European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours

Authors:

Shivaram Avula[1], Andrew Peet[2], Giovanni Morana[3], Paul Morgan[4], Monika Warmuth-Metz[5], Tim Jaspan[6], European Society for Paediatric Oncology (SIOPE)- Brain Tumour Imaging Group.

Affiliations:

1. Alder Hey Children's NHS Foundation Trust, Department of Radiology, Liverpool, United Kingdom
2. Institute of Cancer and Genomic Sciences, University of Birmingham, UK and Birmingham Women's and Children's Hospital NHS Foundation Trust, Birmingham UK
3. University of Turin, Department of Neurosciences, Turin, Italy
4. Nottingham University Hospitals, Department of Medical Physics, Nottingham, UK
5. University of Würzburg, Institute of Diagnostic and Interventional Neuroradiology, Würzburg, Germany
6. Nottingham University Hospitals, Department of Radiology, Nottingham, UK

Corresponding author: Shivaram Avula

Address: Alder Hey Children's NHS Foundation Trust, East Prescot road, Liverpool, United Kingdom L14 5AB

E mail: shivaram.avula@alderhey.nhs.uk

Telephone: +44 151 2525432

ORCID: Shivaram Avula 0000-0003-1742-7206
Andrew Peet 0000-0002-4846-5152
Giovanni Morana 0000-0001-8707-5969
Paul Morgan 0000-0002-5870-1446
Tim Jaspan 0000-0002-3644-9569
Monika Warmuth-Metz 0000-0002-3544-319X

Key words: Paediatric CNS tumour
Imaging guidelines
MRI protocol
SIOP Europe-Brain Tumour Group
Paediatric brain tumour imaging
Paediatric spine tumour imaging

Conflict of Interest

The authors declare that they have no conflict of interest.

European Society for Paediatric Oncology (SIOPE) MRI guidelines for imaging patients with central nervous system tumours.

Introduction

Imaging evaluation of primary tumours of the central nervous system (CNS) and possible CNS dissemination is core to their management in children. Given the infrequency of childhood CNS tumours, multicentre studies provide the best scientific evidence for their management. Standardisation of imaging not only facilitates comparisons of scans for an individual subject across various time points (pre-operative, post-operative and subsequent follow -up imaging) but also aids comparability across multiple centres by the central study co-ordinators and designated radiologists. Standardisation of imaging acquisition therefore is an essential pre-requisite across all centres who participate in paediatric CNS tumour studies.

One of the main challenges involved in designing a standard imaging protocol is the variation in imaging resources across all centres i.e. the manufacturer, the field strength of MR scanners, availability of newer hardware/sequences, advanced imaging capabilities and expertise, radiology department workflow, anaesthetic provision and personnel. For maximum compliance with a protocol, a balance needs to be struck between practicality and image quality. This principle was used to develop a brain tumour imaging protocol for centres in North America following a workshop consisting of members including imaging experts, clinical scientists and patient advocates [1]. They opted for a pragmatic approach, striking a balance between an ideal protocol that may be available only to select specialized centres and a protocol that could be adopted more widely. A standard protocol was also developed by the European Organization of Research and Treatment of Cancer (EORTC) Brain Tumour Group. They developed a basic protocol that was mandatory for all centres and an advanced protocol that was to be adopted by specific sites [1].

Assessment of tumour response to treatment has evolved over many years with transition from the Macdonald criteria [2] to the Response Assessment in Neuro-Oncology (RANO) criteria [3] that addressed the challenges related to contrast enhancement including the pseudoprogression and the pseudoresponse phenomena. There has been further modification of the RANO criteria more recently with recommendations on image acquisition, analysis and detailed definitions of response [4]. These recommendations have acknowledged the need for standardisation of image acquisition in the management of brain tumours mainly focusing on gliomas. More recently the Response Assessment in Pediatric Neuro-Oncology (RAPNO) committee have published recommendations for image acquisition and response assessment more specific to the paediatric population, which vary according to tumour type [5][6-8] . It is important to ensure that there is a basic MRI

protocol for the paediatric CNS tumour population that is achievable across all sites, reviewed periodically and satisfies the minimum requirement for response assessment of the various multicentre cancer studies.

Materials and methods

The European Society for Paediatric Oncology (SIOPE) Brain Tumour Imaging Working Group has developed an imaging protocol based on consensus and evidence from earlier clinical trials. The members of the group consist of neuroradiologists, imaging scientists and clinicians with an interest in brain tumour imaging. The brain imaging working group was recognised formally as discipline group within SIOPE Brain Tumour Group in 2011. The group members communicate on a regular basis including one annual meeting that coincides with the annual SIOPE Brain Tumour Group meeting. One of the main functions of the group is to develop imaging protocols based on evidence to facilitate multicentre trials led by the various SIOPE tumour working groups (e.g. ependymoma, low grade glioma, craniopharyngioma etc.). The protocol has evolved over the past decade and is being updated in response to changes in imaging practices and the specific needs of the various clinical trials. The protocol is based on consensus among the group members either obtained in person and/or using e-mail surveys and at various stages of development. During the consensus process, each MRI sequence used in paediatric CNS tumour imaging was considered based on published evidence and individual practice. The merits and limitation of each sequence, the imaging parameter and plane of acquisition were decided through iterative discussions before reaching consensus. The wide MR imaging capability ranging from relatively small hospitals with limited imaging capacity to dedicated paediatric neuro-oncolgy centres with advanced imaging capability was taken into consideration when deciding on essential and optional sequences. The protocol has been successfully incorporated into a number of multisite studies, including the Low Grade Glioma studies, SIOPE Ependymoma II trial and SIOPE PNET V Medulloblastoma trial[9-11].The protocol comprises a mandatory set of sequences which represent a minimum requirement and additional sequences including advanced multi-modal MRI that are recommended. This protocol was ratified by the group in December 2019.

Imaging protocol

The imaging protocol consists of sequences that are specific for the magnetic field strength (1.5 and 3 Tesla). Advances in MR technology have contributed to vast improvements in quality of imaging on 1.5T and 3T MR scanners. Despite these advances there is a huge variation in the capability of the scanner hardware and software across various centres. The rationale for the sequences and parameters recommended is based on practicality, published evidence where available and the reliability of tumour assessment. The protocol

has been tailored to consist of the minimal essential/mandatory sequences in order to allow effective basic tumour evaluation whilst allowing for the use of additional sequences including multi-modal advanced MRI.
We have provided recommendations on advanced imaging methods including MR spectroscopy (MRS), diffusion tensor imaging (DTI) and perfusion imaging. The advanced imaging recommendations are based on studies performed by the SIOPE group members and are aimed as a guideline and are currently not mandatory.

Brain imaging

Table 1 summarises the essential and optional sequences for brain imaging with the generic sequence technique and the plane of acquisition.

T1 weighted imaging

The T1 weighted (T1W) sequences differ on 1.5T and 3T scanners. 2D T1W spin echo (SE), turbo/fast spin echo (TSE/FSE) sequences are recommended for 1.5 T scanners both prior to and following contrast administration. For 1.5T scanners, the pre-contrast T1W sequence should be obtained in the axial plane along the anterior commissure – posterior commissure (AC-PC) plane. Post-contrast 2D T1W sequences should be obtained in 3 orthogonal planes. The 3D isotropic radio frequency spoiled T1W gradient echo sequence (MPRAGE/SPGR/ Fast SPGR/ 3D TFE/ 3D FFE) is recommended on 3T scanners prior to and following contrast administration. It is important to use an identical acquisition plane and T1W sequence type for the pre-contrast and post-contrast scans. The quality of 3D T1W sequences have been variable on 1.5T scanners with relatively few centres capable of obtaining the high-quality 3D T1W sequences that are now available on newer 1.5T scanners. It is therefore not recommended as an essential sequence at 1.5T. However, it is listed as an optional sequence on the 1.5T scan protocol, particularly to obtain a 3D dataset for neuro-navigation or radiotherapy planning purposes. 3D T1W sequences have the advantage of facilitating volumetric analysis and detection of smaller abnormalities. More recently 3D TSE acquisition (CUBE/SPACE/ VISTA) has been reported to be more sensitive for detecting enhancing brain lesions due to improved contrast resolution, high signal-to-noise ratio, black blood effect and reduced artefact from static field inhomogeneity[12-15]. This sequence is becoming more widely available on newer scanners but was not available on the older systems (or only as an option) and so further validation of this technique in paediatric subjects will be considered in the future when a larger dataset is available. For the 3T protocol an axial 2D T1W sequence following contrast is recommended in addition to

the 3D T1W sequence following contrast administration. The rationale for this is to maintain comparability of the post contrast imaging in case an individual subject needs to undergo scanning on 3T and 1.5T scans at various time points. Another reason is that 2D T1W images contain few vascular or CSF pulsation artefacts. Some centres perform 2D T1 FLAIR, T1W inversion recovery (IR) or T1W gradient echo sequence as the 2D T1W SE/TSE/FSE sequence is suboptimal on some 3T scanners. This is acceptable as long as the diagnostic quality of the imaging is not compromised, and the same sequence is used consistently at all time points for the individual patient. The T1W sequences in the SIOPE protocol are largely compatible with the more recently published RAPNO guidelines for medulloblastoma, low-grade gliomas (LGG) and high-grade gliomas (HGG)[5] [6,7] [8]. The RAPNO medulloblastoma protocol recommends a postcontrast 3D T1W TSE sequence in addition to an axial 2D T1W sequence. The type of 3D sequence has not been specified in the LGG and HGG protocols.

Recently, concern has been raised regarding the long-term effects of gadolinium deposition in the brain, mainly in the globus pallidus and dentate nucleus and more frequently linked to linear gadolinium-based contrast agents than macrocyclic gadolinium-based contrast agents[16] [17] The clinical significance of gadolinium retention in the brain is unknown. We recommend the use of macrocyclic gadolinium-based contrast agents as per the recommendation of the European Medicines Agency [18]. We also recommend appropriate consideration when using gadolinium contrast agents, keeping doses as low as possible to minimise gadolinium accumulation in the brain.

T2 weighted imaging

T2 weighted (T2W) imaging comprises of T2W and T2 weighted fluid attenuated inversion recovery (T2 FLAIR) sequences. We recommend 2D T2W spin echo/ turbo spin echo/fast spin echo (T2W SE/TSE/FSE) sequences in the axial plane. Non-enhancing or poorly enhancing tumours are seen in a wide variety of paediatric tumours. Novel treatment methods including the use of anti-angiogenic agents have reinforced the role of non-contrast sequences in response assessment [19] [3]. Good quality 2D T2W sequences are vital in the characterisation and measurement of non-enhancing tumours. We have recommended the 2D T2W SE/FSE/TSE sequence as it provides images with good signal-to-noise and contrast-to-noise ratios. The axial plane of acquisition parallel to the AC-PC plane is universally followed and a reliable plane for obtaining measurements of the tumour in two dimensions. More recently 3D T2W sequences have gained popularity in neuroimaging. A volumetric T2W sequence does have its advantages particularly with aiding neuronavigation during surgery and volumetric measurement of tumours, but its role in response assessment has not been validated. From anecdotal experience it is felt that the 3D T2W sequence is inferior to 2D T2W sequences in defining tumour margins. This is particularly the case in tumours situated close to CSF spaces where flow-related artefact can mimic solid or cystic tumour (Figure 1).

A balanced steady-state free precession (bSSFP) scan produces heavily T2W images that have superior contrast resolution and can delineate structures situated within and close to CSF. The commonly used sequences on the various MR scanners are CISS, FIESTA, T2 DRIVE and BFFE. The use of 3D bSSFP scans have been shown to be effective in identifying small tumours in the internal auditory canal such as vestibular schwannomas[20,21]. 3D bSSFP scans are also very useful in delineating tumours in the midst of complex post-surgical changes, in characterising tumours that have ill-defined margins and appear isointense to CSF on T2W images and identifying small extra-axial metastatic foci and differentiating them from normal structures in challenging locations such as the internal acoustic canals (Figure 2). The heavily T2 weighted bSSFP sequence has been added to the protocol, for the aforementioned reasons as an optional sequence and can be performed as a 2D or 3D sequence based on the clinical need.

A T2 FLAIR sequence is complementary to T2W images in neuroimaging allowing suppression of signal related to CSF and increases the conspicuity of lesions close to the ventricles and the cortex. We have recommended a 2D acquisition for both 1.5T and 3T MRI as this is the most commonly used method across all centres. The option of acquiring the scan in the axial or coronal plane has been provided, acknowledging the varying preferences in practice among different centres. 3D FLAIR has the advantage of multiplanar reconstruction and enabling volumetric analysis of lesions. It is available in newer MR scanners and has been added as an optional sequence. 3D FLAIR can be used instead of 2D FLAIR but not if 2D sequences have been used for the same individual on previous occasions. The practice of acquiring FLAIR post contrast has been popular and post-contrast 3D T2 FLAIR has been shown to be highly sensitive in identifying leptomeningeal metastasis in single centre studies [22,23]. Routine use of contrast enhanced FLAIR will need further validation in the paediatric brain tumour population, and even if used, should be in addition to pre-contrast FLAIR rather than as a replacement.

Among most SIOPE led brain tumour studies, tumour measurement is performed in 3 orthogonal planes (i.e. anteroposterior [along AC-PC plane], craniocaudal and transverse). In order to obtain the 3 plane measurements in non-enhancing or poorly enhancing tumours, the combination of 2D T2W and 2D T2 FLAIR sequences will need to be obtained in at least two different planes. If both the T2W and T2 FLAIR sequences are obtained in the axial plane, an additional T2W/T2 FLAIR sequence will need to be acquired in a different plane. The use of 3D T2 FLAIR can mitigate this, provided the individual has not had 2D T2 FLAIR imaging previously.

Diffusion Weighted Imaging

Diffusion weighted imaging (DWI) has become established as a standard sequence in neuroradiology. It is extremely valuable in the assessment of tumour cellularity, differential diagnosis, treatment response and in identifying metastases [24] [25] [26] [27]. We recommend 2D echo planar DWI sequence with at least 2 b-values (b = 0 s/mm^2 and b = 1000 s /mm^2). The b=1000 and the ADC maps should be available for interpretation. ADC measurement has some resilience to variations in protocol when acquired on a range of scanners from phantoms and volunteers, providing a good basis for its use as a quantitative biomarker[28].The choice of b-values for acquisition has been the subject of many publications but the choice of 0 s/mm2 and 1000 s/mm is widely used in the brain where perfusion effects are small. The practical application of ADC for diagnosis in children with brain tumours has been tested in a multi-centre setting and shown good diagnostic potential, particularly when combined with advanced analysis methods including histogram analysis and machine learning, although these analysis methods are not widely available clinically[24] . The acquisition of DWI at multiple b-values between 0 s/mm2 and 1000 s/mm2 can separate the effects of water apparent diffusion from perfusion and may further increase the accuracy of DWI biomarkers in a multi-centre setting but a paucity of comparative data for paediatric brain tumours and a current lack of readily available analysis software makes this approach a research tool currently [29].” The choice of b-values for acquisition has been the subject of many publications but the choice of 0 s/mm^2 and 1000 s/mm is widely used in the brain where perfusion effects are small. The acquisition of DWI at multiple b-values between 0 s/mm^2 and 1000 s/mm^2 can give information on perfusion but a lack of comparative data for paediatric brain tumours and a current lack of readily available analysis software makes this approach a research tool currently[29].

Spine imaging

The essential sequence for spine imaging is a sagittal 2D T1W SE/TSE post contrast of the whole spine including the entire dural sac. If there are lesions within the spine suspicious of tumour / metastasis, axial 2D or 3D gradient echo T1W post-contrast sequences should be performed over the regions of interest. Physiological veins over the surface of the cord can be mistaken for nodules of tumour dissemination and axial slices without gaps are essential for all suspicious areas. The T2W sequence of the spine is helpful in the evaluation of intramedullary tumours. We recommend sagittal 2D T2W SE/TSE as an option with axial 2D T2W sequences covering areas suspicious of pathology. In case of a known primary spinal tumour, pre-contrast T1W and T2W sequences should be obtained. The inclusion of the posterior fossa in the field of view of the sagittal T1W post-contrast spine sequence is encouraged particularly in children with posterior fossa tumours as this may demonstrate the late enhancement characteristics of the tumour or reveal subtle areas of recurrence or metastasis. Depending on the height of the patient and the capability of the scanner, this may require two sagittal acquisitions.

1.5T is preferred to 3T for spinal imaging as the quality on older 3T systems is often inferior and more unpredictable. More recent generation 3T scanners now enable good, diagnostic quality spinal imaging but there must be a low threshold to reimage the spine on a 1.5T scanner if it is of a suboptimal quality. Ideally, spinal imaging should be performed prior to surgery to avoid diagnostic problems related to postoperative intraspinal subdural collections[30,31]. Early post-operative spine imaging should therefore be interpreted with caution. If the scan findings are equivocal for metastasis, an early follow up imaging of the spine is recommended 2-4 weeks following surgery. This should include pre-contrast T1 W sequence in addition to the recommended protocol.

The bSSFP sequences (CISS /FIESTA /B FFE) are extremely useful in identifying drop metastases and shown to be particularly useful in detecting small drop metastases (<3 mm) and non-enhancing metastases in the paediatric brain tumour population [32]. 2D or 3D bSSFP sequence of the spine in the sagittal plane (± axial plane) is recommended when there is suspicion of drop metastases (Figure 2). As fat suppression sequences often leads to artefacts and are not specifically necessary for the delineation of meningeal disease they should not be used routinely.

Early post-operative imaging

Optimal evaluation is made within the first 48 hours following surgery. As non-specific intracranial enhancement is often seen 72 hours following surgery the postoperative MRI must be obtained within this time [33,34]. However, even within this time surgically induced contrast-enhancement can be seen [35,36]. This is compounded by surgical technique including the use of haemostatic materials and following electrocoagulation. It is therefore prudent to carefully evaluate the pre- and post-contrast T1W images in combination with the signal intensities on the T2W and T2 FLAIR sequences.

With increasing use of intraoperative MRI, the validity of the final intraoperative scan as the baseline scan has been debated. Based on a single centre study and consensus among the SIOP-E brain imaging group, it has been agreed that the final intraoperative MRI scan is now acceptable as the baseline, provided it is from a 3T scanner (as it has been only validated on 3T), this SIOPE brain tumour protocol is followed, is supervised by a radiologist experienced in children's brain tumours and is reported in consensus with the operating neurosurgeon [37] . The preoperative and final intraoperative sequences must be comparable. On occasions where there has been further resection following the intraoperative scan, this will not qualify as a final intraoperative scan. A further scan after the extended resection using

the full SIOPE protocol should be performed. The final decision to use intraoperative MRI scans rests with the national reference radiologist or radiology panel as the practices vary in different countries.

Comparability with the preoperative MRI is essential for the detection of residual tumour. The size of a possible residuum has to be measured in all three planes. If the residuum is best visible on T2W images, a second plane incorporating a 2D T2W or T2 FLAIR sequence, or a 3D volume, must be employed. A residuum is considered to be any area of persisting pathological signal and/or enhancement that is comparable with the appearance of the pre-operative tumour. DWI is helpful to demonstrate any local surgical or ischaemic injury, which may influence enhancement patterns and tumour evaluation on subsequent examinations. For the evaluation of residual tumour seen on imaging, the surgical report is often valuable and should be available.

Follow up imaging

Timing for follow-up MRI appointments should be planned according to the individual trial protocol or clinical management plan. The protocol similar to that used for the pre-operative imaging is recommended during follow up.
For uniformly enhancing tumours, the post-contrast T1W should be used for the measurement of the diameters. For heterogeneously, poorly or non-enhancing tumours the dimensions on T2W/T2 FLAIR and in pre-contrast T1W sequences can be used. In some instances, therapy-related reduction of enhancement disproportionate to the change in tumour volume may be encountered (Figure 3). The best sequence cannot be predicted at the outset in these tumours. In these circumstances, it is useful to choose the initial sequence on which the tumour was assessed or change the sequence (e.g. due to a change in contrast behaviour) and compare the tumour characteristics with the same sequence on the previous staging MRI to assess response.
In instances where the MRI findings are equivocal for tumour progression/resolution (pseudoprogression/pseudoresponse), an early follow up scan(s) may be required to evaluate for true progression or response. When true progression is confirmed, the initial scan which showed the abnormality should be considered as the time of progression. In the paediatric neuro-oncology setting, pseudoresponse mainly refers to reduction of enhancement following anti-angiogenic therapy without a change in survival outcome and the response assessment in this setting is based on measurement on the T2W and T2 FLAIR sequences [3].

Multimodal advanced MRI

There is increasing experience in the use of a number of advanced MRI techniques which give information on tissue properties and these augment conventional MRI[38]. The individual techniques should be thought of as complimentary and as such a multi-modal approach is most appropriate. We have developed and tested protocols which seek to provide a balance between quality of data and length of acquisition and at the same time give sufficient flexibility that they can be implemented on most MR scanners. We have focused on diffusion imaging, magnetic resonance spectroscopy and perfusion imaging.

Diffusion tensor imaging (DTI) gives information on the directionality of water diffusion and fractional anisotropy maps generated automatically by the scanner can be useful for investigating tumour margins and proximity to nerve tracts[39]. The additional diagnostic value of DTI over standard DWI (which allows the calculation of ADC, but lacks information about the directionality of water diffusion) for children's brain tumours is only just being investigated [40]. The agreed protocol uses isotropic voxels and a number of directions which is aimed at producing Fractional Anisotropy maps. A larger number of directions e.g. 60 would be required to provide detailed tractography, particularly in regions of fibre crossing.

Magnetic resonance spectroscopy (MRS) has been extensively investigated in childhood brain tumours[41,42]. Single voxel spectroscopy is more robust than spectroscopic imaging and is preferred where a profile of the tumour is required for diagnosis or prognostication. For the standard protocol one echo time is chosen to minimise scan time and a short echo time is preferred as it maximises the metabolite information. There are advantages to higher field strength, but a longer repetition time is advised due to longer metabolite and water T2 values. The commonly used PRESS localisation suffers from chemical shift artefacts, which become more apparent at higher field strength and a recent consensus document has advised moving to a semiLASER localisation sequence[43]. MRS data is best analysed quantitatively using software methods which can fit the spectra to obtain metabolite concentrations but it has also been shown that visual interpretation aids diagnostic accuracy when added to conventional MRI[44]. Spectroscopic imaging may be more appropriate than single voxel spectroscopy for large diffuse tumours and may aid the identification of most aggressive regions, but implementation of the technique requires experience and is not part of the routine protocol[45].

Perfusion imaging is perhaps the most challenging technique to agree a consensus protocol due to the existence of multiple methods and variations acquisition and analysis protocols, and few comparative studies have been performed in children. Injection of a gadolinium-based contrast agent is used routinely in MRI of childhood brain tumours and Dynamic Susceptibility Contrast (DSC) – MRI has traditionally been the standard imaging method in the brain. Blood vessel leakiness of the contrast agent leads to incorrect estimates of the Cerebral Blood Volume (CBV), the main parameter measured, and many methods have been used to reduce the effects of this including giving a pre-bolus of contrast agent. We feel that

the standard bolus should not be exceeded in children and should be split if a pre-bolus is desired. There is an increasing trend towards giving a single bolus and making a leakage correction in the post processing supported by studies in adults[46]. A gradient echo sequence is recommended as this is readily available. Arterial spin labelling [47] which requires no contrast injection but does add to the acquisition time is gaining popularity and is likely to form part of future trials. A consensus protocol exists although implementation has not been optimised for children with brain tumours and may not be available on local scanners[48]. Studies using ASL have shown that perfusion is higher in high grade than low grade tumours[49]. It has also been shown that perfusion measured by ASL correlates well with values obtained from DSC-MRI with leakage correction in paediatric brain tumours[50]. ASL perfusion has some limitations in terms of accuracy in children's brain tumour grading but can be effectively combined with DWI, although diffuse midline glioma remains a challenge for both these methods [51].The protocol for advanced MRI has been designed largely to determine tumour properties since the focus of most clinical trials is on the tumour and its response to treatment. However, advanced MRI is commonly used in other settings which are applicable to clinical trials. Surgical planning with a combination of tractography and functional MR to determine eloquent regions of the brain is becoming popular in adults[52]. The effects of treatment on the brain and in particular neurocognition are important and there is increasing interest in combining DTI and resting state BOLD evaluate changes in structural and functional brain connectivity[53] [54] . Whilst a uniform protocol such as the one presented in the supplementary material is a useful starting point for developing the imaging protocol for a clinical trial, adaptations may be required to optimise the acquisition for specific key questions.

Conclusion

The SIOPE brain tumour imaging protocol has been developed over a period of 10 years following consensus among the imaging group members. The recommendations are based on commonly used methods of imaging and their adequate flexibility for the users to comply with the protocol. We have provided guidance on multimodal imaging which will be increasingly used in the future with advances in treatment and imaging methods. The recommendations in this article are solely related to image acquisition; the response assessment criteria have not been discussed in this article as they vary between studies. However, the SIOPE brain tumour protocol is flexible and compliant with most European paediatric neuro-oncology studies and studies employing the RANO/RAPNO criteria.

References

1. Ellingson BM, Bendszus M, Boxerman J, Barboriak D, Erickson BJ, Smits M, Nelson SJ, Gerstner E, Alexander B, Goldmacher G, Wick W, Vogelbaum M, Weller M, Galanis E, Kalpathy-Cramer J, Shankar L, Jacobs P, Pope WB, Yang D, Chung C, Knopp MV, Cha S, van den Bent MJ, Chang S, Yung WK, Cloughesy TF, Wen PY, Gilbert MR, Jumpstarting Brain Tumor Drug Development Coalition Imaging Standardization Steering C (2015) Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro-oncology 17 (9):1188-1198. doi:10.1093/neuonc/nov095
2. Macdonald DR, Cascino TL, Schold SC, Jr., Cairncross JG (1990) Response criteria for phase II studies of supratentorial malignant glioma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 8 (7):1277-1280. doi:10.1200/JCO.1990.8.7.1277
3. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, Degroot J, Wick W, Gilbert MR, Lassman AB, Tsien C, Mikkelsen T, Wong ET, Chamberlain MC, Stupp R, Lamborn KR, Vogelbaum MA, van den Bent MJ, Chang SM (2010) Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28 (11):1963-1972. doi:10.1200/JCO.2009.26.3541
4. Ellingson BM, Wen PY, Cloughesy TF (2017) Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials. Neurotherapeutics 14 (2):307-320. doi:10.1007/s13311-016-0507-6
5. Warren KE, Vezina G, Poussaint TY, Warmuth-Metz M, Chamberlain MC, Packer RJ, Brandes AA, Reiss M, Goldman S, Fisher MJ, Pollack IF, Prados MD, Wen PY, Chang SM, Dufour C, Zurakowski D, Kortmann RD, Kieran MW (2018) Response assessment in medulloblastoma and leptomeningeal seeding tumors: recommendations from the Response Assessment in Pediatric Neuro-Oncology committee. Neuro-oncology 20 (1):13-23. doi:10.1093/neuonc/nox087
6. Fangusaro J, Witt O, Hernaiz Driever P, Bag AK, de Blank P, Kadom N, Kilburn L, Lober RM, Robison NJ, Fisher MJ, Packer RJ, Young Poussaint T, Papusha L, Avula S, Brandes AA, Bouffet E, Bowers D, Artemov A, Chintagumpala M, Zurakowski D, van den Bent M, Bison B, Yeom KW, Taal W, Warren KE (2020) Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 21 (6):e305-e316. doi:10.1016/S1470-2045(20)30064-4
7. Erker C, Tamrazi B, Poussaint TY, Mueller S, Mata-Mbemba D, Franceschi E, Brandes AA, Rao A, Haworth KB, Wen PY, Goldman S, Vezina G, MacDonald TJ, Dunkel IJ, Morgan PS, Jaspan T, Prados MD, Warren KE (2020) Response assessment in paediatric high-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 21 (6):e317-e329. doi:10.1016/S1470-2045(20)30173-X
8. Cooney TM, Cohen KJ, Guimaraes CV, Dhall G, Leach J, Massimino M, Erbetta A, Chiapparini L, Malbari F, Kramer K, Pollack IF, Baxter P, Laughlin S, Patay Z, Young Poussaint T, Warren KE (2020) Response assessment in diffuse intrinsic pontine glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 21 (6):e330-e336. doi:10.1016/S1470-2045(20)30166-2
9. Gnekow AK, Kandels D, Tilburg CV, Azizi AA, Opocher E, Stokland T, Driever PH, Schouten-van Meeteren AYN, Thomale UW, Schuhmann MU, Czech T, Goodden JR, Warmuth-Metz M, Bison B, Avula S, Kortmann RD, Timmermann B, Pietsch T, Witt O (2019) SIOP-E-BTG and

GPOH Guidelines for Diagnosis and Treatment of Children and Adolescents with Low Grade Glioma. Klin Padiatr 231 (3):107-135. doi:10.1055/a-0889-8256
10. International Society of Paediatric Oncology (SIOP) PNET 5 Medulloblastoma. Available at https://ClinicalTrials.gov/show/NCT02066220
11. An International Clinical Program for the Diagnosis and Treatment of Children With Ependymoma. Available at https://ClinicalTrials.gov/show/NCT02265770
12. Bapst B, Amegnizin JL, Vignaud A, Kauv P, Maraval A, Kalsoum E, Tuilier T, Benaissa A, Brugieres P, Leclerc X, Hodel J (2020) Post-contrast 3D T1-weighted TSE MR sequences (SPACE, CUBE, VISTA/BRAINVIEW, isoFSE, 3D MVOX): Technical aspects and clinical applications. J Neuroradiol. doi:10.1016/j.neurad.2020.01.085
13. Majigsuren M, Abe T, Kageji T, Matsuzaki K, Takeuchi M, Iwamoto S, Otomi Y, Uyama N, Nagahiro S, Harada M (2016) Comparison of Brain Tumor Contrast-enhancement on T1-CUBE and 3D-SPGR Images. Magn Reson Med Sci 15 (1):34-40. doi:10.2463/mrms.2014-0129
14. Komada T, Naganawa S, Ogawa H, Matsushima M, Kubota S, Kawai H, Fukatsu H, Ikeda M, Kawamura M, Sakurai Y, Maruyama K (2008) Contrast-enhanced MR imaging of metastatic brain tumor at 3 tesla: utility of T(1)-weighted SPACE compared with 2D spin echo and 3D gradient echo sequence. Magn Reson Med Sci 7 (1):13-21. doi:10.2463/mrms.7.13
15. Kammer NN, Coppenrath E, Treitl KM, Kooijman H, Dietrich O, Saam T (2016) Comparison of contrast-enhanced modified T1-weighted 3D TSE black-blood and 3D MP-RAGE sequences for the detection of cerebral metastases and brain tumours. Eur Radiol 26 (6):1818-1825. doi:10.1007/s00330-015-3975-x
16. Rowe SK, Rodriguez D, Cohen E, Grundy R, Morgan PS, Jaspan T, Dineen RA (2020) Switching from linear to macrocyclic gadolinium-based contrast agents halts the relative T1 - Weighted signal increase in deep gray matter of children with brain tumors: A retrospective study. Journal of magnetic resonance imaging : JMRI 51 (1):288-295. doi:10.1002/jmri.26831
17. Guo BJ, Yang ZL, Zhang LJ (2018) Gadolinium Deposition in Brain: Current Scientific Evidence and Future Perspectives. Front Mol Neurosci 11:335. doi:10.3389/fnmol.2018.00335
18. Agency EM (2017) PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations. https://www.ema.europa.eu/en/news/prac-concludes-assessment-gadolinium-agents-used-body-scans-recommends-regulatory-actions-including. Accessed March 10 2020
19. Hygino da Cruz LC, Jr., Rodriguez I, Domingues RC, Gasparetto EL, Sorensen AG (2011) Pseudoprogression and pseudoresponse: imaging challenges in the assessment of posttreatment glioma. AJNR American journal of neuroradiology 32 (11):1978-1985. doi:10.3174/ajnr.A2397
20. Abele TA, Besachio DA, Quigley EP, Gurgel RK, Shelton C, Harnsberger HR, Wiggins RH, 3rd (2014) Diagnostic accuracy of screening MR imaging using unenhanced axial CISS and coronal T2WI for detection of small internal auditory canal lesions. AJNR American journal of neuroradiology 35 (12):2366-2370. doi:10.3174/ajnr.A4041
21. Ozgen B, Oguz B, Dolgun A (2009) Diagnostic accuracy of the constructive interference in steady state sequence alone for follow-up imaging of vestibular schwannomas. AJNR American journal of neuroradiology 30 (5):985-991. doi:10.3174/ajnr.A1472

22. Utz MJ, Tamber MS, Mason GE, Pollack IF, Panigrahy A, Zuccoli G (2018) Contrast-enhanced 3-dimensional Fluid-attenuated Inversion Recovery Sequences Have Greater Sensitivity for Detection of Leptomeningeal Metastases in Pediatric Brain Tumors Compared With Conventional Spoiled Gradient Echo Sequences. J Pediatr Hematol Oncol 40 (4):316-319. doi:10.1097/MPH.0000000000000957
23. Fukuoka H, Hirai T, Okuda T, Shigematsu Y, Sasao A, Kimura E, Hirano T, Yano S, Murakami R, Yamashita Y (2010) Comparison of the added value of contrast-enhanced 3D fluid-attenuated inversion recovery and magnetization-prepared rapid acquisition of gradient echo sequences in relation to conventional postcontrast T1-weighted images for the evaluation of leptomeningeal diseases at 3T. AJNR American journal of neuroradiology 31 (5):868-873. doi:10.3174/ajnr.A1937
24. Novak J, Zarinabad N, Rose H, Arvanitis T, MacPherson L, Pinkey B, Oates A, Hales P, Grundy R, Auer D, Gutierrez DR, Jaspan T, Avula S, Abernethy L, Kaur R, Hargrave D, Mitra D, Bailey S, Davies N, Clark C, Peet A (2021) Classification of paediatric brain tumours by diffusion weighted imaging and machine learning. Sci Rep 11 (1):2987. doi:10.1038/s41598-021-82214-3
25. Ramaglia A, Tortora D, Mankad K, Lequin M, Severino M, D'Arco F, Lobel U, Benenati M, de Leng WWJ, De Marco P, Milanaccio C, Rossi A, Morana G (2020) Role of diffusion weighted imaging for differentiating cerebral pilocytic astrocytoma and ganglioglioma BRAF V600E-mutant from wild type. Neuroradiology 62 (1):71-80. doi:10.1007/s00234-019-02304-y
26. Kan P, Liu JK, Hedlund G, Brockmeyer DL, Walker ML, Kestle JR (2006) The role of diffusion-weighted magnetic resonance imaging in pediatric brain tumors. Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery 22 (11):1435-1439. doi:10.1007/s00381-006-0229-x
27. Morana G, Alves CA, Tortora D, Severino M, Nozza P, Cama A, Ravegnani M, D'Apolito G, Raso A, Milanaccio C, da Costa Leite C, Garre ML, Rossi A (2017) Added value of diffusion weighted imaging in pediatric central nervous system embryonal tumors surveillance. Oncotarget 8 (36):60401-60413. doi:10.18632/oncotarget.19553
28. Grech-Sollars M, Hales PW, Miyazaki K, Raschke F, Rodriguez D, Wilson M, Gill SK, Banks T, Saunders DE, Clayden JD, Gwilliam MN, Barrick TR, Morgan PS, Davies NP, Rossiter J, Auer DP, Grundy R, Leach MO, Howe FA, Peet AC, Clark CA (2015) Multi-centre reproducibility of diffusion MRI parameters for clinical sequences in the brain. NMR Biomed 28 (4):468-485. doi:10.1002/nbm.3269
29. Meeus EM, Novak J, Withey SB, Zarinabad N, Dehghani H, Peet AC (2017) Evaluation of intravoxel incoherent motion fitting methods in low-perfused tissue. Journal of magnetic resonance imaging : JMRI 45 (5):1325-1334. doi:10.1002/jmri.25411
30. Warmuth-Metz M, Kuhl J, Krauss J, Solymosi L (2004) Subdural enhancement on postoperative spinal MRI after resection of posterior cranial fossa tumours. Neuroradiology 46 (3):219-223. doi:10.1007/s00234-003-1158-y
31. Harreld JH, Mohammed N, Goldsberry G, Li X, Li Y, Boop F, Patay Z (2015) Postoperative intraspinal subdural collections after pediatric posterior fossa tumor resection: incidence, imaging, and clinical features. AJNR American journal of neuroradiology 36 (5):993-999. doi:10.3174/ajnr.A4221
32. Buch K, Caruso P, Ebb D, Rincon S (2018) Balanced Steady-State Free Precession Sequence (CISS/FIESTA/3D Driven Equilibrium Radiofrequency Reset Pulse) Increases the

Diagnostic Yield for Spinal Drop Metastases in Children with Brain Tumors. AJNR American journal of neuroradiology 39 (7):1355-1361. doi:10.3174/ajnr.A5645
33. Albert FK, Forsting M, Sartor K, Adams HP, Kunze S (1994) Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 34 (1):45-60; discussion 60-41. doi:10.1097/00006123-199401000-00008
34. Forsyth PA, Petrov E, Mahallati H, Cairncross JG, Brasher P, MacRae ME, Hagen NA, Barnes P, Sevick RJ (1997) Prospective study of postoperative magnetic resonance imaging in patients with malignant gliomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 15 (5):2076-2081. doi:10.1200/JCO.1997.15.5.2076
35. Lescher S, Schniewindt S, Jurcoane A, Senft C, Hattingen E (2014) Time window for postoperative reactive enhancement after resection of brain tumors: less than 72 hours. Neurosurgical focus 37 (6):E3. doi:10.3171/2014.9.FOCUS14479
36. Bette S, Gempt J, Huber T, Boeckh-Behrens T, Ringel F, Meyer B, Zimmer C, Kirschke JS (2016) Patterns and Time Dependence of Unspecific Enhancement in Postoperative Magnetic Resonance Imaging After Glioblastoma Resection. World neurosurgery 90:440-447. doi:10.1016/j.wneu.2016.03.031
37. Avula S, Jaspan T, Pizer B, Pettorini B, Garlick D, Hennigan D, Mallucci C (2021) Comparison of intraoperative and post-operative 3-T MRI performed at 24-72 h following brain tumour resection in children. Neuroradiology. doi:10.1007/s00234-021-02671-5
38. Peet AC, Arvanitis TN, Leach MO, Waldman AD (2012) Functional imaging in adult and paediatric brain tumours. Nat Rev Clin Oncol 9 (12):700-711. doi:10.1038/nrclinonc.2012.187
39. Ferda J, Kastner J, Mukensnabl P, Choc M, Horemuzova J, Ferdova E, Kreuzberg B (2010) Diffusion tensor magnetic resonance imaging of glial brain tumors. Eur J Radiol 74 (3):428-436. doi:10.1016/j.ejrad.2009.03.030
40. Heather E.L. Rose CDB, Jan Novak, Lesley MacPherson, Shivaram Avula, Theodoros N Arvanitis, Chris A. Clark, Simon Bailey, Dipayan Mitra, Dorothee P Auer, Richard Grundy, Andrew Peet The role of diffusion tensor imaging in the characterisation of paediatric brain tumours - a multi-centre study. In: ISMRM 27th Annual meeting & exhibition, Montreal, Canada, May 2019 2019.
41. Panigrahy A, Krieger MD, Gonzalez-Gomez I, Liu X, McComb JG, Finlay JL, Nelson MD, Jr., Gilles FH, Bluml S (2006) Quantitative short echo time 1H-MR spectroscopy of untreated pediatric brain tumors: preoperative diagnosis and characterization. AJNR American journal of neuroradiology 27 (3):560-572
42. Vicente J, Fuster-Garcia E, Tortajada S, Garcia-Gomez JM, Davies N, Natarajan K, Wilson M, Grundy RG, Wesseling P, Monleon D, Celda B, Robles M, Peet AC (2013) Accurate classification of childhood brain tumours by in vivo (1)H MRS - a multi-centre study. Eur J Cancer 49 (3):658-667. doi:10.1016/j.ejca.2012.09.003
43. Wilson M, Andronesi O, Barker PB, Bartha R, Bizzi A, Bolan PJ, Brindle KM, Choi IY, Cudalbu C, Dydak U, Emir UE, Gonzalez RG, Gruber S, Gruetter R, Gupta RK, Heerschap A, Henning A, Hetherington HP, Huppi PS, Hurd RE, Kantarci K, Kauppinen RA, Klomp DWJ, Kreis R, Kruiskamp MJ, Leach MO, Lin AP, Luijten PR, Marjanska M, Maudsley AA, Meyerhoff DJ, Mountford CE, Mullins PG, Murdoch JB, Nelson SJ, Noeske R, Oz G, Pan JW, Peet AC, Poptani H, Posse S, Ratai EM, Salibi N, Scheenen TWJ, Smith ICP, Soher BJ, Tkac I, Vigneron DB, Howe FA (2019) Methodological consensus on clinical proton MRS of the brain: Review

and recommendations. Magnetic resonance in medicine 82 (2):527-550. doi:10.1002/mrm.27742
44. Manias KA, Gill SK, MacPherson L, Oates A, Pinkey B, Davies P, Zarinabad N, Davies NP, Babourina-Brooks B, Wilson M, Peet AC (2019) Diagnostic accuracy and added value of qualitative radiological review of (1)H-magnetic resonance spectroscopy in evaluation of childhood brain tumors. Neurooncol Pract 6 (6):428-437. doi:10.1093/nop/npz010
45. Marcus KJ, Astrakas LG, Zurakowski D, Zarifi MK, Mintzopoulos D, Poussaint TY, Anthony DC, De Girolami U, Black PM, Tarbell NJ, Tzika AA (2007) Predicting survival of children with CNS tumors using proton magnetic resonance spectroscopic imaging biomarkers. Int J Oncol 30 (3):651-657
46. Hedderich D, Kluge A, Pyka T, Zimmer C, Kirschke JS, Wiestler B, Preibisch C (2019) Consistency of normalized cerebral blood volume values in glioblastoma using different leakage correction algorithms on dynamic susceptibility contrast magnetic resonance imaging data without and with preload. J Neuroradiol 46 (1):44-51. doi:10.1016/j.neurad.2018.04.006
47. Kassner A, Annesley DJ, Zhu XP, Li KL, Kamaly-Asl ID, Watson Y, Jackson A (2000) Abnormalities of the contrast re-circulation phase in cerebral tumors demonstrated using dynamic susceptibility contrast-enhanced imaging: a possible marker of vascular tortuosity. Journal of magnetic resonance imaging : JMRI 11 (2):103-113
48. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, Lu H, MacIntosh BJ, Parkes LM, Smits M, van Osch MJ, Wang DJ, Wong EC, Zaharchuk G (2015) Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magnetic resonance in medicine 73 (1):102-116. doi:10.1002/mrm.25197
49. Dangouloff-Ros V, Deroulers C, Foissac F, Badoual M, Shotar E, Grevent D, Calmon R, Pages M, Grill J, Dufour C, Blauwblomme T, Puget S, Zerah M, Sainte-Rose C, Brunelle F, Varlet P, Boddaert N (2016) Arterial Spin Labeling to Predict Brain Tumor Grading in Children: Correlations between Histopathologic Vascular Density and Perfusion MR Imaging. Radiology 281 (2):553-566. doi:10.1148/radiol.2016152228
50. Novak J, Withey SB, Lateef S, MacPherson L, Pinkey B, Peet AC (2019) A comparison of pseudo-continuous arterial spin labelling and dynamic susceptibility contrast MRI with and without contrast agent leakage correction in paediatric brain tumours. The British journal of radiology 92 (1094):20170872. doi:10.1259/bjr.20170872
51. Hales PW, d'Arco F, Cooper J, Pfeuffer J, Hargrave D, Mankad K, Clark C (2019) Arterial spin labelling and diffusion-weighted imaging in paediatric brain tumours. NeuroImage Clinical 22:101696. doi:10.1016/j.nicl.2019.101696
52. Castellano A, Cirillo S, Bello L, Riva M, Falini A (2017) Functional MRI for Surgery of Gliomas. Curr Treat Options Neurol 19 (10):34. doi:10.1007/s11940-017-0469-y
53. van Dokkum LEH, Moritz Gasser S, Deverdun J, Herbet G, Mura T, D'Agata B, Picot MC, Menjot de Champfleur N, Duffau H, Molino F, le Bars E (2019) Resting state network plasticity related to picture naming in low-grade glioma patients before and after resection. NeuroImage Clinical 24:102010. doi:10.1016/j.nicl.2019.102010
54. Kesler SR, Ogg R, Reddick WE, Phillips N, Scoggins M, Glass JO, Cheung YT, Pui CH, Robison LL, Hudson MM, Krull KR (2018) Brain Network Connectivity and Executive Function in Long-Term Survivors of Childhood Acute Lymphoblastic Leukemia. Brain Connect 8 (6):333-342. doi:10.1089/brain.2017.0574

Figures:

Figure 1.

Axial images from a 3D T2W gradient echo sequence (a & c) are compared with images from a 2D T2W TSE sequence (b & d) in a patient with posterior fossa ependymoma. Flow-related artefact (white arrows) within the 4th ventricle (a) and extra-axial spaces (c) is indistinguishable from solid tumour. These areas are clearly identified as CSF containing spaces (black arrows) on the 2D T2W sequences (b & d)

Figure 2.

Utility of bSSFP sequence in CNS tumour imaging. Sagittal bSSFP weighted image (a) of the lumbar spine demonstrates a 2 mm drop metastasis (white arrow) that is faintly visible (white dotted arrow) on the 2D T2W image (b) and is not evident on the T1W post contrast image (c). Axial bSSFP weighted image (d) prior to 2nd stage resection of an ependymoma (white circle) clearly demonstrates the tumour margins. The non-enhancing tumour is isointense to the brain stem on the T1W post contrast image (e) and cannot be delineated. Post-operative bSSFP image (f) shows a small residuum at the opening of the right internal auditory canal and demonstrates its relationship to the VIIth and VIIIth cranial nerves (curved arrow).

Figure 3.

Axial (a) and coronal (d) T1W post contrast images demonstrates an enhancing optic pathway glioma. The enhancement had almost completely disappeared following treatment with a BRAF inhibitor (b & e). The axial 2D T2W (c) and 2D T2 FLAIR (f) demonstrate the size and extent of the tumour and will be used as the sequence of choice for obtaining 2 or 3 dimensional measurements.