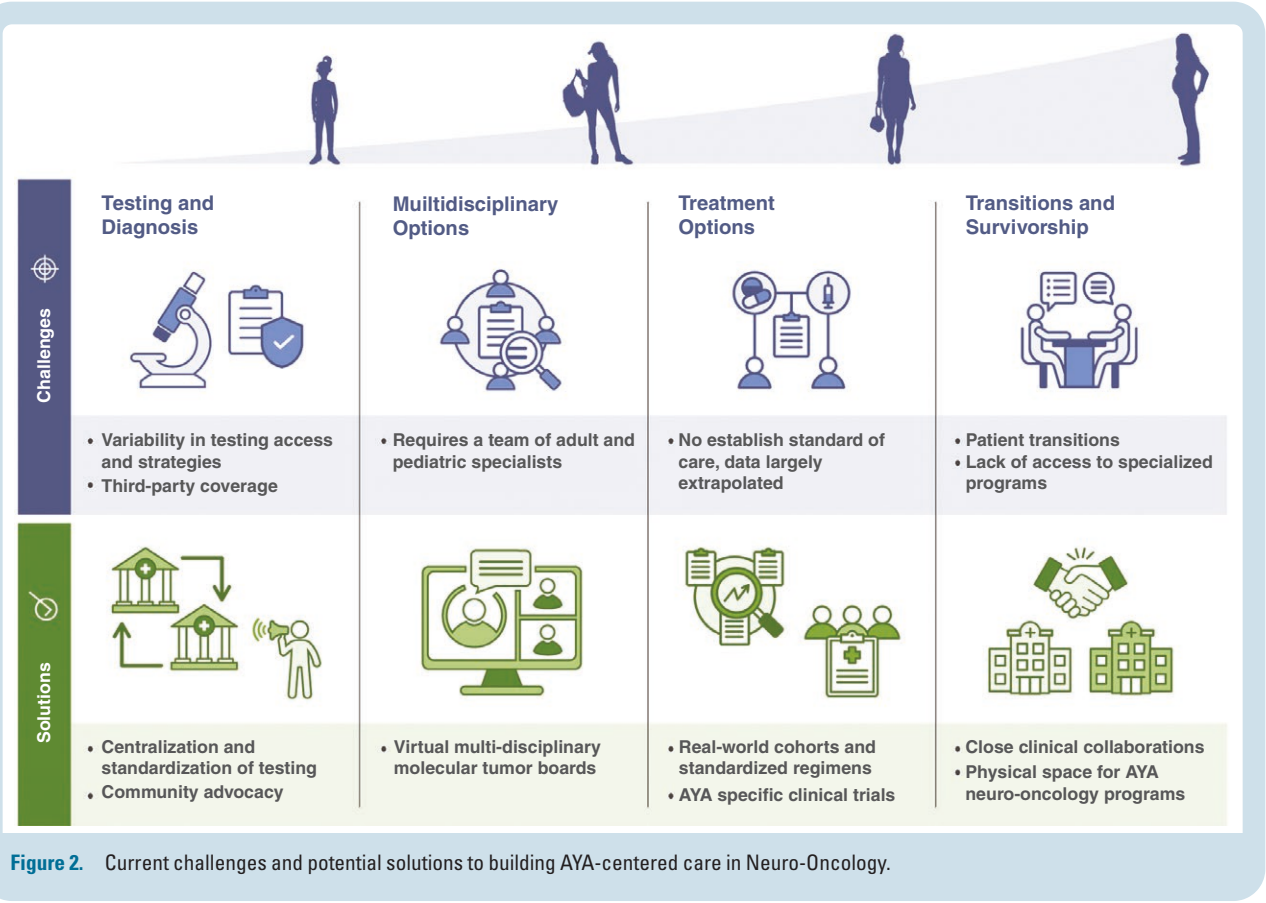

Figure 2. Current challenges and potential solutions to building AYA-centered care in Neuro-Oncology.

leading institutions may represent a cost-effective strategy that can also foster research collaborations. Consensus guidelines for testing that are supported by local stakeholders and reflect the landscape of available platforms and resources can highlight the necessity of rational molecular testing for precision care in AYA.[13,139] Lastly, broader community engagement with regional and national cancer agencies and patient advocacy groups will be required to improve third-party coverage of essential molecular testing in AYA.

Multidisciplinary Teams and Molecular Tumor Boards

Beyond molecular testing, interpretation of relevant variants to identify and access targeted therapies requires the input of adult and pediatric specialists spanning neuro-oncology, radiation-oncology, neurosurgery, neuroradiology and molecular pathology. With the increasing use of technology, virtual multidisciplinary molecular tumor boards can draw much broader participation and foster partnerships across pediatric and adult centers. A unique national effort across Canada initiated by the Canadian AYA Neuro-Oncology Network (CANON) now includes 28 adult and pediatric hospitals across Canada engaged in biweekly AYA molecular tumor boards. Such efforts will improve the care of AYA patients through multidisciplinary discussions involving local experts and can also serve as a referral basis for more advanced molecular testing and molecularly selected clinical trials available at participating institutions.

Standard of Care and Targeted Therapy Approaches

The standard of care approach for many AYA tumors has not yet been established and the treatment approach often depends on institutional practices and physician subspecialty with data largely extrapolated from either pediatric or older adult populations. Specifically, significant differences between pediatric and adult treatment approaches are well documented in AYA pLGG,[140] and AYA CNS GCTs.[124] While clinical trials will help answer some of these essential questions, real-world cohorts and standardized regimens using expert consensus drawing from both the adult and pediatric experience may reduce disparities of care and improve outcomes in real-time.[141] Incorporation of molecular information to inform de-escalation regimens or targeted therapy approaches in well-annotated prospective cohorts may supplement clinical trial efforts in AYA.

Clinical Trials

In addition to a paucity of research data, much of the recent AYA data points to the fact that clinical trial enrollment remains poor among AYA with CNS tumors, with minimal improvement over the past decade.[142] Patient-focused

research and clinical efforts should consider not only the biology but also the psychosocial construct. Clinical trials for AYA patients need to overcome barriers including some inherent to neuro-oncology (molecular heterogeneity, limitations of pre-clinical models) but also issues unique to AYA (age of eligibility, rarity of tumors, access to care, complexity of clinical trial logistics). A recent review of CNS trials for AYA patients highlights 11 categories of interconnected challenges and broad solutions addressing patient and provider-specific issues, in addition to coordination of care, organizational support, and trial design.[143]

While specific clinical trial eligibility criteria have undergone recent modifications to allow for a broader age range (for example, "adult" trials open to patients aged 12 and over),[144] the same trial often needs to be open at pediatric and adult centers to cater to these specific populations due to institutional barriers, leading to segregation of care and logistical challenges around eventual transition for patients. In addition, trial designs must optimize the sample size given the rarity of these tumors (specifically for molecularly directed trials), and multi-institutional and international collaborations are essential as well as innovative approaches such as tele-trials to improve equity of access. Cooperative groups and federal agencies including the NCI and the FDA should provide additional resources and funding to account for the challenges in accruing these patients and to develop high-impact, clinically relevant studies for AYA patients. Some notable ongoing efforts include the development of trials (eg, NCT03893487) that now include pediatric and AYA patients through consortia such as the Pediatric Neuro-Oncology Consortium (PNOC) and the Pediatric Brain Tumor Consortium.

AYA Programs Focus on Survivorship and Transitions of Care

Beyond improving treatment approaches and survival outcomes, focus on improving the quality of survivorship of AYA patients can yield immediate long-term benefits given the unique challenges this population faces with their cancer diagnosis.[145] Physical space for AYA neuro-oncology programs including multidisciplinary clinics with access to AYA health care professionals and patient navigators can facilitate access to essential, specialized programs such as oncofertility, psychosocial oncology, neurocognitive evaluation, and genetic counseling. In addition, close clinical collaborations across pediatric and adult institutions allow the seamless transition of pediatric patients to adult institutions in cases where care cannot continue at pediatric centers. Importantly, these collaborative clinics can foster ongoing research collaborations and provide a unique platform for AYA-focused clinical trials and for the study of long-term outcomes. Loco-regional collaborative programs with central referrals to specialized centers can also be explored. Specifically, AYA patients with Grade 2 tumors treated at NCI-designated Comprehensive Cancer Centers or COG sites in the United States were found to have mitigated inferior outcomes.[146] As treatments evolve, issues related to early (< 5 years since primary treatment) and late survivorship will need to be more rigorously studied as patients attempt to transition to a "new normal" while living with an uncertain prognosis. PNOC and COG/National Clinical Trials Network have research protocols to look at the longitudinal effects of treatment in the AYA populations. Given the relative rarity of AYA CNS tumors, there will need to be data standardization and synchronization for the study of long-term effects and survivorship.

It is important to note that while this review presents the AYA CNS oncology experience and recommendations through a predominantly North American and European clinical lens, there are unique challenges pertaining to the care of AYAs within low- and middle-income regions. The age of transition to adult care also varies internationally, with some centers reporting an age of transition of 12 years, although neuro-oncology-specific data is lacking. Future efforts should focus on capturing the AYA CNS oncology experience globally.[147] Lastly, more than ever, AYA-focused clinical or research programs should incorporate a review of possible health inequities and actively seek the involvement of underrepresented patients to ensure appropriate inclusion of all AYA patients.[148]

Conclusions

Neuro-oncological care of AYA patients should actively engage academic leaders, institutions, and patient and physician advocates from both the pediatric and adult neuro-oncology world to cover the spectrum of diagnoses seen in AYA. While AYA-centered efforts are still in their infancy, establishing AYA as a distinct group within neuro-oncology will help mobilize advocacy and advance research efforts to inform standards of practice, establish relevant clinical trials, and provide treatment strategies to improve patient outcomes.

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Conflict of interest statement

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