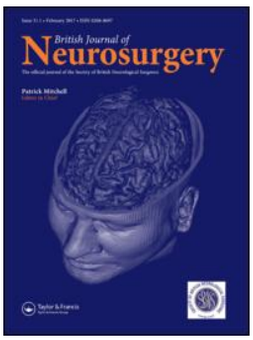

British Journal of Neurosurgery

ISSN: 0268-8697 (Print) 1360-046X (Online) Journal homepage: https://www.tandfonline.com/loi/ibjn20

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To cite this article: Elwira Szychot, John Goodden, Gillian Whitfield & Sarah Curry (2020): Children's Cancer and Leukaemia Group (CCLG): review and guidelines for the management of meningioma in children, teenagers and young adults, British Journal of Neurosurgery, DOI: 10.1080/02688697.2020.1726286

To link to this article: https://doi.org/10.1080/02688697.2020.1726286

Published online: 02 Mar 2020.

BRITISH JOURNAL OF NEUROSURGERY
https://doi.org/10.1080/02688697.2020.1726286

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REVIEW ARTICLE

Children's Cancer and Leukaemia Group (CCLG): review and guidelines for the management of meningioma in children, teenagers and young adults

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ABSTRACT

Primary tumours of the meninges are rare accounting for only 0.4–4.6% of all paediatric tumours of the central nervous system. Due to the rarity of these tumours in children, and the consequent absence of collaborative prospective trials, there is no clear consensus on how the unique characteristics of paediatric meningiomas impact clinical status, management approach, and survival. Much of the evidence and treatment recommendations for paediatric meningiomas are extrapolated from adult data. Translating and adapting adult treatment recommendations into paediatric practice can be challenging and might inadvertently lead to inappropriate management. In 2009, Traunecker *et al.* published guidelines for the management of intracranial meningioma in children and young people on behalf of UK Children's Cancer and Leukaemia Group (CCLG). Ten years later we have developed the updated guidelines following a comprehensive appraisal of the literature. Complete surgical resection is the treatment of choice for symptomatic meningiomas, while radiotherapy remains the only available adjuvant therapy and may be necessary for those tumours that cannot be completely removed. However, significant advances have been made in the identification of the genetic and molecular alterations of meningioma, which has not only a potential value in the development of therapeutic agents but also in surveillance of childhood meningioma survivors. This guideline builds upon the CCLG 2009 guideline. We summarise recommendations for the diagnosis, treatment, surveillance and long-term follow-up of children and adolescents with meningioma.

ARTICLE HISTORY
Received 22 March 2019
Revised 31 October 2019
Accepted 3 February 2020

KEYWORDS
Meningioma; brain tumour; management; children; teenagers; young adults

Introduction

Meningiomas are rare intracranial tumours arising from arachnoid cap cells of the meninges. Due to the rarity of these tumours in children, and the consequent absence of collaborative prospective trials, there is no clear consensus on how the unique characteristics of paediatric and adolescent meningiomas impact clinical status, management approach, and survival. Much of the evidence and treatment recommendations for paediatric and adolescent meningioma are extrapolated from adult data. This is not ideal, as the biology of these tumours differs from adult meningiomas.[1] Additionally, we must consider that children and adolescents have much longer to endure morbidity from the disease or treatment, as well as requiring surveillance for many years.

This guideline builds upon the Children's Cancer and Leukaemia Group (CCLG) guidelines published in 2007[2] discussing paediatric and adolescent meningioma, including epidemiology, clinical presentation, pathogenesis, diagnostic procedures, therapeutic decision-making, surgical and radio-therapeutic approaches, as well as the potential role for chemotherapy and experimental agents.

In the absence of paediatric and adult trials data, the level of evidence to provide recommendations for the diagnosis and treatment of meningiomas in childhood and adolescence is low compared with other tumours. The available paediatric literature is based on small retrospective studies over extensive time periods, during which the imaging techniques, pathological criteria and surgical advances have led to shifts in definitions of disease, making comparison of results difficult.

These guidelines have been developed following PubMed and Medline search for relevant articles published between January 2007 and June 2019 with the terms: 'meningioma', 'paediatric', 'pediatric', 'adolescent', 'teenagers', and 'young adults' and a comprehensive appraisal of the literature. We acknowledge that the majority of evidence available pertains to meningioma in adults, and therefore we explored the adult publications also where applicable.

We summarise recommendations for the diagnosis, treatment, surveillance and long-term follow-up of children and adolescents with meningioma. The guideline has also been discussed and approved by the members of the paediatric neuro-oncology group of the UK CCLG.

Epidemiology

Incidence

Meningiomas are the most common primary brain tumours diagnosed in adults, representing 30% of primary CNS neoplasms.[1] In contrast, meningiomas account for only 0.4–4.6% of all paediatric tumours of the central nervous system (CNS). In England there are about five new cases per year of meningioma in

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Table 1. Number of newly diagnosed meningioma cases in England from 2001 to 2015.

Age band	Count of registrations
0–4	17
5–9	17
10–14	47
15–19	76
20–24	141
Total	298

NCRAS, PHE, CASref accessed 4 Jul 2018.

Table 2. Differences between paediatric and adolescent meningioma in comparison to adult meningioma.[1,3–10]

	Paeadiatric and adolescent meningioma	Adult meningioma
Incidence	1–3% of all CNS tumours	30% of all CNS tumours
Mean age at diagnosis	13.7 years	65 years
Male to female ratio	Pre-pubertal: 1.9:1 Post-pubertal: 1:1.6	1:2
Histological classification[a]		
WHO Grade I	78.9%[b]	65–80%
WHO Grade II	9.9%[b]	4.7–16.9%
WHO Grade III	8.9%[b]	1.0–2.8%
5-year OS		
WHO Grade I	93%[b]	90%
WHO Grade II	87%[b]	85%
WHO Grade III	72%[b]	64%
5-year EFS		
WHO Grade I	81%[b]	75%
WHO Grade II	69%[b]	50%
WHO Grade III	41%[b]	23%

[a]WHO grading incidence is data from prior to the revised WHO 2016 histopathological grading, although this is unlikely to have altered the figures substantially.
[b]Survival data are from the most comprehensive Kotecha meta-analysis, however, included only children who had undergone surgery.

children (<15 years of age) and five new cases in those aged 15–19 years (Table 1).

Age and sex distribution in children and young adults

Two peaks exist in the age distribution of meningioma in children and young adults. The first peak reflects infantile type meningiomas, presenting at a median age of 2–3 years with a short history, while the second peak reflects those presenting in the second decade of life whose clinical course mirrors that of adults.[2] Infantile meningioma is extremely rare, representing only 4% of the paediatric cases.[1] In adults, meningioma has a female predominance, but this is altered for children (Table 2).

Biology/aetiology

Meningiomas may be sporadic but there are a number of risk factors, which predispose to their development. The most common risk factors include prior treatment with radiotherapy and genetic syndromes, such as Neurofibromatosis (NF) type 2 (NF2) and much less commonly, Neurofibromatosis type 1 (NF1). Much rarer associations include Gorlin's syndrome (especially if they have received prior irradiation), and Rubenstein Taybi.[1,11,12] Rare forms of familial meningiomas also exist.

Secondary to irradiation

Children and young adults who have received radiotherapy for CNS tumours, acute lymphoblastic leukaemia and even benign conditions, such as tinea capitis, have an increased risk of meningioma. In 2017 Bowers *et al.* reported on mortality and morbidity associated with meningioma after cranial radiotherapy in a cohort of 169 childhood cancer survivors.[13] The report revealed that nearly 6% of childhood cancer survivors exposed to cranial radiotherapy will be diagnosed with a meningioma by the age of 40, with no plateau in incidence.

Radiation-induced tumours have been defined as those fulfilling the following criteria: development of a tumour in the radiation field, existence of a sufficient latency period, different histological findings between the primary irradiated tumour and the radiation-induced neoplasm and absence of familial predisposition.[14–16] The difference in latency has been described elsewhere.[17–20]

Association with inherited genetic disease

Neurofibromatosis

Approximately 15% of paediatric meningiomas develop in patients with NF, of which NF2 accounts for 10% and NF 1 for 3.4%.[1] Meningiomas are seen in 53% of people with NF2. Previously meningioma risk in NF1 was reported to be that of the general population, but Kotecha's meta-analysis suggests an NF1-related meningioma prevalence of 3.4%. Therefore, healthcare professionals should remain vigilant in assessing for stigmata of NF1 and NF2.[1]

Meningiomas associated with NF2 have a lower frequency of brain invasion than sporadic paediatric meningiomas. However, patients with NF2 are prone to the development of multifocal or multiple meningiomas.[1] Patients with NF2 also have a higher risk of developing meningiomas of the spinal canal and optic nerve sheath.[3,16] Loss of NF2 gene expression (22q11) occurs in the vast majority of NF2-associated meningiomas and in at least 40–60% of sporadic cases.

Gorlin syndrome, or multiple basal cell carcinoma syndrome, is an autosomal dominant inherited familial syndrome associated with meningiomas. Individuals with Gorlin syndrome are also at increased risk of medulloblastoma, the treatment of which may then dispose to radiation-induced meningioma.[21,22]

Familial meningioma

Recently, a new hereditary tumour predisposition syndrome has been discovered, resulting in an increased risk for spinal and intracranial clear cell meningiomas (CCMs) in young patients. Heterozygous loss-of-function germline mutations in the *SMARCE1* gene are causative, giving rise to an autosomal dominant inheritance pattern.[23–25] Because of the few reported cases so far, the lifetime risk of developing meningiomas for *SMARCE1* mutation carriers is unclear and the complete tumour spectrum is unknown. Gerkes *et al.* suggest that those with a *SMARCE1* mutation should have a yearly MRI head and clinical examination until aged 18 and 3 yearly thereafter, for surveillance.[23] More research is required in this area.

Schwannomatosis

Meningiomas may be seen in people with schwannomatosis. Germline mutations in *SMARCB1* are present in up to 50% of familial cases and much less frequently in sporadic cases.

Other

Meningioangiomatosis (0·4% of cases), Castleman's disease, and Rubenstein-Taybi syndrome.[1,3,4]

Histopathology

The majority of paediatric meningiomas are WHO grade I (Table 2). Meningothelial and fibroblastic meningiomas constitute the major subtypes of grade I meningiomas, and represented about 55% of childhood meningiomas.[1] The incidence of WHO II and WHO III meningiomas in children was reported as 4.7–7.2%, but it is unclear how these percentages would be affected by the WHO 2016 classification.[26,27] Paediatric meningiomas have often being described as 'more aggressive' than their adult counterparts, however, evidence is conflicting. Although the histological variant of a tumour has an impact on further treatment and prognosis, the overall survival after 15 years of follow-up appears to be independent of WHO histological grade in children and adolescents, with meningioma grade affecting relapse-free survival (RFS) but not overall survival (OS).[1] Although many concur that a higher MIB-L1 is associated with a higher tumour grade, this requires caution in interpretation as there is an overlap and inter-institutional variability in reporting MIB-L1.

Although in most cases the diagnosis of meningioma can be made safely using the WHO guidelines, a second opinion is encouraged when in doubt. Registration for tumour banking and constitutional DNA sampling are recommended as part of national tissue banking studies (https://www.cclg.org.uk/tissue-bank).

Molecular biology

Important advances have been achieved in the identification of the genetic and molecular alterations of meningioma and the signalling pathways involved. However, molecular mechanisms described in the literature have mainly been derived from adult meningioma and remain poorly validated in children and young adults. Meningioma was the first solid tumour in adults associated with a characteristic cytogenetic abnormality, monosomy 22.[1] By far the most frequent cytogenetic event in meningiomas is monosomy 22/del(22q) in association or not with various mutations of the NF2 gene. However, other isolated chromosomal alterations and gene mutations, together with more complex karyotypes, have also been reported at relatively high frequencies, usually in association with more aggressive tumour behaviour.[28] Chromosome 1p and 14q deletions are frequently found in childhood meningiomas.[29] Chromosome 1p deletion is the second most common chromosomal alteration in adult meningiomas and is typically associated with more aggressive tumour type and higher tumour recurrence rates.[28,30,31] However, in children, this association was weaker than reported in adult meningiomas, because these deletions were also frequently evident in histologically benign meningiomas.[1] In adults, monosomy 14/del(14q) represents the third most common chromosomal alteration in meningiomas and has been identified as a prognostic indicator for tumour recurrence.[31,32]

Kirches *et al.* have published molecular data on meningiomas in children and young adults which illustrates that they are genetically distinct from their adult counterparts.[33] Forty-one meningioma samples from 37 paediatric patients (female 17, age range 1–21years) were analysed and Sanger sequencing of 22 tumours revealed no AKT, SMO or KLF4/TRF47 mutations, which are sometimes seen in skull base meningiomas.

There have been some studies outlining the differences between radiation induced meningiomas and sporadic meningiomas. Angihotri *et al.* characterised 31 radiation-induced meningiomas and found NF2 rearrangements in 12/31.[34] Mutational aberrations known to be associated with sporadic meningioma (e.g. AKT1, KLF4, TRAF7 and SMO) were not observed in this cohort. Combined losses of chromosomes 1p and 22q were common in those radiation-induced meningiomas (16/18 cases) and chromosomal aberrations were more complex than those observed in their sporadic counterparts.

Presenting symptoms and location

Meningiomas frequently cause symptoms late, only after they have grown to a large size or caused CSF obstruction. Presenting symptoms depend on tumour location. Meningiomas in childhood have been described in unusual locations, e.g. intraparenchymal or deep in the sylvian fissure.[25]

The majority of patients present with signs and symptoms of raised intracranial pressure, seizures, cranial nerve deficits, visual and motor disturbances.[1] Infants may present with enlarging head circumference.

Spinal meningiomas represent between 13% and 16% of meningiomas in children and may present with back pain, motor or sensory symptoms, bladder or bowel neuropathy or symptoms of spinal cord compression.

Metastases occur rarely at diagnosis (~0.15% of patients) and are identified more often at relapse.[1]

Neuroimaging

MRI is the imaging modality of choice. Diagnostic clues which indicate a dural-based mass lesion include cortical buckling and cortical vessels.

Contrast enhancement can be strong and uniform on MRI and CT.[35] A characteristic but not pathognomonic feature is the 'dural tail sign', which may be less frequently seen in paediatric tumours.[36] Calcifications (up to 50% cases) and cystic transformation are more common in children.[37] As with other CCLG protocols, post-operative imaging should occur within 48-h of surgery.

Management

Staging investigations

1. MRI of the brain with contrast remains the standard investigation in all patients.
2. *Consider* MRI of the spine to assess for multiplicity.
3. Delineation of some meningiomas can be challenging. The expression of somatostatin receptor 2 in meningiomas may be *considered* to discriminate them from healthy tissue, using peptide ligands such as 68Ga-Dotatate or 90Y-Dotatoc as PET tracers.[38–40] *However, this approach has not been validated in paediatric studies so far.

Treatment

A multidisciplinary approach including the neurosurgeon, clinical and paediatric oncologist, neuroradiologist, neuropathologist, and

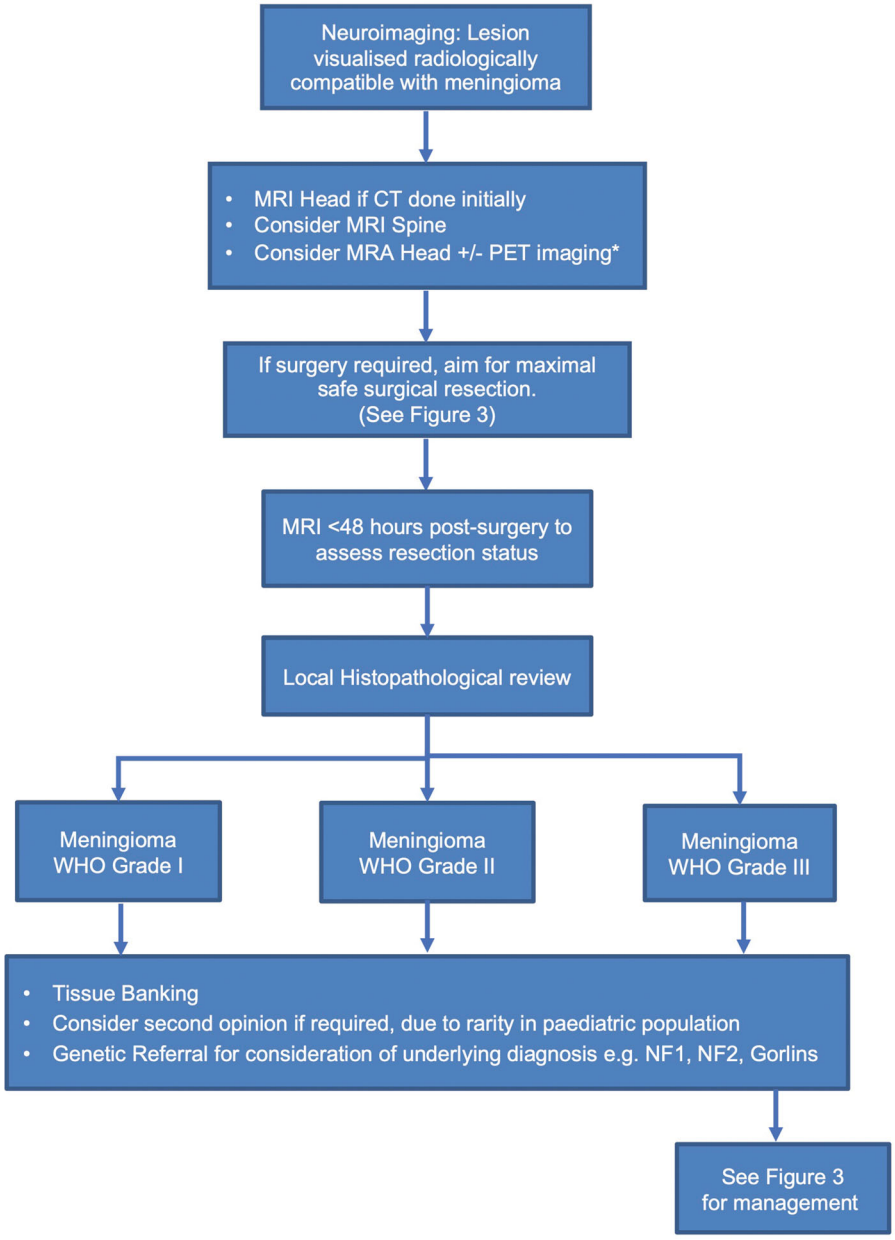

Figure 1. Initial management of suspected meningioma.

if indicated ENT surgeon or ophthalmologist and neurologist is advised to develop a treatment plan that will be tailored to the patient's age, tumour site and predicted clinical tumour behaviour. Access to adult surgical expertise is particularly important for specific tumour sites more commonly encountered in adult practice, i.e. skull base and for this subgroup of patients' referral to specialised neurosurgical services might be necessary (Figure 1).

Observation only

The merits of over-aggressive surgery and radiation therapy versus observation in childhood and adolescents must be carefully considered on a case-by-case basis.

Analysis of SEER data by Dudley *et al.* revealed that a 'watch-and-wait' approach was frequently used in 381 children and adolescents, diagnosed with meningioma.[3] The report showed that paediatric meningiomas are treated similarly to meningiomas in adolescents with GTR in 43% of cases, irradiation therapy in 14% of children and 12% of young adults and a similar mortality rate of 4.5% in both age groups.[3]

The treatment strategy for asymptomatic meningioma is controversial even in adults. Key to an optimal decision is a careful evaluation of the growth possibilities of the meningioma by taking clinical and radiological factors into consideration. A meta-analysis of 777 patients with meningioma, performed by Zeng *et al.*, identified tumour calcification and low MRI T2 signal intensity as two factors predicting the possibility of a slow growing meningioma.[41] Similar findings were previously published by Oya *et al.*[42] Incidental meningiomas in adults have been successfully managed with 'watch-and-wait' approach as long as the growth rate remained slow. However, the reason for observation was frequently determined by the age above 60 years and/or other co-morbidities.[41–44]

Asymptomatic, incidental meningiomas have been identified in 2.3% adult autopsies.[45] A Finnish population-based study

Table 3. Simpson grade and extent of resection.

Simpson grade	Simpson grading definition	Extent of resection – summary
Grade I	Gross total resection of tumour, dural attachment and abnormal bone	Gross total resection (GTR)
Grade II	Gross total resection of tumour, coagulation of dural attachment	Gross total resection
Grade III	Gross total resection of tumour without resection or coagulation of dural attachments or extradural extension (e.g. invaded or hyperostotic bone)	Gross total resection
Grade IV	Partial resection of tumour	Subtotal resection
Grade V	Biopsy of tumour	Subtotal resection

noted that 21% meningiomas were identified at autopsy and notified through death certificates.[46]

1. **Key recommendations for observation:** A conservative approach is acceptable in asymptomatic young adults with indolent tumours.[47,48] Those patients can be managed by observation using annual clinical reviews and MRI surveillance scans, after an initial observation interval of 6 months as per the European Association of Neuro- Oncology guidelines (EANO).[7]
2. However, observation is not recommended in children under the age of 3 years since anaplastic histology or other aggressive variants are more frequently observed and may require further treatment.[1]

Surgery

Complete surgical resection is the treatment of choice for symptomatic meningiomas. The extent of resection is defined by the Simpson Grade – as judged by the surgeon intra-operatively[49] (Table 3).

Nevertheless, the effect of gross-total resection (GTR) versus partial resection on PFS remains poorly defined for both paediatric and adult populations. Retrospective case series described in the literature may only represent a fraction of treated children. Kotecha *et al.* published a meta-analysis of 677 children and adolescents with meningioma, treated with surgical excision, and showed that the extent of initial resection is a decisive prognostic factor in paediatric meningiomas.[1]

These data suggest that a GTR should be achieved where safely possible. Furthermore, in cases where complete macroscopic resection cannot be achieved at initial surgery, some authors recommend a staged approach to surgery with 'second look' and even 'third look' surgery in order to avoid or postpone radiotherapy treatment.[50] However, the risks of repeat surgery should also be balanced against those of adjunctive treatments such as radiotherapy.

The optimum balance between extent of resection and neurological functional outcome (the 'onco-functional balance') is a vitally important matter for careful MDT discussion ahead of surgery. As always, a balance between safe surgical tumour removal and risk of morbidity needs to be considered for each patient.

The neurosurgeon and MDT should also *consider* whether pre-operative embolisation may help achieve a better extent of resection or reduce the complication risk. There is evidence that, in large paediatric and adolescent tumours, embolisation could reduce the peri-operative morbidity.[51–53] However, the calibre of vessels is small in children and the risk of embolisation-related consequences are higher.[51,54] The use of embolisation does, of course, need to be balanced against the risk of secondary oedema and misdiagnosing the tumour as a higher grade due to post-embolisation necrosis being interpreted as primary tumour necrosis.

Most paediatric meningiomas (65%) are dural-based and supratentorial. The usual presentation is a hemispheric, superficial mass with wide dural base, although tumours with no dural attachment in children are described. If the dural attachment is at the skull base or along one of the venous sinuses, the surgeon will not be able to excise that dura and will have to use diathermy to cauterise the origin instead. This, however, comes with an increased risk of recurrence.[55–57]

Intra-operative techniques such as image-guided surgery (frameless stereotaxy) and intraoperative imaging (iCT, iMRI, iUS) have been shown to improve resection rates and safety for other tumour types, and should therefore be considered for paediatric meningioma surgery.

As skull-base tumour locations are relatively more common in adults, very experienced surgical teams specialising in skull base approaches have developed.[47] It is therefore recommended that the paediatric neurosurgeon works jointly with a specialist adult skull-base neurosurgical colleague, and potentially also alongside allied specialist ENT or maxillo-facial surgeons. The use of intraoperative neurophysiology monitoring of the relevant cranial nerves is recommended when operating in the cerebello-pontine angle.

According to Kotecha *et al.*, one of the most common causes of death in children and adolescents treated for meningioma is due to intraoperative or post-operative complications, accounting for nearly 24% of events.[1] Careful MDT decision-making is therefore of paramount importance.

For tumours not safely accessible by surgery, or after incomplete surgical resection, stereotactic radiosurgery (SRS) may be considered for small tumours/tumour portions of 3 cm maximal diameter, where dose to vital structures (e.g. optic nerve, chiasm and brainstem) can be appropriately limited.[1] This however, requires careful MDT discussion including a clinical oncologist. Treating a tumour remnant only may leave the child vulnerable to nearby relapse in the original tumour bed. Furthermore, some patients develop symptomatic peri-tumoural oedema, usually within the first year after SRS treatment. This appears to be most common for non-skull-base meningiomas (reported in ~10–45% of cases), and is less common for skull-base tumours (probably <10%).[58,59] It can cause worsening of existing symptoms, or new neurological symptoms including seizures. Treatment is usually aimed at symptomatic relief and may include steroids and anticonvulsants. Occasionally surgery may also be required.

Following surgery, a post-operative MRI scan should normally be performed within 48 h to assess the extent of resection. If this shows significant/unexpected tumour residuum, the MDT should consider an early second-look procedure to complete the resection, if this can be achieved safely.

Key recommendations for surgery (see also Figure 2):

1. Aim to achieve GTR, and consider staged surgery for large tumours or those with difficult access.
2. *Consider* pre-operative embolisation – especially for highly vascular tumours

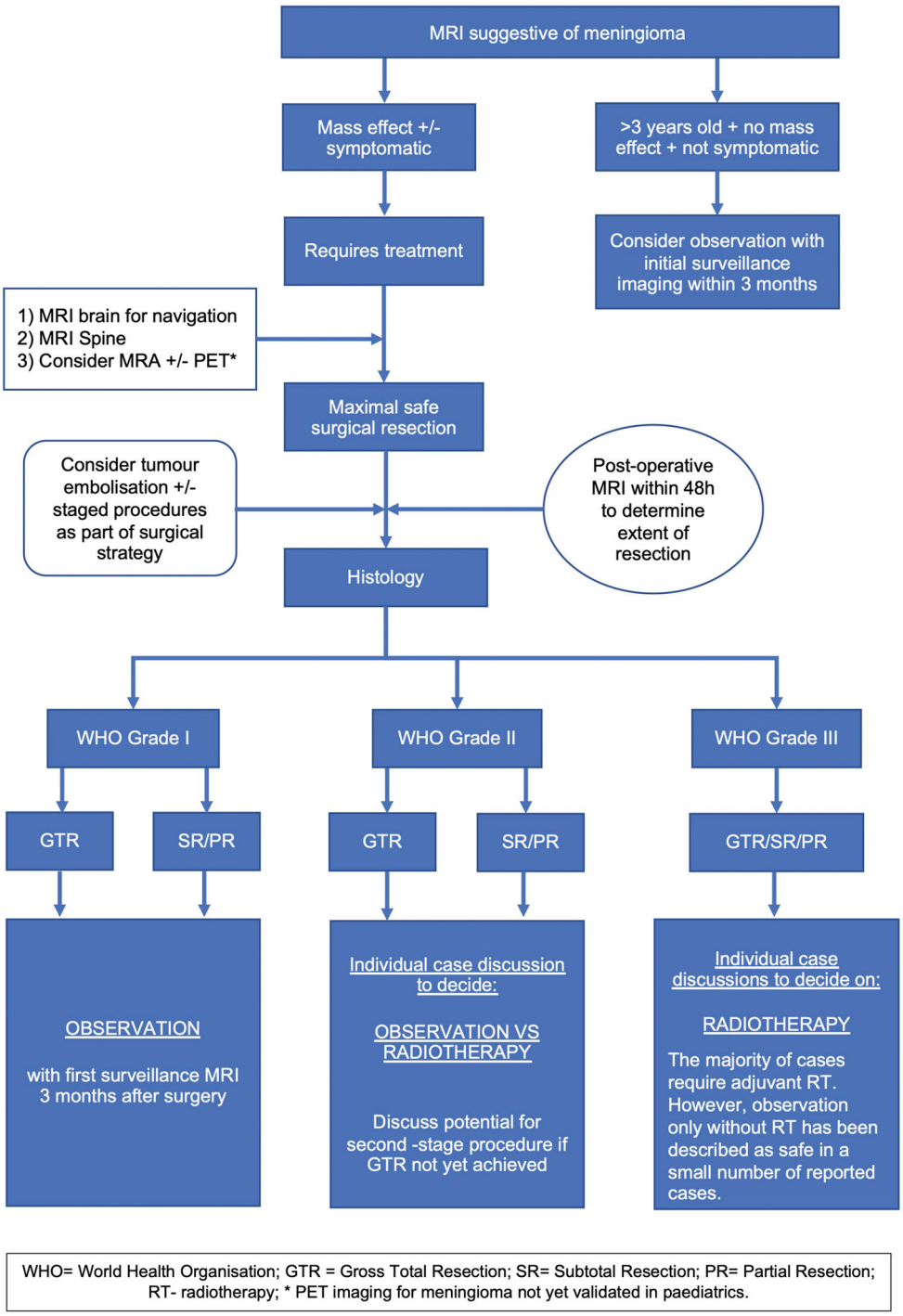

Figure 2. Management of meningioma in children and young adults.

3. *Consider* joint operating with sub-specialised adult neurosurgery colleague
4. *Consider* intra-operative imaging (iUS, iCT, iMRI) and intra-operative neurophysiology for tumours near cranial nerves or eloquent regions.
5. Post-operative imaging is required within 48-h

Radiotherapy

Radiotherapy remains the only available adjuvant therapy for meningiomas, and while consideration must be given to the risks of radiation given to children in the long term, it may be necessary for those tumours that cannot be completely removed.[60] However, the lack of high-quality data means that there is a marked institutional variation in meningioma management.

Literature review

Guidelines issued by the CCLG in 2007 suggested consideration of radiotherapy for anaplastic WHO Grade III meningiomas at the time of primary diagnosis, irrespective of surgical outcome.[2] In some centres, radiotherapy is limited to WHO Grade III

tumours in children above the age of 3 years and WHO Grade II in those above the age of 8 years.[51] A systematic review, published by Kaur *et al*., on the role of adjuvant radiotherapy showed significant improvement in local tumour control, especially after subtotal resection.[60] In total, 14 studies dating from 1994 to 2011 analysing atypical meningioma, malignant meningioma, or both were included in the review. The median 5-year PFS was 54.2% and OS 67.5% for atypical meningiomas and 48% and 55.6%, respectively, for malignant meningioma. The complication rates were 11.1% for atypical and 5.1% for malignant meningiomas. Incomplete resection and radiation dose of less than 50 Gy conferred significantly poorer 5-year PFS.[60] However, this was an adult cohort and therefore we cannot extrapolate this data directly to the paediatric setting. Additionally, a limitation of this review was that it was based mainly on retrospective, non-comparative studies that use heterogeneous grading systems.

In contrast, the meta-analysis by Kotecha *et al*. did not find PFS and OS benefits of upfront irradiation.[1] However, it is likely that this retrospective analysis suffers from major biases, and that the irradiated patients were a worse prognostic group for reasons that are not apparent from the included variables.[2]

Clearly, there is an urgent need for prospective clinical trials for meningiomas. The ROAM/EORTC-1308 trial, which opened in 2015, is the first multi-centre randomised controlled phase III trial in meningioma. It is designed to determine whether early adjuvant radiotherapy reduces the risk of tumour recurrence following complete surgical resection of atypical meningiomas. ROAM includes only patients aged 16 and above but will inform future neurosurgery and neuro-oncology practice for older teenagers and adults (NIHR Clinical Research Network (CRN)).[49]

Radiotherapy indications

Given the lack of high-quality data, guidelines[6,59] are based on expert opinion and the available evidence, particularly from adult practice. In adults, indications for radiotherapy are:

- WHO grade I tumours:
  - Inoperable Grade I lesions (e.g. base of skull, cavernous sinus and optic nerve)
  - Tumours with subtotal resection, either post-operatively or on radiological progression (consider also re-operation)
  - Recurrent tumours (consider also re-operation)
- WHO grade II tumours:
  - After complete resection, a significant recurrence risk (~40% or more) remains; the ROAM trial in adults is comparing adjuvant versus delayed radiotherapy. Children and TYAs would generally be observed after complete resection.
  - After subtotal resection, there is usually a strong case for proceeding to post-operative radiotherapy, but depending on histopathology, tumour location, previous behaviour and patient factors and choice, some tumours may be observed closely and treated on radiological progression (further surgery first should always be considered to maximise local control).
- WHO grade III meningioma:
  - Radiotherapy is indicated even after complete resection (resect completely if possible, even if second look surgery is needed).

In children and TYAs, radiotherapy would usually be withheld if possible, until no more surgical options are available, but this decision must be individualised.

The decision whether to use radiotherapy in childhood and adolescence should take into account patient's and tumour-specific factors including age, genetic predisposition, tumour location and further operability, neurological status, tumour recurrences and tumour grade associated risk of recurrence or aggressive behaviour. Radiotherapy in children can be associated with significant morbidity, including effects on neurocognitive function, which may lead to lifelong impairment.

Focal radiotherapy may be considered in benign, WHO Grade I and atypical WHO Grade II meningiomas after multiple relapses not amenable to further surgical interventions or evidence of clinically relevant progression after incomplete resection, particularly if the tumour threatens to compromise vital functions, such as vision.

Anaplastic, grade III meningiomas are highly likely to recur regardless of resection status, albeit less so after GTR. Therefore, adjuvant radiotherapy should be considered at the time of primary diagnosis regardless of surgical outcome.

Fractionated radiotherapy and stereotactic radiosurgery

Preference should be given to deliver conventionally fractionated radiotherapy. Only exceptional cases, in which the tumour or tumour bed is small enough (less than approximately 2.5–3 cm) and appropriately located, are amenable to SRS. Where SRS is being considered, it is essential that the case is discussed by the multidisciplinary team including an experienced clinical neuro-oncologist familiar with both SRS and fractionated radiotherapy modalities. If SRS is indicated, the child must be referred to one of the two centres which are nationally commissioned for paediatric SRS, namely Leeds or University College Hospital, London.

In the UK, WHO grade I and II meningiomas are on the standard indication list for NHS funded proton therapy for children and young adults up to around 25 years of age. In general, all children and young adults for whom radiotherapy is planned should be referred for consideration of proton therapy which has the capability to reduce exposure of non-target tissues to radiotherapy and reduce late effects of treatment. It will therefore become relatively uncommon for such patients to be irradiated in their local centre with photons, with the exception at least at present of WHO grade III tumours.

Dose prescription

Doses of 50–55 Gy in conventional fractionation are generally recommended for WHO grade I and II tumours. Doses up to 60 Gy should be considered for WHO III meningiomas, and some WHO grade II tumours (especially with residual gross tumour), where it is safe to do so. This guideline recommends that in children and young adults, such higher doses should preferably be given in 1.8 Gy fractions (i.e. 59.4 Gy in 33 fractions, rather than 60 Gy in 30 fractions as is used in older adults). The following are suggested doses, representing a risk adapted approach:

- Skull base/near critical OARs, or optic nerve/orbital meningiomas with residual vision, or large volume:
  - WHO grade I: 50 Gy in 30 fractions (or 50.4 Gy in 28 fractions)
  - WHO grade II: 54 Gy in 30 fractions

- WHO grade III, completely resected: 54 Gy in 30 fractions,
- WHO grade III, subtotally resected: 54–59.4 Gy in 1.8 Gy fractions (depending on tumour behaviour, age, PTV volume, residual tumour volume, ability to treat GTV to high dose while respecting OAR tolerances, etc.)

- Remote from critical OARs, small to moderate volume:
  - WHO grade I: 54 Gy in 30 fractions
  - WHO grade II age <3 years: 54 Gy in 30 fractions
  - WHO grade II age ≥3 years: 54 Gy or 59.4 Gy in 1.8 Gy fractions (depending on high risk features, age, PTV volume, residual tumour volume, location, etc.)
  - WHO grade III, completely resected, age <3 years: 54 Gy in 30 fractions
  - WHO grade III, completely resected, age ≥3 years: 54 - 59.4 Gy in 1.8 Gy fractions (depending on tumour behaviour, age, PTV volume, residual tumour volume)
  - WHO grade III, subtotally resected: 54 – 59.8 Gy in 1.8 Gy fractions (depending on tumour behaviour, age, PTV volume, residual tumour volume)

Chemotherapy and pharmacotherapy

Medical therapy has been employed for meningiomas which are refractory to surgery or radiotherapy. Chemotherapy, hormonal therapy and targeted therapies have been explored. Little data are available regarding the use of systemic chemotherapy in the paediatric setting. While there have been some reports of modest benefit from chemotherapy, and more recently from interferon alpha-2β, therapeutic options remain limited.[61]

Chemotherapy

Previous studies have shown little benefit in the treatment of meningiomas with a single agent or combination of chemotherapy.[62–65] In 2010 Collins *et al.* reported a radiological response of incidental meningioma in an adult patient treated, for non-small cell lung cancer, with cisplatin and gemcitabine combined with CP-751, 871, an IGF-1R inhibitor.[66] The report showed a reduction in meningioma size while on therapy and an increase in size when therapy was discontinued. In adults, hydroxyurea, a ribonucleotide reductase inhibitor, offered initial promise in a small case series, in which a positive radiologic response was achieved in three of four patients with recurrent meningioma. However, subsequent studies of hydroxyurea showed that patients usually display a stable response, followed by progressive disease. The median PFS on hydroxyurea may range from 2 to 77 months.[67–69] In 2016 Lucchesi *et al.* reported on a 2-year-old boy diagnosed with a relapsed malignant meningioma after initial surgery. In view of the rapid progression, young age and the lack of effective therapeutic alternatives, he was successfully treated with multimodal therapy, including chemotherapy according to a protocol for soft tissue sarcomas (EpSSG NRSSTS 2005).[70]

Interferon

In 2008 Chamberlain *et al.* conducted a prospective phase II study evaluating the efficacy of interferon-alpha (aIFN) in 35 patients with recurrent meningiomas, who failed treatment with surgery, radiotherapy, and chemotherapy.[71] None achieved complete or partial response to aIFN, however, meaningful palliation was achieved with a progression-free survival (PFS) of 54% at 6 months. Additionally, stabilisation of a proportion of progressive meningiomas with aIFN in adults was reported in a small single-centre experience.[61]

Hormone therapy

Meningiomas have been associated with a dysregulation of number of hormonal axes. Female preponderance among post-pubertal patients, tumour growth during pregnancy, and the risk reduction seen after menopause or oophorectomy indicate the impact of hormone exposure in tumour development.

Following the description of progesterone receptors in meningiomas, an anti-progesterone agent, Mifepristone, was evaluated in adults showing a modest response in a minority of patients in several single-arm trials.[72,73] In contrast, Tamoxifen, an anti-estrogen, did not demonstrate efficacy in two phase II trials.[74,75] Finally, a double-blind placebo-controlled phase III randomized trial showed no impact of Mifepristone on OS and PFS in progressive or recurrent meningioma.[76]

Meningiomas also demonstrate activation of the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis. The somatostatin analogue, Octreotide, appeared to have some efficacy in maintaining stable disease in three adults with refractory meningioma.[77] In addition, a retrospective analysis of eight Octreotide-treated patients with progressive WHO grade I meningiomas demonstrated 100% PFS at 48 months.[78] However, these results were not confirmed in phase II trials that recruited higher proportions of patients with grade II–III meningiomas demonstrating a median PFS ranging from 4 to 5 months.[79,80] Pasireotide LAR, along-acting somatostatin analog, has shown limited activity in recurrent meningiomas.[81]

Therapy with radiolabelled $DOTA^{0}$-Tyr^{3}-Octreotide (DOTATOC) was tested in a phase II trial and demonstrated stable disease in most cases of progressive meningioma with a mean OS of 8.6 years. However, the tumour grade distribution was not reported in this study.[82]

Non-hormonal targeted therapies

Expanding knowledge of meningioma biology will hopefully stimulate the development of novel therapeutics. All available data are based on adult experience so far.

In 2017 Gerlstein *et al.* described a patient whose intracranial meningioma showed a 24% radiological volume reduction after treatment with Nivolumab, a monoclonal antibody targeting PD-1, for a concomitant advanced lung cancer.[83] Trials of Nivolumab (NCT03173950, http://www.clinicaltrials.gov) and another PD-1 inhibitor, Pembrolizumab (NCT03279692, http://www.clinicaltrials.gov), for meningioma are currently recruiting.

Meningiomas are often vascularized tumours and might therefore be amenable to antiangiogenic therapy. In particular, malignant meningiomas produce high levels of vascular endothelial growth factor (VEGF).[84] In 2010 Puchner *et al.* described the first patient with a substantial regression of an anaplastic meningioma on therapy with the VEGF antibody, Bevacizumab.[84] In two recent retrospective case series, Bevacizumab showed efficacy in maintaining stable disease in refractory meningiomas.[85,86] Lou *et al.* reported a PFS of 85.7% at 6 months and 50% at 17.9 months among 14 patients with WHO grade I–III meningiomas.[85]

Key recommendations for chemotherapy and pharmacotherapy

Data supporting the use of pharmacotherapy in meningiomas are weak, but the strength of the evidence might soon improve with the identification of targetable mutations. A molecular classification of meningiomas is expected to be developed in the near future, and this classification has the potential to direct individualised meningioma-specific therapy.

Currently, no specific recommendations can be made for chemotherapy in paediatric or adult meningiomas. Overall, pharmacotherapy could be considered in the setting of relapsed or refractory mengioma where surgical and radiotherapy options have been exploited or are not viable options.

Supportive care and genetic evaluation

All patients should be referred to the geneticists for investigations of genetic diseases including NF-2. Laboratory diagnosis of NF-2 relies on the detection of DNA mutations in the NF-2 gene on chromosome 22 leading to an abnormal merlin protein. Furthermore, linkage studies from at least two affected family members are helpful.[87] The presence of Gorlin syndrome should also be excluded if there is clinical suspicion. See section on inherited conditions for more details.

Prognosis

Evidence regarding the prognosis of paediatric meningiomas is conflicting. Despite multiple reports of children harbouring 'more aggressive' subtypes of meningioma, there overall prognosis is good. This fact warrants careful scrutiny of the treatment modalities employed, on a case-by-case basis, in order to maximise cure while minimising disease and treatment related morbidity.

Overall survival for meningioma in childhood and adolescence is 90% at 5 years, 81% at 10 years and 73% at 15 years.[1] Patients aged 3–12 years have better OS than those younger than 3 years or those age 12 or above.[1] These data are however based on the largest meta-analysis and comprises children and young adults who have had surgery. These figures are therefore biased towards those tumours which required intervention and were operable and have not included the observation only cases, or radiotherapy alone cases, which are bound to exist.

The extent of initial surgical resection is the strongest independent prognostic factor for meningioma in childhood and adolescence. Those patients who undergo GTR have better PFS and OS than patients who have subtotal resections.[1] For recurrent benign meningioma in children, re-operation increases survival time.[60]

Presence of NF2 is associated with worse PFS and OS. This may be due to the fact that these patients are at risk of developing multiple benign tumours and thus may require multiple interventions at various time points which is balanced according to the natural history of the disease as opposed to upfront intervention.

Children and adolescents with meningioma have better survival outcomes than do adults with meningioma, when comparing PFS and OS according to WHO histological grade.[1,88,89] (Table 2).

Follow-up and surveillance

Data for the optimal follow-up schedule for meningiomas are weak. Therefore, the following recommendations are based more on expert consensus opinion than evidence (Figure 3).

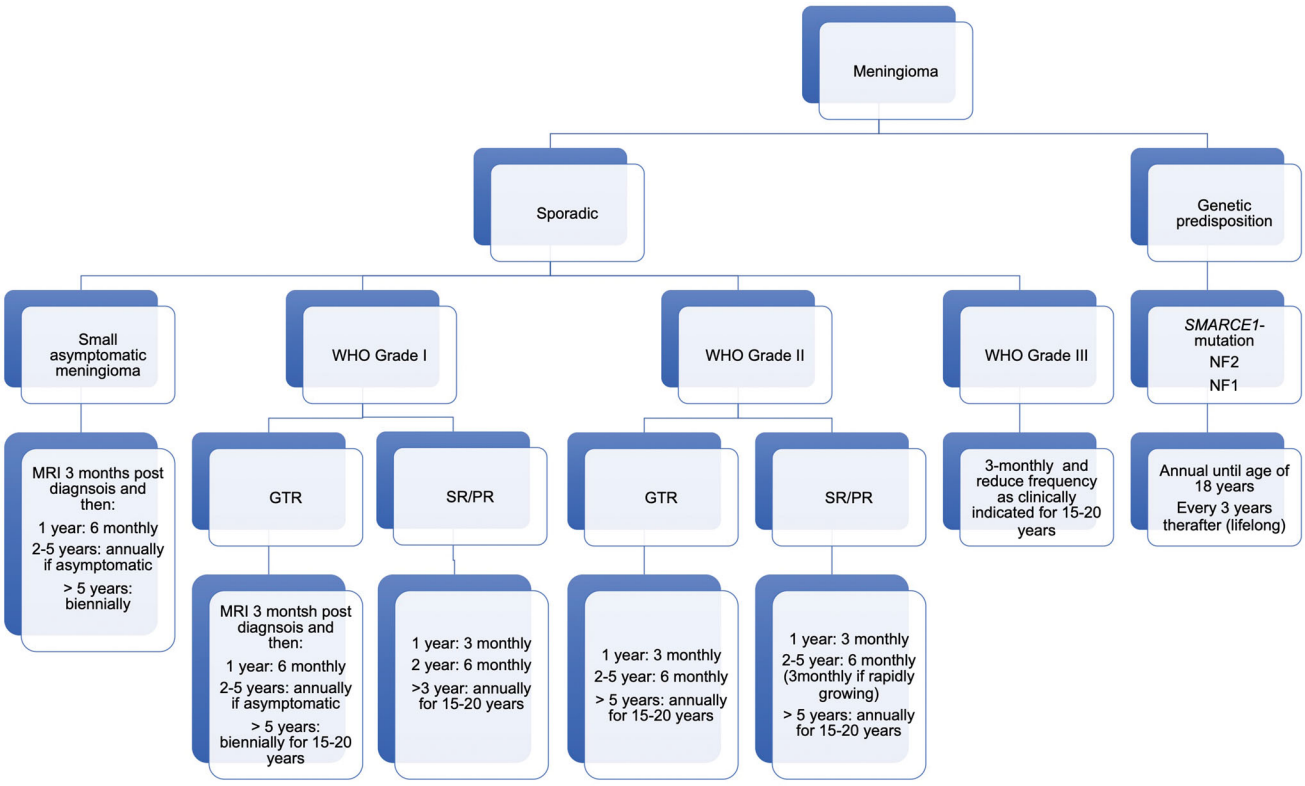

Figure 3. Follow-up and surveillance.[7,23] Modified based on guideline development team opinion. GTR: Gross total resection; SR: subtotal resection; PR: partial resection.

Children and adolescents should be followed-up clinically by a paediatric neurosurgeon or paediatric, clinical or medical, oncologist. In some cases, they should be accompanied by additional specialists, e.g. an ophthalmologist when cranial nerve function is threatened. Follow-up intervals may vary substantially, depending not only on resection status, tumour grade, size, and location of the tumour, but also on age and the patient's general and neurological status.

The dynamics of small, asymptomatic meningiomas should be assessed with MRI with contrast 3 months after initial diagnosis, and then annually as long as the patient remains asymptomatic. After 5 years, this interval can be doubled.[7]

Monitoring after initial treatment depends on the extent of resection and grading of the tumour. All patients require an MRI within 48 h of resection to document resection status. As the risk of recurrence is high in patients with grade III meningioma, neuro-imaging should be considered every 3 months for at least the first 2 years post-diagnosis.

Long-term follow-up

Follow-up is required to prevent future potentially irreversible neurological sequelae and for optimal timing of any potential intervention. The duration of follow-up is unclear, however neuro-imaging surveillance is recommended for 15–20 years post-diagnosis (especially for patients with germline mutations) as late recurrences do occur. Life-long surveillance should be initiated in NF2 and considered in patients with other genetic predispositions.

Patients presenting with meningioma in childhood and adolescence should routinely be assessed for NF1 and NF2, and regularly monitored for the future development of features of these conditions if not present at diagnosis.[1] Referral to a geneticist is recommended to facilitate screening for neurofibromatosis and associated rare genetic conditions.[1] Patients with NF2 should be considered a special risk category, necessitating close life-long follow-up.

Unusual metastatic locations can occur at relapse, particularly for grade II and III tumours. Clinicians should be mindful of the possibility of extra-cranial metastases in aggressive tumours, though routine screening for this is not recommended.

Conclusion

The levels of evidence for the diagnosis, treatment and surveillance recommendations for children and adolescents with meningiomas are low. Translating and adapting adult treatment recommendations into paediatric practice can be challenging and might inadvertently lead to inappropriate management. The medical community needs to develop research studies for this rare disease group, including investigation into the biology of diseases and treatment options including molecularly targeted approaches.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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