Child's Nervous System
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REVIEW ARTICLE

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

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Abstract

Introduction Standardisation of imaging acquisition is essential in facilitating multicentre studies related to childhood CNS tumours. It is important to ensure that the imaging protocol can be adopted by centres with varying imaging capabilities without compromising image quality.

Materials and method An imaging protocol has been developed by the Brain Tumour Imaging Working Group of the European Society for Paediatric Oncology (SIOPE) based on consensus among its members, which consists of neuroradiologists, imaging scientists and paediatric neuro-oncologists. This protocol has been developed to facilitate SIOPE led studies and regularly reviewed by the imaging working group.

Results The protocol consists of essential MRI sequences with imaging parameters for 1.5 and 3 Tesla MRI scanners and a set of optional sequences that can be used in appropriate clinical settings. The protocol also provides guidelines for early post-operative imaging and surveillance imaging. The complementary use of multimodal advanced MRI including diffusion tensor imaging (DTI), MR spectroscopy and perfusion imaging is encouraged, and optional guidance is provided in this publication.

Conclusion The SIOPE brain tumour imaging protocol will enable consistent imaging across multiple centres involved in paediatric CNS tumour studies.

Keywords Paediatric CNS tumour · Imaging guidelines · MRI protocol · SIOP Europe-Brain Tumour Group · Paediatric brain tumour imaging · Paediatric spine tumour imaging

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 (preoperative, postoperative and subsequent follow-up imaging) but also aids comparability across multiple centres by the central study coordinators 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,

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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 selected 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 mainly in the context of adult population. 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 [5–8]. It is important to ensure that there is a basic MRI protocol for the paediatric CNS tumour population that is achievable across all sites and 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 the 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). 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 a 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 multimodal 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 1.5-T and 3-T 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 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.

Table 1 Essential sequences

Sequence	Technique	Parameters	Plane
1.5-Tesla scanner			
T1W	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial (along AC-PC axis)
T2W	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial
T2 FLAIR	2D TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial or coronal
T1W + contrast	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial, coronal and sagittal
DWI with ADC	2D EPI	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable) b = 0 and 1000. ADC maps reconstructed on-line	Axial
3-Tesla scanner			
T1W	3D gradient echo (MPRAGE/IR SPGR/Fast SPGR/3D TFE/3D FFE)	Slice thickness ≤ 1 mm with no slice gap. An isotropic voxel resolution of 1 mm × 1 mm × 1 mm is desirable depending on scanner capability	Axial or sagittal
T2W	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1mm (10% of slice thickness is desirable)	Axial
T2 FLAIR	2D TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial or coronal
T1W + contrast	2D SE, TSE/FSE	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable)	Axial
T1W + contrast	3D gradient echo (MPRAGE/IR SPGR/Fast SPGR/3D TFE/3D FFE)	Slice thickness ≤ 1 mm with no slice gap. An isotropic voxel resolution of 1 mm × 1 mm × 1 mm is desirable depending on scanner capability	Axial or sagittal, to match pre-contrast
DWI with ADC	2D EPI	Slice thickness ≤ 4 mm and slice gap ≤ 1 mm (10% of slice thickness is desirable) b = 0 and 1000. ADC maps reconstructed on-line	Axial
Resolution parameters: field of view: 230 mm (range 220–250 mm depending on head size); matrix size–minimum 256 (512 is desirable for better resolution; 96–128 for EPI sequences)			
Optional sequences			
Sequence	**Technique**	**Plane**	
T1W	3D gradient echo (on 1.5 T)/3D T1 TSE	Axial or sagittal	
T2 FLAIR	3D gradient echo*	Axial or sagittal	
Heavily weighted T2W	2D or 3D CISS/B FFE/FIESTA**	Axial or coronal or sagittal	
Advanced MRI	DTI, perfusion and spectroscopy		

*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 heavily weighted T2W sequence localised to a region of interest is useful in assessment of lesions (in particular poorly/non-enhancing) within the extra-axial space or along the parenchymal surface

Additional sequences for the orbit need to be considered in optic pathway gliomas [6]

T1-weighted imaging

The T1-weighted (T1W) sequences differ on 1.5-T and 3-T scanners. 2D T1W spin echo (SE) and turbo/fast spin echo (TSE/FSE) sequences are recommended for 1.5-T scanners both prior to and following contrast administration. For 1.5-T 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 3-T 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 has been variable on 1.5-T scanners with relatively few centres capable of obtaining the high-quality 3D T1W sequences that are now available on newer 1.5-T scanners. It is therefore not recommended as an essential sequence at 1.5 T. However, it is listed as an optional sequence on the 1.5 T 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 detecting 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 3 T protocol, an axial 2D T1W sequence 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 3 T and 1.5 T 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 3-T 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) [5–8]. The RAPNO medulloblastoma protocol recommends a post-contrast 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, which is 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 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 [3, 19]. 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 is 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 neuro-navigation 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 (Fig. 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 has 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 in identifying small extra-axial metastatic foci and differentiating them from normal structures in challenging locations such as the internal auditory canals (Fig. 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 1.5 T and 3 T 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.

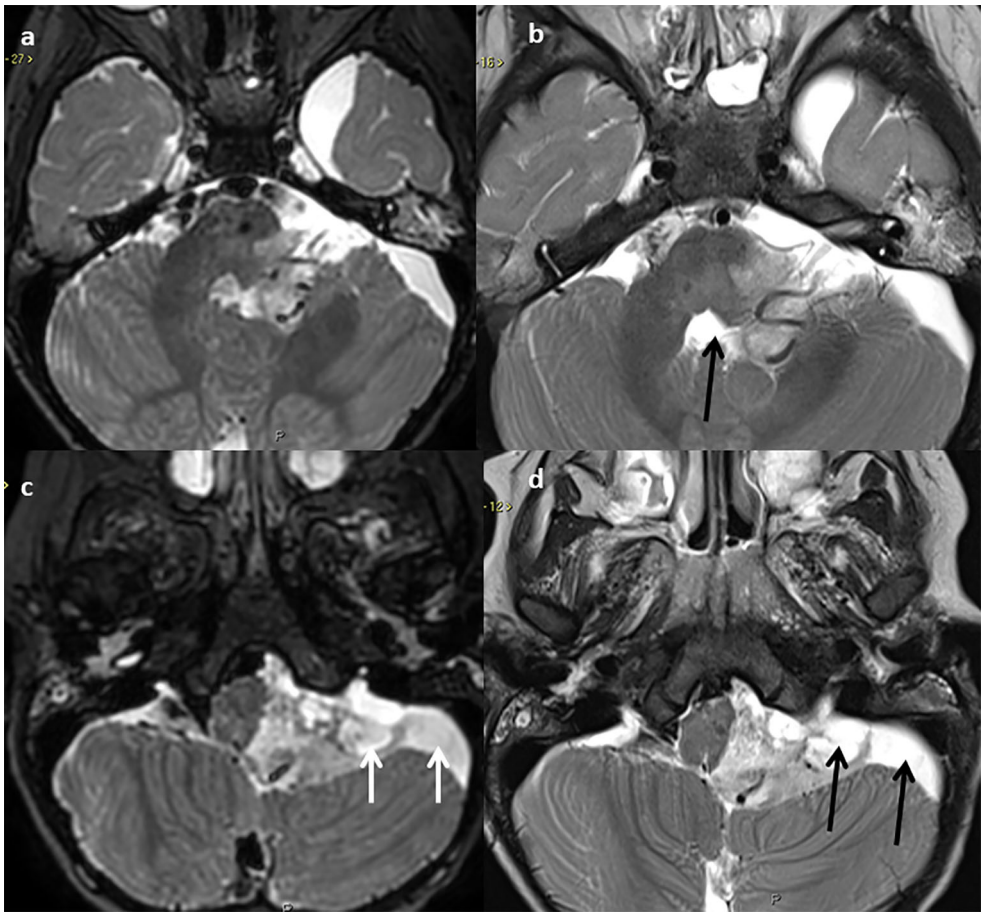

Fig. 1 Axial images from a 3D T2W gradient echo sequence (**a**, **c**) are compared with images from a 2D T2W TSE sequence (**b**, **d**) in a patient with posterior fossa ependymoma. Flow-related artefact (white arrows) within the 4th ventricle (**a**) and extra-axial spaces (**c**) is indistinguishable from solid tumour. These areas are clearly identified as CSF-containing spaces (black arrows) on the 2D T2W sequences (**b**, **d**)

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 and treatment response and in identifying metastases [24–27]. 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/mm^2 and 1000 s/mm^2 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 multicentre 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/mm^2 and 1000 s/mm^2 can separate the effects of water apparent diffusion from perfusion and may further increase the accuracy of DWI biomarkers in a multicentre setting but a paucity of comparative data for paediatric brain tumours and a current lack of readily available analysis software make this approach a research tool currently [29].

Spine imaging

Table 2 summarises the essential and optional sequences for spine imaging with the generic sequence technique and the plane of acquisition.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

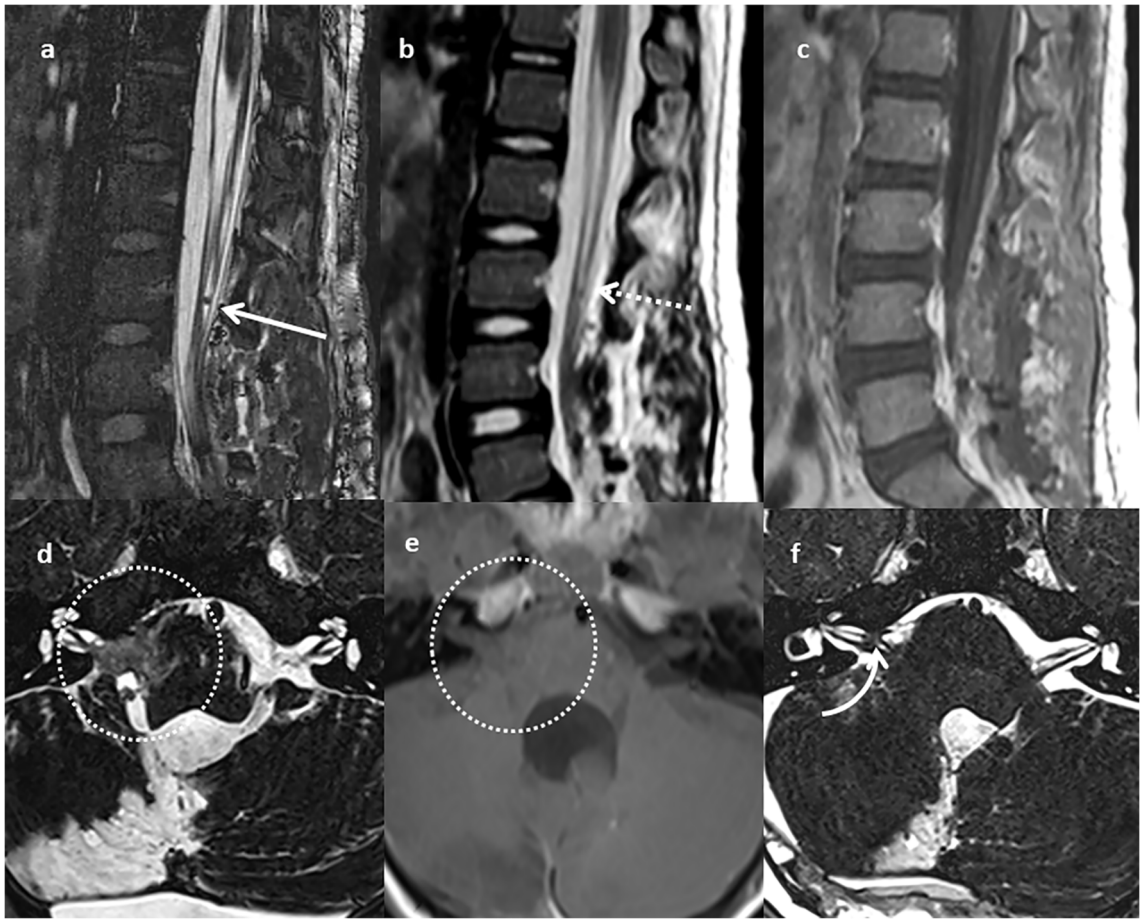

Fig. 2 Utility of bSSFP sequence in CNS tumour imaging. Sagittal bSSFP weighted image (**a**) of the lumbar spine demonstrates a 2-mm drop metastasis (white arrow) that is faintly visible (white dotted arrow) on the 2D T2W image (**b**) and is not evident on the T1W post-contrast image (**c**). Axial 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. Postoperative 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)

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.

1.5 T is preferred to 3 T for spinal imaging as the quality on older 3 T systems is often inferior and more unpredictable. More recent generation 3-T scanners now enable good, diagnostic quality spinal imaging but there must be a low threshold to reimage the spine on a 1.5-T 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 postoperative 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 T1W sequence in addition to the recommended protocol.

The bSSFP sequences (CISS/FIESTA/B FFE) are extremely useful in identifying drop metastases, and are particular 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 (Fig. 2). As fat suppression sequences often lead to artefacts and are not specifically necessary for the delineation of meningeal disease, they should not be used routinely.

Early postoperative imaging

Optimal evaluation is made within the first 48 h following surgery. As non-specific intracranial enhancement is often seen 72 h 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 SIOPE brain imaging group, it has been agreed that the final intraoperative MRI scan is now acceptable as the baseline, provided it is from a 3-T scanner (as it has been only validated on 3 T); 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 preoperative 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 preoperative 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 (Fig. 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) is required to evaluate for true progression or response. When true progression is confirmed, the initial scan which showed the abnormality should be considered 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].

Multi-modal 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, are 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

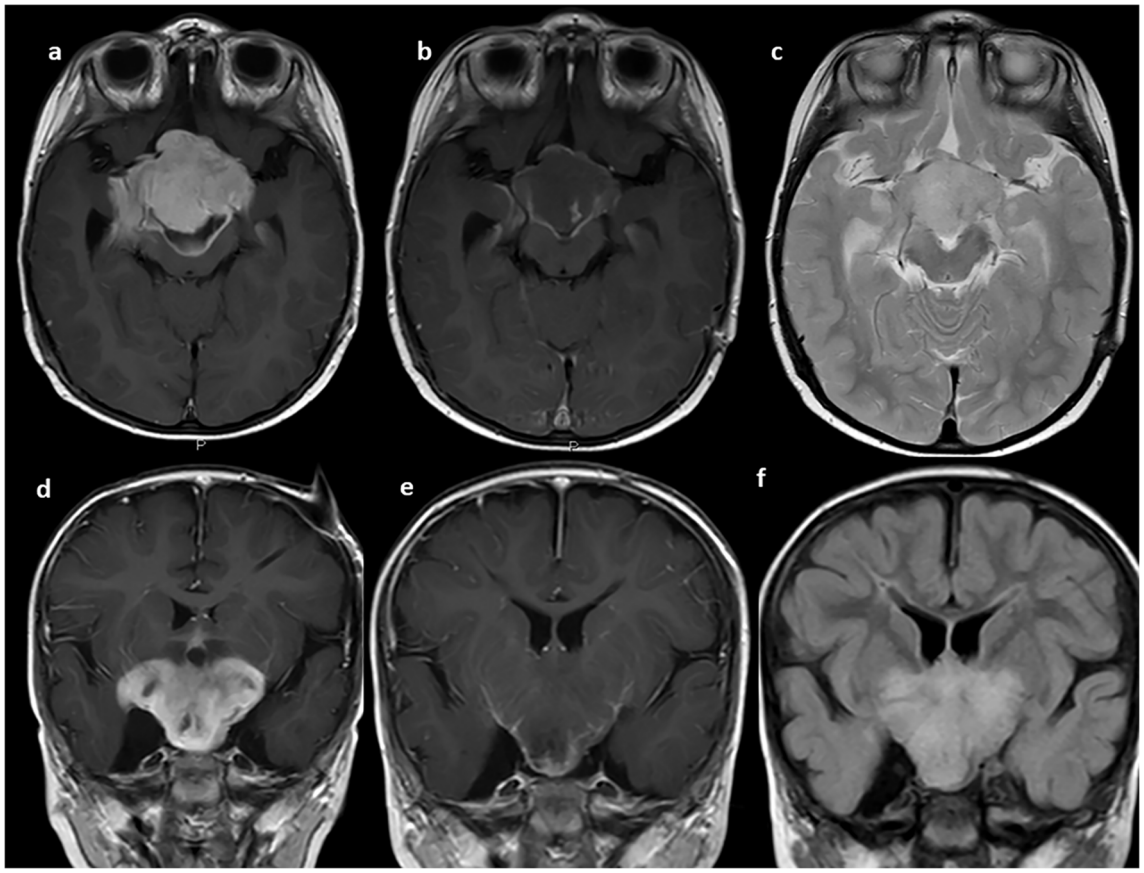

Fig. 3 Axial (**a**) and coronal (**d**) T1W post-contrast images demonstrate an enhancing optic pathway glioma. The enhancement had almost completely disappeared following treatment with a BRAF inhibitor (**b**, **e**). The axial 2D T2W (**c**) and 2D T2 FLAIR (**f**) demonstrate the size and extent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

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 of 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 in 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 to 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 multi-modal 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.

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Declarations

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