Title: Response Assessment in Pediatric High-Grade Glioma: Recommendations from the Response Assessment in Pediatric Neuro-Oncology Working Group

Authors:

*Craig Erker MD – Division of Pediatric Hematology/Oncology, Department of Pediatrics, Dalhousie University and IWK Health Centre, Halifax, Nova Scotia, Canada

*Benita Tamrazi MD – Department of Radiology, Keck School of Medicine University of Southern California and Children's Hospital of Los Angeles, Los Angeles, California, USA

Prof Tina Y Poussaint MD – Department of Radiology, Boston Children's Hospital, Boston, Massachusetts, USA

Sabine Mueller MD – Departments of Neurology, Neurosurgery, and Pediatrics, University of California San Francisco, San Francisco, California, USA

Daddy Mata-Mbemba MD - Department of Diagnostic Imaging, Dalhousie University and IWK Health Centre, Halifax, Nova Scotia, Canada

Enrico Franceschi MD - Department of Medical Oncology, Azienda USL, Bologna, Italy and IRCCS Institute of Neurological Sciences, Bologna, Italy

Alba A Brandes MD - Department of Medical Oncology, Azienda USL, Bologna, Italy and IRCCS Institute of Neurological Sciences, Bologna, Italy

Arvind Rao PhD – Departments of Computational Medicine and Bioinformatics and Radiation Oncology, University of Michigan, Ann Arbor, Michigan, USA

Kellie B Haworth MD – Division of Neuro-Oncology, Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

Prof Patrick Y Wen MD - Center For Neuro-Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Prof Stewart Goldman MD - Department of Haematology, Oncology, Neuro-Oncology, and Stem Cell Transplantation, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA

Gilber Vezina MD - Department of Radiology, Children's National Medical Center, Washington, DC, USA

Prof Tobey J MacDonald MD - Department of Pediatrics, Aflac Cancer and Blood Disorders Center, Emory University School of Medicine, Atlanta, GA, USA

Prof Ira J Dunkel MD - Department of Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Paul S Morgan PhD – Department of Medical Physics and Clinical Engineering, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK

Tim Jaspan MD – Department of Radiology, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK

[#]Prof Michael D Prados MD - Department of Neurosurgery, University of California San Francisco (UCSF), San Francisco, California, USA

[#]Katherine E Warren MD – Department of Pediatric Oncology, Dana Farber Cancer Institute and Boston Children's Cancer and Blood Disorders Center, Boston, Massachusetts, USA

* Share first author
[#] Share last author

Corresponding Author:
Craig Erker
Dalhousie University and the IWK Health Centre, Halifax, 5850 University Avenue, Nova Scotia, B3K 6R8, Canada
Email: craig.erker@iwk.nshealth.ca
Phone: 902-470-3743

Conflict of Interest Disclosure:
T.Y.P. reports grants from PBTC Neuroimaging Center, outside the submitted work.

E.F. reports grants from Cellgene, outside the submitted work.

P.Y.W. Research Support include funding from Agios, Astra Zeneca, Beigene, Eli Lily, Genentech/Roche, Kazia, MediciNova, Merck, Novartis, Oncoceutics, Sanofi-Aventis, Vascular Biogenics and VBI Vaccines. Advisory Boards include Agios, Astra Zeneca, Bayer, Blue Earth Diagnostics, Immunomic Therapeutics, Karyopharm, Kiyatec, Puma, Taiho, Vascular Biogenics, Deciphera, VBI Vaccines and Tocagen. Speaker for Merck and Prime Oncology.

I.J.D. reports non-financial support from Apexigen, grants from Bristol-Myers Squibb, personal fees from Celgene, grants from Novartis, grants, personal fees and non-financial support from Roche-Genentech, outside the submitted work.

P.S.M reports grants from F Hoffmann-La Roche, outside the submitted work; and Co-chair of the SIOPE Brain Tumor Imaging Group.

T.J reports grants from Hoffman-La Roche, during the conduct of the study.

The other authors declared no conflicts of interest.

Author Contributions:

Craig Erker, Michael D Prados, and Katherine E Warren lead the consensus panel and organized all discussions and meetings

Craig Erker, Benita Tamrazi, Michael D Prados, and Katherine E Warren were the main writers of the manuscript

All other authors Craig Erker, Benita Tamrazi, Tina Y Poussaint, Sabine Mueller, Daddy Mata-Mbemba, Enrico Franceschi, Alba A Brandes, Arvind Rao, Kellie B Haworth, Patrick Y Wen, Stewart Goldman, Gilbert Vezina, Tobey J. Macdonald, Ira J Dunkel, Paul S Morgan,Tim Jaspan, Michael D Prados and Katherine E Warren contributed equally to the literature search, data

collection, consensus panel participation, data analyses, and final manuscript review and approval

Publication: This manuscript has not been submitted to another journal and has not been published in whole previously. However, an abstract form has been submitted to the 2020 ISPNO Conference in Karuizawa, Nagano, Japan with permission from Lancet Oncology.

Funding: This research was funded in part through the NIH/NCI Cancer Center Support Grant P30 CA008748

Acknowledgments: P.S.M is a member of the UK National Institute of Health Research Nottingham Biomedical Research Centre

Abstract

Response criteria for pediatric high-grade glioma (pHGG) has varied both historically and across different cooperative groups. The Response Assessment in Neuro-Oncology (RANO) working group has developed response criteria for adult HGG and was not created for the unique challenges in pHGG. An international Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group was established to develop response assessment criteria for pHGG. Current practice and literature were reviewed to identify major issues. In areas where scientific investigation was lacking, consensus was reached through an iterative process. Recommendations from RAPNO for response assessment include the use of magnetic resonance imaging (MRI) of both the brain and spine, assessing clinical status, and the use of corticosteroids or anti-angiogenic agents. Imaging standards for brain and spine are defined. Compared to the adult RANO, there is a higher reliance on T2/FLAIR imaging and inclusion of diffusion-weighted imaging. Consensus recommendations and response definitions have been established and, similar to other RAPNO recommendations, prospective validation in clinical trials is warranted.

Key Words

CNS tumor, high-grade glioma, pediatric, RANO, Response

Pediatric HGG RAPNO Search Strategy and Selection Criteria References for this review were identified through searches of PubMed with the search terms “high-grade glioma,” “pediatric,” “radiologic assessment, “response,” “leptomeningeal,” “pseudoprogression,” “immunotherapy,” “advanced imaging,” “health-related quality of life,” circulating tumor DNA,” “radiomics”, “*MGMT* methylation” and “RANO,” from 1990 until June 2019. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Introduction

Pediatric high-grade gliomas (pHGG) account for 8-12% of CNS tumors in children with the majority having a non-brainstem location.[1,2] Pediatric HGGs are the leading cause of cancer-related death in children under 19 years of age and include a variety of different World Health Organization (WHO) grade III and IV histologies as well as H3 K27M-mutant diffuse midline glioma (DMG).[3,4] This report focuses on DMG and other biopsy-proven pHGG entities but excludes anaplastic ependymoma and diffuse intrinsic pontine glioma (DIPG) whether or not biopsied. Compared to non-pontine DMG, DIPG is better correlated with pontine size and T2/FLAIR measurements. DIPG response assessment is, therefore, the subject of a separate RAPNO working group. For non-pontine DMG, it is unclear how to best assess their response and are currently included in this consensus statement as apposed to inclusion with DIPG. In the future, it may become evident whether or not DMG patients should be incorporated separately from other pHGG for response assessment purposes. Excluding DIPG, pHGG have a 3-year event-free survival (EFS) and overall survival (OS) of roughly 10 and 20% respectively.[5] Significant recent advances towards understanding the biology of pHGG have strongly influenced new clinical trial design and endpoints.[6,7] However, there are no specific criteria to unify response assessment across studies.

The Children's Oncology Group (COG) has traditionally relied on MRI for objective response assessment although non-standardized clinical assessment and time from completion of radiation therapy are also considered when assessing progressive disease (PD). Other working groups such as the Pediatric Brain Tumor Consortium (PBTC), use criteria similar to COG but incorporate neurologic status, corticosteroid dosing, and durability of response. Several Société Internationale D'Oncologie Pédiatrique (SIOP) studies have defined response using radiographic assessment only.[8,9] Recently the international multicenter study, High-grade glioma Efficacy and tolerability Research of Bevacizumab in Young children and adolescents (HERBY) compared the addition of bevacizumab to radiotherapy-temozolomide in pHGG and incorporated RANO assessments.[10-13] Using RANO, the HERBY study required a high adjudication rate for the expert panel radiological read, resulted in notable differences in date of progression comparing local to central review, and increased read times per patient, in part, due to inconsistent lesion diameter measurements, highlighting the need for consensus criteria.[14]

There are several differences between pediatric and adult HGGs with regard to tumor biology, tumor location, higher likelihood of leptomeningeal dissemination, and an increased frequency of non-enhancing tumors.[15] These differences and the use of a variety of response assessments for pHGG across different studies have led herein to the development of standardized response assessment criteria from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group.[16] The RAPNO pHGG subcommittee consists of pediatric and adult neuro-oncologists, neuro-radiologists and experts in imaging informatics. This committee developed a consensus statement and established a unified response assessment for pHGG by first identifying major challenges, reviewing existing literature and current practices, and finally developing recommendations through an iterative process.

Current Challenges with Response Assessment in pHGG

Lack of Imaging Standards for pHGG Clinical Trials

Conventional MRI is the current standard for response assessment in pHGG. However, MRI time points and protocols may vary between institutions and clinical trials. Furthermore, some sequence acquisition recommendations are inconsistent across studies, and may or may not include advanced imaging.[14]

For baseline scans in newly diagnosed disease, Ellingson et al. challenged the use of post-operative MRI in adult glioblastoma clinical trials[10] due to the propensity to develop pseudoprogression within the first 12 weeks of chemoradiotherapy. In adult glioblastoma, it is now recommended to use the first post chemoradiotherapy MRI as the baseline scan, as opposed to the first post-operative MRI[10] to reduce the challenges posed by blood products, increased vascular permeability, imaging variation secondary to surgical complexity, and perisurgical steroid use. Despite this recommendation, many pediatric clinical trials still include the post-operative MRI as baseline imaging in the response assessment period.

Measurable and Non-measurable Disease

Response assessment in brain tumors is highly dependent on radiographic criteria, and several methods have been proposed for measuring extent of disease including the traditional WHO two-dimensional method (product of the longest diameter and its longest perpendicular diameter)[17] as well as the recommended one-dimensional method implemented by the RECIST criteria (sum of the longest dimensions). However, in the last decade, in part due to the infiltrative nature of gliomas causing inherent challenges for linear measurements, 3D volumetric assessment is gaining popularity, although the best measuring technique, i.e. that which most correlates with outcomes, is not known.

Pediatric HGGs are often diffusely infiltrative with ill-defined margins and inhomogeneous contrast enhancement, making tumor measurement, and hence, identification of response challenging. Historically, measurable disease for HGGs has been defined by the extent of contrast enhancement, with response assessment recommendations published by Macdonald in 1990 focusing entirely on enhancing lesions as surrogates of tumor burden.[18] However, contrast enhancement serves as a marker for regions of blood-brain barrier disruption and is not specific for tumor[16] with the differential diagnosis including infection, post-surgical changes, as well as radiation injury and treatment-related inflammation.[13]

Defining non-measurable disease and determining whether this component should be quantitatively addressed is controversial. In the initial MacDonald criteria, the non-enhancing T2 and fluid-attenuated inversion recovery (FLAIR) infiltrative tumor component was not included as changes attributed to concomitant medications, such as steroids, could not be delineated from treatment-related changes.[18] This is a notable limitation, as changes in non-enhancing tumor may occur prior to changes in contrast-enhancing portions of the tumor.[19-21] In 2010, the RANO working group attempted to address these limitations by incorporating T2/FLAIR changes into response criteria.[11] Due to inherent difficulty in accurately measuring non-enhancing tumor, a subjective approach was proposed, with progression defined as "significant" increase in T2/FLAIR changes felt to represent tumor as opposed to other non-

neoplastic processes such as post-surgical changes, radiation injury, demyelination, ischemic injury, or infection.[11,12] Unlike RANO, the COG and PBTC have traditionally allowed for quantitative two-dimensional measurement of non-enhancing tumor and incorporated this into their response assessment.

The best way to evaluate non-enhancing tumor for response assessment is a critical question as pHGGs often contain non-enhancing infiltrative components or can be entirely non-enhancing. Therefore the use of contrast enhancement as a surrogate for tumor burden in pHGGs often underestimates the overall extent of tumor and can lead to inaccurate response assessment. In the HERBY study, diagnostic (pre-operative) imaging showed that 32 of 98 cases had little or no enhancement[15] while after surgery this number increased to nearly 80% of lesions predominately appearing as a non-enhancing infiltrative mass with increased T2/FLAIR signal.[22] This experience suggests that only a minority of newly diagnosed pHGG would be expected to have significant contrast-enhancing disease after primary surgery. Furthermore, contrast enhancement in pHGG is almost never the sole determinant used to determine progression in pHGG and generally is accompanied by non-enhancing tumor growth on T2/FLAIR and/or clinical decline.[14] Given these findings, changes in non-enhancing tumor are important to characterize in pHGG response assessment.

Spine Imaging for Leptomeningeal Dissemination Detection

Plaque-like or nodular dissemination of tumor to the leptomeninges of the brain or spinal cord can occur in pHGG but is less common compared to other tumors such as medulloblastoma and ependymoma.[23] Primary or secondary leptomeningeal dissemination rates in pHGG ranges between 10% -30% and impacts OS.[15,22,24-26] In the HERBY trial, spinal leptomeningeal disease occurred in both DMG and hemispheric pHGG, although more frequently in subjects with DMG, and in several cases, the spine was the only involved site.[15] In pHGG, there is no standard for obtaining initial or follow-up spine imaging and routine evaluation of spinal disease in the context of clinical trials is frequently not performed. Prior recommendations for response assessment of adult HGG per the RANO committee have not included imaging protocols for the spine. The known occurrence of primary and secondary leptomeningeal dissemination in pHGG underlines the need for clear recommendations.

Imaging Changes Related to Therapy

Pseudoresponse is a term used to describe radiographic improvement with overall decreased edema and/or contrast enhancement secondary to the normalization effect of anti-angiogenic agents on the permeability of leaky endothelium without a change in survival outcome.[27] In these cases, there is generally no increased diffusivity as is seen in pseudoprogression. Clinical trials using bevacizumab in recurrent adult gliomas have demonstrated a high response rate (up to 63%) based on imaging with decreased contrast enhancement, without concordant improved survival suggesting a high rate of pseudoresponse.[28-31] In addition, corticosteroids reduce capillary permeability, stabilize the blood-brain barrier and lessen the inflammatory response, which is illustrated by reduced measurable enhancing tumor as well as the surrounding non-enhancing components on MRI.[32,33] Fortunately, unlike adult HGG, pseudoresponse is uncommon in pHGG.[15]

Pseudoprogression occurs when imaging shows a transient increase in tumor size due to treatment-related increase in blood-brain barrier permeability resulting in increased edema and/or contrast enhancement.[34] Pseudoprogression occurs most frequently within the first 3 months after chemoradiotherapy, limiting the evaluation for PD during this initial time period and occurs in approximately 7-12% of pHGG.[13-15] Other treatment-related changes that may raise concern for pseudoprogression include increased enhancement such as treatment-related inflammation, radiation effects, seizure activity, postsurgical changes, and radiation necrosis.[11] Pseudoprogression highlights an additional challenge encountered in pHGG radiologic assessment.

Defining refractory disease

Many early phase clinical trials in children allow subjects to enroll with what is called refractory disease, but in many cases, these trials do not clearly define refractory disease nor indicate how potential residual active disease should be assessed.[35-38] An ambiguous definition of refractory disease may be reasonable when the goal is to define safety and tolerability of a medication. However, when the trial objective is to evaluate response in the setting of stable or refractory disease, results may be skewed. In addition, it is not possible to radiographically distinguish between treatment effect and true refractory disease.

Immunotherapy for pHGG

Children with CNS tumors are increasingly enrolled in immunotherapy trials. Immunotherapeutic treatment modalities can incite an inflammatory response at the tumor site, conferring significant difficulty in deciphering inflammatory changes from true progressive disease using standard MRI techniques. In these situations, patients may be either prematurely removed from trials that are benefitting them, or alternatively, patients with truly progressive disease may be inappropriately continued on trial due to presumed inflammatory response, resulting in inaccurate response assessments. Unfortunately, clinical providers thus face considerably difficult clinical decision making regarding the appropriateness of therapy continuation for patients receiving immunotherapies.

Guidelines for immunotherapeutic response assessment are currently in place through the adult neuro-oncology working group, immunotherapy Response Assessment in Neuro-Oncology (iRANO).[39] These iRANO criteria do not currently address expected, and sometimes substantial, variations observed between different immunotherapeutic modalities such as route of administration, pharmacokinetics, mechanism of action, expected timing and duration of response, and tumor-specific variables such as the amount of target tumor antigen present.[40,41] It is recognized that even within the same therapeutic family, agents may have significant differences in response time or frequency of pseudoprogression.[42] Currently, symptomatic tumor growth is classified as tumor progression by iRANO, as differentiating true progression from pseudoprogression is challenging.[43] There is also a need to have clear indications and assessment criteria for the use of corticosteroids or other immunosuppressive agents, as these immunomodulating medications may impact immunotherapy efficacy.[41] The iRANO criteria will

thus eventually require an update, as more data are required to fully develop and validate future recommendations.

Repeat biopsy in the setting of determination of disease progression

In cases where imaging is not adequate to determine response assessment, often in the setting of immunotherapy, novel therapeutics, or radiation therapy, tissue confirmation should be explored.[39,44] However a consensus as to when and how to approach repeat biopsy in pHGG has not been clearly articulated, and no published guidelines exist on the issue.

Non-radiographic assessments in pHGG

Clinical improvement or worsening without clear imaging changes may occur in pHGG.[25] The adult neuro-oncology community has developed the Neurologic Assessment in Neuro-Oncology (NANO) scale.[45] However, in pediatrics, a similar tool has yet to be developed and the determination of clinical progression remains largely subjective.

Defining Overall Response

Overall response rate (ORR) is defined as the proportion of patients whose tumor achieved a partial response (PR) or complete response (CR). In treatment naïve patients, historical ORRs vary significantly, can range from 0 to more than 40% despite minimal advances in survival, likely owing to a lack of precision in measurements and inconsistent definitions.[8,13,22] ORR is also subject to interobserver variability, confounded by irregularly shaped tumors, treatment effects, multifocal disease, as well as the difficulty to clearly define non-enhancing tumor margins. Regarding historical ORR, the PR criteria put forth by RANO of ≥ 50% decrease in the sum of products of perpendicular diameters from baseline may not capture all patients deriving true response from therapy. Therefore modification the ORR definition to better represent pHGG is worth exploration. In addition, measures other than ORR, such as disease control rate, may more accurately assess the benefit of cytostatic therapies.[9,46,47]

RAPNO RECOMMENDATIONS

The RAPNO pHGG committee recommends the combined use of radiographic and clinical evaluations in order to assess response in clinical trials.

Radiologic Recommendations for Response Assessment in pHGG

Imaging Standards for Clinical Trials

A standardized brain MRI protocol was recently recommended by the Brain Tumor Imaging Standardization Steering Committee (BTISS) for endpoint assessment in clinical trials of adult glioblastoma[48] taking into consideration acquisition feasibility ranging from small community centers to large academic institutions. Given that children often require anesthesia to minimize motion artifact, it is recommended that imaging the entire neuro-axis, when applicable, occur in one session to reduce anesthetic risks. Similar to RANO and BTISS, the RAPNO pHGG committee recommends acquiring anatomic images with sequences readily available at most centers to address primary study endpoints. Ideally, patients should be imaged with the same method and magnet strength throughout the trial period.[48]

Diffusion-weighted imaging (DWI) is now used in nearly all centers as part of standard MRI protocols. It is used to identify hypercellularity, which often corresponds to grade, where lower apparent diffusion coefficient (ADC) values correspond to higher grade and cellularity.[49-51] This can be helpful in pHGG to identify the hypercellular component of the tumor, which may not be enhancing, as well as metastatic leptomeningeal deposits (Figure 1). Diffusion is also helpful in the assessment of PD versus pseudoprogression where differences in diffusivity can contribute to distinguish hypercellular tumor (decreased ADC values) from inflammation related to pseudoprogression (increased ADC values) (Figure 2).[52-55] Additionally, DWI plays a critical role in identifying progressive non-enhancing tumor in patients on anti-angiogenic therapy such as bevacizumab.[56] When assessing diffusion, perfusion, and spectroscopy sequences in the HERBY trial, DWI was the most likely to directly modify tumor response assessment[14] and the most consistently obtained technique across institutions.[13] Given its potential benefit, RAPNO unanimously integrated DWI into pHGG response assessment.

Brain Imaging

In keeping with prior recommendations of RAPNO and RANO committees as well as the BTISS committee, protocol sequence recommendations are listed in Table 1. Basic standard protocol for tumor assessment includes the following sequences: T1-weighted images pre and post intravenous contrast administration, T2, T2 FLAIR and diffusion. As per prior recommendations, it is ideal to acquire T1-weighted images utilizing isotropic volume (3D) MR sequences for improved resolution and the ability to reconstruct the images in any plane as well as to perform volumetric assessments of tumor. The post-contrast T1 images can be acquired in 3D or alternatively in 2D T1-weighted images (at least 2 planes) utilizing T1 techniques such as SE, TSE/FSE or FLAIR if 3D techniques are not available. In either case, it is important for the techniques to be identical in terms of plane of acquisition and type of acquisition for the pre-contrast and post-contrast images. Slice thickness for 2D acquisition should be no greater than 4 mm. Of note, a specific recommendation is not provided for the type of 3D T1 acquisition (gradient-based versus spin-echo based technique) due to a lack of consensus regarding best technique. This allows for greater leeway among institutions with more limited MRI sequence selections that may be involved in patient recruitment for clinical trials.

Spine Imaging

Given the rates of primary and secondary leptomeningeal dissemination discussed earlier, standardization is necessary for full neuro-axis imaging despite the current lack of literature for established protocols. In order to maintain continuity with prior recommendations provided by RAPNO for spine imaging in medulloblastoma patients, the same specific protocol recommendations are made (Table 2).[57]

<u>Assessing Measurable and Non-Measurable Disease</u>

RAPNO defines measurable disease as tumor that is ≥ 1 cm or ≥ two times in both perpendicular diameters of the MRI axial slice thickness to decrease the partial volume effect plus the interslice gap. Standard 2-dimensional measurements using the largest tumor diameter and its largest perpendicular should be used. Most pHGGs will have only one lesion present to serve as the target lesion for response assessment. If, however, multiple measurable lesions are

present, up to 3 of the largest can be selected as "target" lesions based on their size and ability to be consistently measured.[58,59] The sum of the products of the perpendicular diameters of target lesions should be used to determine response assessment. All other lesions will be considered non-target lesions. If a target lesion becomes non-measurable then attempts to continue to measure the lesion should occur unless it has disappeared.[58] Determination of progressive disease, in this case, will only be permissible only if the lesions again enlarge to again meet criteria for measurable disease.

RAPNO defines non-measurable disease in pHGGs as tumor too small to be accurately measured, < 1 cm in at least one perpendicular dimensions or < two times the MRI slice thickness plus the interslice gap. Leptomeningeal disease is generally non-measurable unless nodular areas are present. If leptomeningeal disease is present, it is assessed in a binary fashion, i.e. present or absent on MRI. Recognizing that what might appear as predominately necrotic tumor can still contain viable disease, it may be included in response assessment if its inclusion best represents the tumor. However, cystic lesions should be excluded from target lesion assessment unless the cyst is integrated within the solid component or not readily separable from the solid tumor component.

Time points for radiologic assessments

Newly diagnosed and Relapsed/Progressive pHGG Time points

MRI scans for response assessment on clinical trials should occur no less than every 3 months if within the first year after diagnosis and considered for a slow increase of the interval thereafter. On the other hand, the frequency of MRI in the relapse setting should occur more frequently, as often as every 2 months, while on clinical trial.

Post-operative brain imaging and considerations for baseline imaging

In clinical trials assessing efficacy of concurrent chemoradiation, the post-surgical scan may be used as a baseline scan. There is general agreement that the initial postsurgical MRI should ideally take place within the first 24 hours, but within 72 hours after surgery is acceptable, to limit the effects of increased enhancement representing post-surgical granulation tissue which may mimic residual tumor.[60] If there are extensive postsurgical changes that decrease the ability to assess residual disease and or mimic tumor infiltration, a second follow up MRI is recommended within 2-3 weeks after surgery. If the post-radiation scan is specified as the clinical trial baseline examination, it should be performed 4-8 weeks after radiation therapy is completed. In clinical trials for relapsed disease, the baseline MRI should be completed within 3 weeks prior to enrollment to minimize missing rapid progression.

Spine MRI

The committee recommends spine imaging be completed concurrently with the brain MRI prior to clinical trial entry. If there is disease on spinal imaging prior to clinical trial entry then spine MRI should be followed at the same time points as brain MRI. If there is no evidence of spinal disease at clinical trial entry, it is permissible to monitor with brain MRI alone and complete further spine imaging as clinically indicated. However, in cases where a CR is being considered, evaluation of the entire neuraxis is required.

In the case of a pHGG located primarily in the spine, a brain MRI should be completed prior to clinical trial entry and continued at the same time points as for the primary lesion. There is not enough evidence about the spread of pHGG spinal primary tumors and their frequency of brain metastases. In addition, the burden of adding a brain MRI to a spine is small compared to the addition of a spine MRI for a primary lesion in the brain. Finally, if the preoperative spine MRI is not obtained or there is significant artifact degradation, the baseline spine MRI should ideally be obtained within the first 24 hours, but within 72 hours after surgery is acceptable.

Clinical, Non-Imaging, Recommendations for Response Assessment in pHGG

Refractory Disease

Advanced imaging may be helpful to differentiate treatment effects from recurrent/residual tumor but no imaging modality has sufficient specificity to conclusively differentiate the two.[11] Any attempted definition of refractory disease may lead to altered outcome measures including a longer duration of time to progression compared to tumors that were enrolled with definitive disease progression. It was unanimous among the pHGG RAPNO working group that refractory disease, however defined, should not be utilized in response assessment.

Immunotherapy for pHGG

It is recommended that the pediatric neuro-oncology community work alongside iRANO counterparts in any further update of those criteria. In the meantime, the existing initial iRANO criteria will be used for pHGG assessments recognizing the limitations of those criteria.[39] Furthermore, biomarkers that may act as surrogates to determine inflammatory response in the setting of immunotherapy and/or pseudoprogression should also be explored further as these may become essential for clinical trials where inflammatory responses are expected.

Repeat biopsy

The pHGG RAPNO group recommends repeat biopsy when imaging is ambiguous and the results may determine whether to continue therapy versus a recommendation for a change in treatment. When considering whether or not to pursue repeat biopsy, the physician team should respect both the patient and parent's preferences while accounting for clinical factors and surgical risks of a repeat biopsy. If repeat biopsy is completed and reveals true PD, new molecular information may be gained that could influence subsequent therapies.[61] However, in many cases, there may be a lack of access to alternative clinical trials or salvage therapies. Therefore, in some cases, repeat biopsy may not be clinically justified.

Repeat biopsy also has technical limitations resulting from tumor heterogeneity and regional or spatial factors, where the biopsied sample may not be adequately representative. There is also a lack of standard pathological criteria to differentiate from true PD from treatment-related changes such as pseudoprogression. Completing image-guided biopsies may not be possible in all institutions which may necessitate consideration for referral to centers skilled in these techniques.

If pursued, a repeat biopsy should occur be performed with spatially annotated imaging correlates using multiple biopsies directed at the ambiguous region to minimize sampling bias. If both enhancing and non-enhancing regions are present then both areas should be biopsied when safe and feasible. Assessment of both tumor-bearing regions as well as surrounding inflammatory tissue and the microenvironment should all be considered to help interpret pathologic results. In cases where substantial tumor is resected, rather than biopsy only, the post-procedure MRI should serve as a new baseline. Systematic repeat biopsies within clinical trials may further help to distinguish PD from treatment-related changes based on morphologic, cellular and/or molecular features and should be done in concert with advanced imaging techniques so that, in the future, we may be able to accurately distinguish these changes without invasive procedures.

Clinical Trial Endpoint Considerations in pHGG Response Assessment

The RAPNO pHGG committee has recommended the creation of a minor response (MR) category which includes ≥ 25% reduction of the sum of the products of the two perpendicular diameters of all target lesions in addition to other radiographic and clinical parameters. This is different than the RAPNO DIPG response criteria which will not have a MR category, but instead, accept a 25% reduction for PR criteria based upon previously published data which is lacking for pHGG.[62] The addition of a MR category for pHGG allows better comparison of PR criteria to historical cohorts, new correlations with clinical trial endpoints, and expansion of the definition for ORR.

In addition, other endpoints could be considered in the context of response assessment. In trials where cytostatic therapy is used or sustained disease stability is of clinical importance, the disease control rate (SD + MR + PR + CR) at a pre-specified number of weeks/months may be helpful to determine clinical benefit. Also, corticosteroid use can impact response assessment and have considerable side-effects, therefore their use has been recently developed into an endpoint for pediatric neuro-oncology patients through RANO, although requires further validation.[63] The use of these additional endpoints should be considered on a trial to trial basis.

Non-radiographic assessments in pHGG

In pediatrics, performance scores have been shown to correlate with OS,[64] and include the Karnofsky performance score (KPS) performance status for patients ≥ 16 years of age or the Lansky performance score (LPS) for patients < 16 years of age. In addition, the Eastern Cooperative Oncology Group (ECOG) performance status may be used. Using performance score as a surrogate for clinical status, or neurologic deterioration unrelated to a comorbid condition, in pHGG response assessment is the current RAPNO recommendation until validated neurologic assessment tools are available for pediatric patients with brain tumors. When using performance score assessment tools, it is important to account for comorbid events unrelated to tumor, medication usage, interrater subjectivity, and difficulty with interpretation in infants.

In addition to performance score, use of medications that may impact response assessment such as corticosteroids and/or anti-angiogenic agents and are now considered by RAPNO in determination pHGG response assessment.

Cerebral spinal fluid assessment
There is a lack of literature supporting the standard use of staging lumbar CSF making its recommended use for response assessment unclear. Exploration of CSF for malignant cells should continue to be assessed and correlated with CSF biomarkers and imaging findings to further refine response assessment. If CSF cytology is assessed and found to be positive, it must be re-assessed and found to be negative to meet criteria for complete response.

RAPNO Recommendations for Response Assessment
Based on the literature, existing practice, and experience, the committee has developed criteria for defining response or progression in patients with pHGG enrolled in clinical trials (Table 3). Importantly, many pHGGs have little or no enhancement but generally have well-defined margins that can be identified for measurement with T2/FLAIR.[15] However, in some cases of hemispheric pHGG, defining non-enhancing tumor margins for measurement is unclear due to difficulty in differentiating tumor from vasogenic edema. In these cases, concurrent involvement of T2/FLAIR signal within gray matter structures or the presence of diffusion restriction supports tumor involvement over edema. Therefore assessing non-enhancing or minimally enhancing tumor with quantitative measurements is recommended. RAPNO recommends the sequence most representative of the tumor be used to determine response assessment whether this is T1 contrast-enhancing disease or T2/FLAIR in tumors with minimal or no enhancement on baseline MRI. The sequence selected for measurable disease at baseline should then continue to be used moving forward. For DWI, there are limitations for its use in quantitative measures due to susceptibility effects of post-surgical change and or hemorrhage in the tumor as well as differences in field strength acquisition parameters. Therefore RAPNO recommends, DWI as a qualitative measure for response assessment.

In order to determine objective response (CR, PR or MR) or stable disease, *all* criteria must be met including those of measurable disease, DWI, new lesion assessment, clinical status, and anti-angiogenic and/or corticosteroid use. For PR, RAPNO recommends a ≥50% decrease of measurable disease in the bidirectional product of perpendicular diameters lasting at least 8 weeks, but recognize that ≥25% reduction is a meaningful decrease and should be considered a MR. However, MR may be more subject to interrater variability due to the smaller changes needed compared to PR.

If any response assessment criterion is not initially assessed, then objective response is considered indeterminate with the exception of DWI. If DWI is not obtained at baseline then determination of tumor response or progression is acceptable with the omission of that criterion moving forward. RAPNO has selected sequences for response assessment because of their widespread use and acceptance which is hoped to limit the transition time needed to implement these new response criteria.

Determination of PD may occur when meeting any of the following criteria: ≥ 25% increase measurable disease, presence of a new lesion, or worsening clinical status. As DWI has not previously been used alone to determine PD, it must be used in conjunction with other

radiographic determinants. Similar to RANO, medications such as anti-angiogenic or corticosteroid use will not be used to determine progression in the absence of clinical deterioration. It is recognized that using T2/FLAIR measurement to determine PD offers challenges specifically with differentiating PD from vasogenic edema. The RAPNO committee suggests PD is more likely when increases in T2/FLAIR changes are accompanied by any or all of the following: 1) new or increased contrast enhancement, 2) new or enlarging area of diffusion restriction, 3) new/enlarging area of infiltrative changes involving gray matter structures.

In order to determine response, whether CR, PR, MR, or SD all tumors must meet the criteria over 2-time points at least 8 weeks apart. RAPNO recommends a minimum of least 8 weeks between imaging time points in order to document response, instead of 4 weeks per RANO, as it is difficult to obtain MRI scans in a 4-week interval due to several factors including the frequent need for anesthesia. In times when PD is unclear a short interval repeat MRI in 4-8 weeks with consideration of repeat biopsy may be performed and the PD be backdated to the initial time point where concern was noted.

Clinical or neurologic deterioration is best determined by the treating physician, while performance score can be used an assessment tool. For the LPS or KPS a decline from 100 or 90 to 70 or less, a decline of at least 20 from 80 or less, or a decline from any baseline to 50 or less, for at least 7 days, should be considered clinical deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the ECOG performance scores from 0 or 1 to 2, or 2 to 3 would be considered neurologic deterioration.[11]

The RAPNO guidelines do not have an upper age limit but were specifically designed with pHGG in mind. As many pediatric clinical trials include patients > 18 years old, it is recommended that one primary response assessment be chosen. If the clinical trial is largely represented by adult glioblastoma multiforme, then RANO should be primarily used. For the adolescent and young adult (AYA) population, it would be reasonable to compare RANO and RAPNO and their associations with ORR, EFS and OS. There are several differences between RAPNO and RANO which are demonstrated on Table 4.

Due to the relatively low frequency and poor outcomes of pHGG, clinical trials are frequently single-arm studies that require well-defined and uniform historic control information. The pHGG RAPNO recommendations may make direct comparison to historical endpoints more challenging. Although it is hoped these response criteria will add value, in some cases, new benchmarks may need to be established for future comparisons. Specifically, the addition of MR to objective response along with PR and CR may increase the ORR compared to historical controls. As a result, clinical trial endpoints will need to be correlated and validated with these new RAPNO criteria.

Future Considerations for Response Assessment in pHGG

The Role of Advanced Imaging

Advanced MR imaging techniques can complement conventional MRI sequences and provide additional physiologic/functional information. Techniques including Perfusion Weighted

Imaging (PWI) and Magnetic Resonance Spectroscopy (MRS) can be useful in the evaluation of treatment-related changes such as differentiation between pseudoprogression and true PD,[65] and they have been shown to help predict a patient's tumor grade.[66,67] In pHGGs for instance, PWI rCBV > 1.4 has been correlated with shorter survival in those treated with Erlotinib.[68]

Although there are advantages with the use of advanced imaging techniques, the standardization and implementation of these techniques across various imaging centers are challenging. There is additional expertise needed for interpretation, increased cost, and accessibility challenges across institutions that also require consideration.[11,69] Overall advanced imaging methods with PWI and MRS remain largely experimental, although their use may be considered in times of ambiguous imaging with or without repeat biopsy in clinical trials. Further prospective data are needed before incorporation into response assessment.[14]

Volumetric Analysis

Volumetric analysis requires isotropic 3D sequence acquisition with post-processing software that is becoming more widely available and increasingly automated. In adult high-grade gliomas, Shah et al demonstrated that volumetric analysis was comparable to linear methods of tumor measurement.[70] In pHGG, data is limited, but Warren et al demonstrated that detecting PR does not appear to be dependent on the measurement method but volumetric measurements may provide higher accuracy for detecting MR and PD.[71] Furthermore, a study looking at pediatric low-grade gliomas demonstrated a 20% discordant response assessment between traditional 2D measurements and volumetric analysis which may be augmented in pHGG where non-spherical infiltrative tumors with non-enhancing components are common.[72] Further prospective research is required in pHGG in order to implement volumetric techniques for clinical trials.

Use of biomarkers in response assessment

Biomarkers to assess response will be extremely valuable, and although there are currently no validated biomarkers to use in conjunction with radiologic response criteria in pHGG, this is an area of growing interest.

Unlike adult HGGs, *MGMT* methylation status has not been shown to have a consistent impact on EFS or OS, nor is it associated with pseudoprogression.[6,73,74] However, in pHGG, *MGMT* promoter methylation status frequently correlates with H3.3 G34 and IDH1 mutations while it is uncommon in tumors with H3.3/H3.1 K27 mutations which are associated with worse outcomes.[6,75] Therefore H3 K27M status is of more prognostic significance than *MGMT* promoter methylation status and is now being increasingly stratified in the settings of clinical trials.

The ability to assess circulating tumor DNA (ctDNA) in plasma and cerebrospinal fluid (CSF) for pHGGs has been demonstrated for several important mutations including *H3F3A*, *TP53*, *ATRX* and *IDH1* among others.[61,76-78] In addition, ctDNA may be useful in assessing disease response in pHGG but requires further investigation.[77,79]

The fields of radiomics and radiogenomics are growing quickly and may aid in future response assessment criteria.[80] However, few studies currently exist in pHGGs.[81] Radiomics offers promise, but significant challenges remain including reliance on multiple data sources, variations in imaging protocols, field strengths, settings in image-reconstruction/preprocessing algorithm, MRI vendors, and genetic profiling techniques. Radiomic data needs to be standardized and harmonized, followed by validation in order for its benefits to be incorporated into the clinical setting and response assessment.

Health-related quality of life

Health-related quality of life (HRQoL) is an important clinical outcome assessment but its use in pHGG is limited due to sparse long term data, missing time points, and confounded by steroid use and comorbid conditions. In pediatric neuro-oncology, the patient-reported outcomes measurement information system (PROMIS) and PedsQL are the two most commonly used HRQoL measures.[82,83] Further integration of HRQoL and patient-reported outcome measures into pediatric neuro-oncology response may offer guidance into non-radiographic response assessment and further investigation is planned to be undertaken separately through RAPNO.

Conclusion

Pediatric HGGs are a unique group of tumors with a poor prognosis that require a unifying response assessment. The variation of response assessment criteria used across historical trials and the inclusion of refractory tumors in relapse trials further supports the need for standardized response criteria. These recommendations represent an initial effort to uniformly assess response and future advancements should be incorporated as appropriate. We recognize the lack of current validation of these guidelines, and as such, consideration for retrospective assessment against well-defined cohorts should be considered in addition to prospective assessment to evaluate feasibility and corroboration with patient outcomes.

References

1. Bondy ML, Scheurer ME, Malmer B, et al. Brain tumor epidemiology: consensus from the Brain Tumor Epidemiology Consortium. *Cancer* 2008; **113**(S7): 1953-68.
2. McCrea HJ, Bander ED, Venn RA, et al. Sex, age, anatomic location, and extent of resection influence outcomes in children with high-grade glioma. *Neurosurgery* 2015; **77**(3): 443-53.
3. Ostrom QT, Gittleman H, Fulop J, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. *Neuro-oncology* 2015; **17**(suppl_4): iv1-iv62.
4. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta neuropathologica* 2016; **131**(6): 803-20.
5. Cohen KJ, Pollack IF, Zhou T, et al. Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro-oncology* 2011; **13**(3): 317-23.
6. Mackay A, Burford A, Carvalho D, et al. Integrated molecular meta-analysis of 1,000 pediatric high-grade and diffuse intrinsic pontine glioma. *Cancer Cell* 2017; **32**(4): 520-37. e5.

7. Mackay A, Burford A, Molinari V, et al. Molecular, pathological, radiological, and immune profiling of non-brainstem pediatric high-grade glioma from the HERBY phase II randomized trial. *Cancer Cell* 2018; **33**(5): 829-42. e5.
8. Hargrave D, Geoerger B, Frappaz D, et al. A phase II single-arm study of irinotecan in combination with temozolomide (TEMIRI) in children with newly diagnosed high grade glioma: a joint ITCC and SIOPE-brain tumour study. *Journal of neuro-oncology* 2013; **113**(1): 127-34.
9. Chastagner P, Kalifa C, Doz F, et al. Outcome of children treated with preradiation chemotherapy for a high-grade glioma: Results of a French Society of Pediatric Oncology (SFOP) pilot study. *Pediatric blood & cancer* 2007; **49**(6): 803-7.
10. Ellingson BM, Wen PY, Cloughesy TF. Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. *Neurotherapeutics* 2017; **14**(2): 307-20.
11. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28**(11): 1963-72.
12. Wen PY, Chang SM, den Bent Van M, Vogelbaum MA, Macdonald DR, Lee EQ. Response Assessment in Neuro-Oncology Clinical Trials. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2017; **35**(21): 2439-49.
13. Jaspan T, Morgan P, Warmuth-Metz M, et al. Response assessment in pediatric neuro-oncology: implementation and expansion of the RANO criteria in a randomized phase II trial of pediatric patients with newly diagnosed high-grade gliomas. *American Journal of Neuroradiology* 2016; **37**(9): 1581-7.
14. Rodriguez D, Chambers T, Warmuth-Metz M, et al. Evaluation of the Implementation of the Response Assessment in Neuro-Oncology Criteria in the HERBY Trial of Pediatric Patients with Newly Diagnosed High-Grade Gliomas. *American Journal of Neuroradiology* 2019; **40**(3): 568-75.
15. Gutierrez DR, Jones C, Varlet P, et al. Radiological evaluation of newly diagnosed non-brainstem pediatric high-grade glioma in the HERBY phase II trial. *Clinical Cancer Research* 2020.
16. Warren KE, Poussaint TY, Vezina G, et al. Challenges with defining response to antitumor agents in pediatric neuro-oncology: a report from the response assessment in pediatric neuro-oncology (RAPNO) working group. *Pediatr Blood Cancer* 2013; **60**(9): 1397-401.
17. Miller A, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *cancer* 1981; **47**(1): 207-14.
18. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; **8**(7): 1277-80.
19. Gállego Pérez-Larraya J, Lahutte M, Petrirena G, et al. Response assessment in recurrent glioblastoma treated with irinotecan-bevacizumab: comparative analysis of the Macdonald, RECIST, RANO, and RECIST + F criteria. *Neuro Oncol* 2012; **14**(5): 667-73.
20. Nowosielski M, Wiestler B, Goebel G, et al. Progression types after antiangiogenic therapy are related to outcome in recurrent glioblastoma. *Neurology* 2014; **82**(19): 1684-92.
21. Radbruch A, Lutz K, Wiestler B, et al. Relevance of T2 signal changes in the assessment of progression of glioblastoma according to the Response Assessment in Neurooncology criteria. *Neuro Oncol* 2012; **14**(2): 222-9.
22. Grill J, Massimino M, Bouffet E, et al. Phase II, Open-Label, Randomized, Multicenter Trial (HERBY) of Bevacizumab in Pediatric Patients With Newly Diagnosed High-Grade Glioma. 2018.
23. Duffner PK, Horowitz ME, Krischer JP, et al. Postoperative chemotherapy and delayed radiation in children less than three years of age with malignant brain tumors. *N Engl J Med* 1993; **328**(24): 1725-31.
24. Benesch M, Wagner S, Berthold F, Wolff JE. Primary dissemination of high-grade gliomas in children: experiences from four studies of the Pediatric Oncology and Hematology Society of the German Language Group (GPOH). *J Neurooncol* 2005; **72**(2): 179-83.

25. Lucas Jr JT, Cooper DA, Hwang S, et al. Prognostic Relevance of Treatment Failure Patterns in Pediatric High-Grade Glioma: Is There a Role for a Revised Failure Classification System? *International Journal of Radiation Oncology* Biology* Physics* 2017; **99**(2): 450-8.
26. Wagner S, Benesch M, Berthold F, et al. Secondary dissemination in children with high-grade malignant gliomas and diffuse intrinsic pontine gliomas. *British journal of cancer* 2006; **95**(8): 991.
27. Tamrazi B, Mankad K, Nelson M, D'Arco F. Current concepts and challenges in the radiologic assessment of brain tumors in children: part 2. *Pediatr Radiol* 2018; **48**(13): 1844-60.
28. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* 2009; **27**(5): 740-5.
29. Vredenburgh JJ, Desjardins A, Herndon JE, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. *Clin Cancer Res* 2007; **13**(4): 1253-9.
30. Norden AD, Drappatz J, Wen PY. Novel anti-angiogenic therapies for malignant gliomas. *Lancet Neurol* 2008; **7**(12): 1152-60.
31. Narayana A, Raza S, Golfinos JG, et al. Bevacizumab therapy in recurrent high grade glioma: Impact on local control and survival. *Journal of Clinical Oncology* 2008; **26**(15_suppl): 13000-.
32. Cosio B, Torrego A, Adcock I. Molecular mechanisms of glucocorticoids. *Archivos de Bronconeumología ((English Edition))* 2005; **41**(1): 34-41.
33. Watling CJ, Lee DH, Macdonald DR, Cairncross JG. Corticosteroid-induced magnetic resonance imaging changes in patients with recurrent malignant glioma. *Journal of Clinical Oncology* 1994; **12**(9): 1886-9.
34. Brandsma D, Stalpers L, Taal W, Sminia P, van den Bent MJ. Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. *Lancet Oncol* 2008; **9**(5): 453-61.
35. Geoerger B, Kieran MW, Grupp S, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. *European journal of cancer* 2012; **48**(2): 253-62.
36. MacDonald TJ, Vezina G, Stewart CF, et al. Phase II study of cilengitide in the treatment of refractory or relapsed high-grade gliomas in children: a report from the Children's Oncology Group. *Neuro-oncology* 2013; **15**(10): 1438-44.
37. Cole KA, Reid JM, Liu X, et al. Abstract CT144: Pediatric phase I trial of the WEE1 inhibitor AZD1775 and irinotecan in patients with refractory solid and CNS malignancies; A Children's Oncology Group Study (ADVL1312). AACR; 2017.
38. Wetmore C, Daryani VM, Billups CA, et al. Phase II evaluation of sunitinib in the treatment of recurrent or refractory high-grade glioma or ependymoma in children: a children's Oncology Group Study ACNS1021. *Cancer medicine* 2016; **5**(7): 1416-24.
39. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *The Lancet Oncology* 2015; **16**(15): e534-e42.
40. Roth P, Valavanis A, Weller M. Long-term control and partial remission after initial pseudoprogression of glioblastoma by anti–PD-1 treatment with nivolumab. *Neuro-Oncology* 2017; **19**(3): 454-6.
41. Mount CW, Majzner RG, Sundaresh S, et al. Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M+ diffuse midline gliomas. *Nature medicine* 2018; **24**(5): 572.
42. Kline C, Liu SJ, Duriseti S, et al. Reirradiation and PD-1 inhibition with nivolumab for the treatment of recurrent diffuse intrinsic pontine glioma: a single-institution experience. *Journal of neuro-oncology* 2018; **140**(3): 629-38.
43. Bouffet E, Larouche V, Campbell BB, et al. Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency. *Journal of clinical oncology* 2016; **34**(19): 2206-11.

44. Valenzuela RF, Ocasio L, Bhattacharjee MB, et al. Nimg-24. Pathology Confirmed Radiographic Diagnosis Of True Progression And Pseudo-progression Made By Advanced Brain Tumor Imaging. *Neuro-Oncology* 2017; **19**(suppl_6): vi147-vi.
45. Nayak L, DeAngelis LM, Brandes AA, et al. The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria. *Neuro-oncology* 2017; **19**(5): 625-35.
46. Reardon DA, Galanis E, DeGroot JF, et al. Clinical trial end points for high-grade glioma: the evolving landscape. *Neuro-oncology* 2011; **13**(3): 353-61.
47. MacDonald TJ, Arenson EB, Ater J, et al. Phase II study of high-dose chemotherapy before radiation in children with newly diagnosed high-grade astrocytoma: final analysis of Children's Cancer Group Study 9933. *Cancer: Interdisciplinary International Journal of the American Cancer Society* 2005; **104**(12): 2862-71.
48. Ellingson BM, Bendszus M, Boxerman J, et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. *Neuro Oncol* 2015; **17**(9): 1188-98.
49. Guo AC, Cummings TJ, Dash RC, Provenzale JM. Lymphomas and high-grade astrocytomas: comparison of water diffusibility and histologic characteristics. *Radiology* 2002; **224**(1): 177-83.
50. Hayashida Y, Hirai T, Morishita S, et al. Diffusion-weighted imaging of metastatic brain tumors: comparison with histologic type and tumor cellularity. *AJNR Am J Neuroradiol* 2006; **27**(7): 1419-25.
51. Herneth AM, Guccione S, Bednarski M. Apparent diffusion coefficient: a quantitative parameter for in vivo tumor characterization. *Eur J Radiol* 2003; **45**(3): 208-13.
52. Asao C, Korogi Y, Kitajima M, et al. Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor recurrence. *AJNR Am J Neuroradiol* 2005; **26**(6): 1455-60.
53. Hein PA, Eskey CJ, Dunn JF, Hug EB. Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury. *AJNR Am J Neuroradiol* 2004; **25**(2): 201-9.
54. Matsusue E, Fink JR, Rockhill JK, Ogawa T, Maravilla KR. Distinction between glioma progression and post-radiation change by combined physiologic MR imaging. *Neuroradiology* 2010; **52**(4): 297-306.
55. Zeng QS, Li CF, Liu H, Zhen JH, Feng DC. Distinction between recurrent glioma and radiation injury using magnetic resonance spectroscopy in combination with diffusion-weighted imaging. *Int J Radiat Oncol Biol Phys* 2007; **68**(1): 151-8.
56. Pope WB, Young JR, Ellingson BM. Advances in MRI assessment of gliomas and response to anti-VEGF therapy. *Current neurology and neuroscience reports* 2011; **11**(3): 336-44.
57. Warren KE, Vezina G, Poussaint TY, et al. Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from the Response Assessment in Pediatric Neuro-Oncology committee. *Neuro Oncol* 2018; **20**(1): 13-23.
58. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer* 2009; **45**(2): 228-47.
59. Bogaerts J, Ford R, Sargent D, et al. Individual patient data analysis to assess modifications to the RECIST criteria. *European journal of cancer* 2009; **45**(2): 248-60.
60. Cairncross JG, Pexman JW, Rathbone MP. Post-surgical contrast enhancement mimicking residual brain tumour. *Canadian Journal of Neurological Sciences* 1985; **12**(1): 75-.
61. Mueller S, Jain P, Liang WS, et al. A pilot precision medicine trial for children with diffuse intrinsic pontine glioma–PNOC003: a report from the Pacific Pediatric Neuro-Oncology Consortium. *International journal of cancer* 2019.
62. Poussaint TY, Kocak M, Vajapeyam S, et al. MRI as a central component of clinical trials analysis in brainstem glioma: a report from the Pediatric Brain Tumor Consortium (PBTC). *Neuro-oncology* 2011; **13**(4): 417-27.
63. Arvold ND, Armstrong TS, Warren KE, et al. Corticosteroid use endpoints in neuro-oncology: Response Assessment in Neuro-Oncology working group. *Neuro-oncology* 2018; **20**(7): 897-906.

64. Carceller F, Bautista FJ, Jiménez I, et al. Prognostic factors of overall survival in children and adolescents enrolled in dose-finding trials in Europe: An Innovative Therapies for Children with Cancer study. *European Journal of Cancer* 2016; **67**: 130-40.
65. van Dijken BR, van Laar PJ, Holtman GA, van der Hoorn A. Diagnostic accuracy of magnetic resonance imaging techniques for treatment response evaluation in patients with high-grade glioma, a systematic review and meta-analysis. *European radiology* 2017; **27**(10): 4129-44.
66. Dangouloff-Ros V, Deroulers C, Foissac F, et al. Arterial Spin Labeling to Predict Brain Tumor Grading in Children: Correlations between Histopathologic Vascular Density and Perfusion MR Imaging. *Radiology* 2016; **281**(2): 553-66.
67. Astrakas LG, Zurakowski D, Tzika AA, et al. Noninvasive magnetic resonance spectroscopic imaging biomarkers to predict the clinical grade of pediatric brain tumors. *Clin Cancer Res* 2004; **10**(24): 8220-8.
68. Lucas JT, Knapp BJ, Uh J, et al. Posttreatment DSC-MRI is Predictive of Early Treatment Failure in Children with Supratentorial High-Grade Glioma Treated with Erlotinib. *Clin Neuroradiol* 2018; **28**(3): 393-400.
69. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28**(11): 1963-72.
70. Shah GD, Kesari S, Xu R, et al. Comparison of linear and volumetric criteria in assessing tumor response in adult high-grade gliomas. *Neuro-oncology* 2006; **8**(1): 38-46.
71. Warren KE, Patronas N, Aikin AA, Albert PS, Balis FM. Comparison of one-, two-, and three-dimensional measurements of childhood brain tumors. *Journal of the National Cancer Institute* 2001; **93**(18): 1401-5.
72. D'Arco F, O'Hare P, Dashti F, et al. Volumetric assessment of tumor size changes in pediatric low-grade gliomas: feasibility and comparison with linear measurements. *Neuroradiology* 2018; **60**(4): 427-36.
73. Carceller F, Fowkes LA, Khabra K, et al. Pseudoprogression in children, adolescents and young adults with non-brainstem high grade glioma and diffuse intrinsic pontine glioma. *Journal of neuro-oncology* 2016; **129**(1): 109-21.
74. Jakacki RI, Cohen KJ, Buxton A, et al. Phase 2 study of concurrent radiotherapy and temozolomide followed by temozolomide and lomustine in the treatment of children with high-grade glioma: a report of the Children's Oncology Group ACNS0423 study. *Neuro-oncology* 2016; **18**(10): 1442-50.
75. Korshunov A, Ryzhova M, Hovestadt V, et al. Integrated analysis of pediatric glioblastoma reveals a subset of biologically favorable tumors with associated molecular prognostic markers. *Acta neuropathologica* 2015; **129**(5): 669-78.
76. Huang TY, Piunti A, Lulla RR, et al. Detection of Histone H3 mutations in cerebrospinal fluid-derived tumor DNA from children with diffuse midline glioma. *Acta neuropathologica communications* 2017; **5**(1): 28.
77. Panditharatna E, Kilburn LB, Aboian MS, et al. Clinically relevant and minimally invasive tumor surveillance of pediatric diffuse midline gliomas using patient-derived liquid biopsy. *Clinical Cancer Research* 2018; **24**(23): 5850-9.
78. Martínez-Ricarte F, Mayor R, Martínez-Sáez E, et al. Molecular diagnosis of diffuse gliomas through sequencing of cell-free circulating tumor DNA from cerebrospinal fluid. *Clinical Cancer Research* 2018; **24**(12): 2812-9.
79. Li Y, Pan W, Connolly ID, et al. Tumor DNA in cerebral spinal fluid reflects clinical course in a patient with melanoma leptomeningeal brain metastases. *Journal of neuro-oncology* 2016; **128**(1): 93-100.

80. Zhou M, Scott J, Chaudhury B, et al. Radiomics in Brain Tumor: Image Assessment, Quantitative Feature Descriptors, and Machine-Learning Approaches. *AJNR Am J Neuroradiol* 2018; **39**(2): 208-16.
81. Lucas J, Hsu C-Y, Lu Z, et al. HGG-35. COMBINATIONS OF QUANTITATIVE AND QUALITATIVE MRI FEATURES IDENTIFY PROGNOSTIC AND MOLECULAR SUBGROUPS OF SUPRATENTORIAL PEDIATRIC HIGH-GRADE GLIOMA. *Neuro-Oncology* 2018; **20**(Suppl 2): i96.
82. Dobrozsi S, Yan K, Hoffmann R, Panepinto J. Patient-reported health status during pediatric cancer treatment. *Pediatric blood & cancer* 2017; **64**(4): e26295.
83. Schulte F, Russell KB, Cullen P, et al. Systematic review and meta-analysis of health-related quality of life in pediatric CNS tumor survivors. *Pediatric blood & cancer* 2017; **64**(8): e26442.