Peninsula and Somerset, Wiltshire, Avon and Gloucestershire (SWAG) Cancer Services

Children's Cancer Network Group

Clinical Guidelines

April 2019

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VERSION CONTROL

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Paediatric Oncology Clinical Guidelines Contents

1. Introduction

The following guidelines pertain to the management of paediatric malignancies for the Peninsula and SWAG Children's Cancer Network (CCN).

The CCN refers to the Children's Cancer and Leukaemia Group Guidelines, the National Institute for Health and Clinical Excellence Guidelines (NICE) and other relevant guidelines and clinical trial protocols, as detailed in the tables below.

Primary care clinicians should refer to the NICE guidelines *Suspected Cancer: recognition and management of suspected cancer in children, young people and adults* (2015) for information on the signs and symptoms that are relevant when considering referrals to the Paediatric Oncology Services.

The guidelines should be reviewed alongside the CCN Constitution, which provides an overview of how the CCN operates, outlining the general working processes, patient referral pathways and the guidelines to which the CCN adheres.

The CCN is committed to offering all eligible patients entry into clinical trials where available.

2. Clinical Guidelines

2.1 Leukaemia

Table 1.

	Trial/guideline	**Trial Yes/No**	**Location**
Acute Lymphoblastic Leukaemia (ALL)			
De novo age 1-25	UKALL2011	Y (closed to recruitment)	Research portal

	UK ALL guidelines 2019	N	Research portal
Refractory	UK ALL guidelines 2019	N	Research portal
De novo Ph+	UK Philadelphia positive ALL guidelines	N	Research portal
De novo Infant	UK Guidelines (Interfant 2006 standard treatment arms)	N	Research portal
Relapse	UK relapsed ALL guidelines	N	Research portal
	Inotuzumab phase 2 (Q2 2018)	Y	-
	Daratumomab (Q2 2018)	Y	-
Relapse/refractory	CARPALL/Amelia/UCarT Kymriah (NHS funded CarT)	Y N	Great Ormond Street Hospital GOSH/Manchester/Newcastle
Acute Myeloid Leukaemia (AML)			
De novo	MyeChild	Y	Research portal
Relapse	Fla-Ida or similar, proceed to Stem cell transplant after 1-2 cycles	N	Chemocare
DS-AML	ML-DS 07	N	Research portal
Juvenile myelomonocytic leukaemia (JMML)			
De novo/relapse	EWOG/MDS	N	Research portal
Chronic Myeloid Leukaemia (CML)			
De novo/relapse	UK guidelines	N	Research portal
	Nilotinib phase 2 (closed to recruitment) Bosutinib phase 2 (RMH, Q2 2019)	Y	Research portal

2.2 TUMOURS MANAGED BY THE SOLID TUMOUR MDT

All malignant and benign solid tumours must be discussed at the Solid Tumour MDT. Where no oncological management is required in a benign tumour eg ovarian teratoma, this is clearly stated in the MDT outcome and follow-up recommendation is made by the MDT with regard to clinical follow-up and any monitoring that might be required. Where a malignant diagnosis is confirmed the MDT will make a recommendation based on current recommendations. Where a clinical trial is available the MDT will ensure that all patients who are eligible are offered recruitment onto a clinical trial and where this is declined by the family the reasons are recorded on the screening log and in the patient record. Where no clinical trial is available patients are treated according to current nationally recommended treatment guidelines which may be found on the CCLG website and on the NIHR HUB (available to the wider network). Where there is a rare diagnosis that does not have a guideline available then the MDT will recommend appropriate opinions eg adult-type cancer will be referred to the relevant site specific MDT for further advice, patient is referred to a National Advisory Panel or recognised appropriate second opinions are sought. In some instances there are MDT agreed local guidelines and these are ratified by the MDT and available to the network as required.

At relapse we strongly encourage all patient to have a repeat biopsy where clinically feasible and after discussion with the family. Where an early phase trial is the recommended strategy in relapse/refractory setting, re-biopsy may be a requirement. However, we are imminently due to open SMPaed (Stratified Medicine Paediatrics: Genomic Characterisation of Relapsed Paediatric Cancers for Diagnostics and Stratified Therapy) which is a very is a molecular profiling platform that will generate genomic, transcriptomic, and epigenetic (methylation) data in children, teenagers and young adults with relapsed/refractory solid cancers (including brain cancers) with four principle aims:

1. to detect and clinically report the presence of genomic alterations in patients who require molecular confirmation of targets for registration onto precision medicine clinical trials.

2. to increase the accuracy of tumour diagnosis through the inclusion of genomic data.

3. to contribute to the assembly of a comprehensive evidence-dataset on the prevalence of genomic alterations and a means to prioritise their importance.

4. to identify genomic alterations that increase in frequency between time of diagnosis and relapse.

All children, teenagers and young adults with relapsed/refract tory solid paediatric tumours (including brain tumours and lymphoma) will be eligible to take part but the patient must have had a recent biopsy/operation to obtain tumour tissue on which molecular tests can be performed.

Table 2 - Lymphoma and Recticulo-endothelial malignancy

Diagnosis	Trial/guideline	Trial Y/N	Location
B-cell Non-Hodgkin Lymphoma (BNHL) High risk / BNHL – not meeting high risk criteria / Primary Mediastinal Large B-cell Lymphoma (PMBCL)	According to Inter B-NHL Ritux 2010 Guidelines for the management of Burkitt/Burkitt-like and B large cell NHL (2003) DA-EPOCH-R (According to Inter B-NHL Ritux 2010).	Closed trial	Research portal
Anaplastic Large Cell Lymphoma	Dr D Williams Letter of closure and interim guidelines for treatment of ALCL Version 3.0 02.08.2010 (Confirmed still valid, Oct 2014).	N	Research portal
Lymphocyte Predominant Hodgkin Lymphoma (LPHL)	EuroNET PHL- LP1	Closed trial	Bristol only
Relapsed Lymphocyte Predominant Hodgkin Lymphoma (LPHL)	R'CHOP	N	Research portal
Classical Hodgkin Lymphoma + Relapse	CCLG Hodgkin Lymphoma, July 2013	N	Research portal
Recticulo-endothelial malignancy	Not applicable		

Table 3 - Sympathetic nervous system tumours

Diagnosis	Trial/guideline	Trial Y/N	Location
Treatment and management of newly diagnosed patients with high-risk neuroblastoma	**Treatment and management of patients with high-risk NBL - CCLG statement**	Closed trial	Research portal
Options for the	**Relapsed/progressive**	N	Research portal

Treatment of Patients with Relapsed/Progressive High-Risk Neuroblastoma - MARCH 2015	**high risk neuroblastoma**		
Treatment of Patients with Low/Intermediate Risk Neuroblastoma - JANUARY 2015	**LINES**	N	Research portal
Immunotherapy and High Risk Neuroblastoma	**Immunotherapy and High Risk Neuroblastoma**	N	Research portal

Table 4 - Retinoblastoma

New cases of Retinoblastoma are referred to quaternary services, Birmingham Royal Children's Hospital

Diagnosis	Trial/guideline	Trial Y/N	Location
Retinoblastoma - 1st line treatment	**Retinoblastoma Guideline - UHB**	N	Research portal
Unilateral Retinoblastoma following primary enucleation	**Advanced Retinoblastoma UHB Guideline**	N	Research portal

Table 5 - Renal tumours

Diagnosis	Trial/guideline	Trial Y/N	Location
WILMS tumour	CCLG Clinical Management Guideline; **Wilms Tumour Guideline**	N	Research portal
Relapsed Wilms tumour	Currently no guideline available – discuss with consultant	N	N/A
Adrenocortical tumours (ACT) and Adrenocortical carcinoma (ACC)	Version 2.0, June 2007	N	Research portal

Table 6 - Hepatic tumours

New cases of primary hepatic tumours are referred for discussion to the NSCG designated liver transplant centre, Birmingham Children's Hospital NHS Foundation Trust

Diagnosis	Trial/guideline	Trial Y/N	Location
Liver Tumours	Paediatric Hepatic International Tumour Trial (PHiTT) open clinical trial for all liver tumours.	Y	Research portal

Table 7 - Malignant Bone and Soft Tissue Sarcomas

New cases of primary bone tumours are referred for discussion to the NSCG designated Bone tumour service at Royal orthopaedic Hospital, Birmingham for biopsy and surgical management

Diagnosis	Trial/guideline	Trial Y/N	Location
Osteosarcoma	**Osteosarcoma chemotherapy**	Closed trial	Research portal
Mifamurtide	**Mifamurtide NICE guidance**	N	Research portal
Relapsed Sarcoma (bone and soft tissue) (LOCAL GUIDELINE)	**Gemcitabine and Docetaxol - Paediatric oncology solid tumour MDT January 2016 Version 1.0**	N	Bristol only
Ewing sarcoma	**OPEN CLINICAL TRIAL Euro-Ewing 2012 (phase 3)**	Y	Research portal
Relapsed and refractory Ewing sarcoma	**OPEN CLINICAL TRIAL (phase 2) rEECur**	Y	Research portal
Rhabdomyosarcoma	**RMS Guidelines March 2019**	Closed trial	Research portal
Relapsed Rhabdomyosarcoma	**Relapsed RMS – (phase 2) VIT**	N	Research portal
Non-rhabdomyosarcoma soft tissue sarcoma NRSTS) treatment recommendations January 2017	**NRSTS guideline**	Closed trial	Research portal

Table 8 - Any other malignancies

Diagnosis	Trial/guideline	Trial Y/N	Location
Langerhans Cell Histiocytosis (LCH)	**OPEN CLINIC TRIAL - LCH IV**	Y	Research portal
Extracranial Germ Cell Tumours	**Extracranial Germ Cell Tumour Guidelines**	N	Research portal
Paediatric Endocrine tumours	**Version 2.0 June 2007 above (ACC & ACT) and Oct 2005**	N	Research portal
Melanoma	**All new cases of melanoma are routinely discussed with the Specialist Skin Cancer MDT**	N	Research portal
Melanotic Neuroectodermal Tumour of Infancy (MNTI)	**Version 1.0, Aug 2004- rebranded with no other change made Sep 2011**	N	Research portal

Nasopharyngeal carcinoma	**Guidelines for the investigation and management of nasopharyngeal carcinoma Version 4.0, October 2013**	N	Research portal

2.3 CNS Tumours

The Bristol Neuro-Oncology MDT strongly recommends that all brain tumours are sent for molecular profiling in Newcastle upon Tyne NHS Foundation Trust (embryonal tumour) and Great Ormond Street Hospital (GOSH) (non-embryonal tumour). Referral of patient samples for molecular profiling requires these patients to be consented routinely for tissue banking.

Currently few guidelines are available on the CCLG website for brain and spinal tumours. Commonly used guidelines are available on The Hub. The Paediatric Oncology pharmacists hold any guidelines that are only available as a hard copy.

Initial Management:

1. The initial priority is to stabilize the patient, and to deal with acute neurological complications, principally raised intra-cranial pressure, spinal cord compression or epileptic seizures. Initial management of the majority of patients with a CNS tumour will be surgical – biopsy or resection. Rarely, surgery may not be indicated and initial management shouldy be medicalThese exceptions are:Anterior optic pathway tumours, where surgical biopsy is likely to lead to significant morbidity. These are usually diagnosed radiologically to be low grade astrocytomas. Occasionally, a hamartoma may present in a similar manner. The purpose of surgical resection would be only to reduce compression on adjacent structures. More radical resection should only be considered following formal MDT review.

2. Patients with a CNS tumour and proven elevated alpha fetoprotein (AFP) or Human Chorionic Gonadotrophin (HCG) suggestive of a secretory germ cell tumour. Biopsy is NOT required and these patients are at risk from post-biopsy haemorrhage. Surgical management is limited to relief of obstructive hydrocephalus and collection of CSF for cytology and measurement of AFP, HCG and Placental Alkaline Phosphatase.

3. Patients with radiologically diagnosed diffuse intrinsic pontine astrocytoma/glioma (DIPA or DIPG). These patients do not normally undergo surgical intervention, except to relieve obstructive hydrocephalus. The large majority (90-95%) of these tumours are high grade astrocytomas, which cannot be surgically removed. Biopsy is not generally recommended outside of a clinical trial, as treatment for both high and low grade brainstem tumour is with radiotherapy. For further information see below.

Surgical Management

The purpose of a surgical procedure is

1) to relieve raised intracranial pressure
2) to obtain pathological tissue to allow an accurate diagnosis,
3) where possible, to remove the tumour.

The strong presumption is that an attempt at complete surgical resection should be made, unless this would be associated with major disability. Resection may be at the time of the initial operation, or following confirmation of tumour histology. A second, or third attempt to achieve complete surgical clearance may be made depending on histological diagnosis, but additional surgeries (apart from those to manage an acute neurosurgical emergency) will be discussed by the Neuro-oncology MDT beforehand.

Pathological specimens

Intraoperative diagnostic assessment is helpful in planning the extent of surgical resection and may aid in identifying the location of the margins of the tumour. This is achieved through the provision of smears or fresh tissue to the Department of Neuropathology (NBT), for cytological assessment of the smears or for preparation of smears or frozen sections from the fresh tissue. Except when the biopsy specimens are very small (e.g. in the case of needle biopsies), some fresh tumour tissue is also frozen for storage at -80°C for later genetic analysis, as required. In most cases, the greater part of the resected tissue is fixed in buffered 10% formalin for assessment of paraffin sections by neuropathologists. The processing and assessment of the tissue is undertaken in a Neuropathology Department with CPA accreditation, by specialist neuropathologists who perform to a satisfactory standard in the National Neuropathology EQA Scheme and fulfil the Royal College of Pathologists requirements for Continuing Professional Development. Over 80% of reports are issued within 4 days (including weekends and public holidays) of receipt of the specimen. Molecular genetic analysis of tumour tissue (e.g. assessment of chromosome 1p/19q deletion, MGMT promoter methylation, peripheral PNET translocations, etc) is performed by the Molecular Genetics Unit at Southmead Hospital in collaboration with the Department of Neuropathology. Where relevant (eg PNET-MB) real time assessment of biological factors can be performed and tissue is also with consent sent to CCLG tumour bank, referred for 100,000 genome project or Meteor (molecular characterization study).

Table 9

Disease	Guideline and version	Molecular analysis Local (Send away)	Surgical points	Radiotherapy points
Ependymoma				
Ependymoma accounts for 6-12 % of all brain tumours in the paediatric population. Nearly 50% of patients are diagnosed under the age of 5 years (Nazar et al 1990, Grill et al 2001). Ependymomas may arise in relation to any part of the ventricular system: Posterior fossa-50-60% Supratentorial -30-40% Intraspinal - 0-10%. The mainstay of treatment is surgical resection	SIOP Ependymoma II trial is now open. This will cover all subgroups of tumour (localised, metastatic, < 12 months and > 12 months) with both observational and randomised arms and is the recommended strategy of the MDT. Relapsed patients in the first instance should be offered more surgery where possible to achieve CR and second attempt at radiotherapy. There is an arm to the Ependymoma study for infants, children not entered into the study under 12 months should be treated with chemotherapy alone		The MDT acknowledge the importance of second look surgery with an aim to surgical CR before adjuvant therapy, this is discussed in SIOP Ependymoma II with panel review for cases incompletely resected cases. All attempts to consider further surgery should be considered before moving on to further treatment. Imaging-confirmed complete surgical resection leads to improved event free and overall survival. Conversely incomplete resection increases the likelihood of recurrence	For families not consenting to trial entry MDT recommend: Localised disease PTV= residual tumour and tumour bed plus an anatomically confined 0.5-1cm margin for subclinical spread and 0.5cm margin for setup error. Dose= 59.4Gy in 33# over 6 1⁄2 weeks unless <18 months old with gross total resection when dose is 54Gy in 30# in 6 weeks OAR= spinal cord and optic chiasm most commonly. Dose limited to 100% of dose of first 30# then shielded

	according to the 'Baby Brain' protocol of alternating VCR / Carboplatin; VCR / MTX; VCR / Cyclophosphamide and Cisplatin		(Perilongo et al 1997, Horn et al 1999, Timmermann et al 2000). Second look surgery in order to achieve surgical clearance is associated with improved prognosis (Foreman et al 1996).	thereafter to <70% of dose from remaining 3# If metastatic and ≥ 3year old: Craniospinal radiotherapy 39.6Gy in 22# in 4 1⁄2 weeks then boost primary and metastatic sites to total dose of 54-59.4Gy Proton therapy where there would be a positive impact on late effects Metastatic disease – craniospinal radiotherapy 39.6Gy with boost to primary and metastatic sites to 59.4Gy where safe to do so
Recurrent ependymoma The 5-year event-free survival of ependymoma in most series is less than 50%. Most recurrences occur within the first two years following initial	Chemotherapy may have value in recurrent ependymoma. Oral etoposide has been reported to have a high rate of stabilization and response (Sangra, M et al, 2009, Chamberlain 2002).		Re-operation is the mainstay of treatment. The role of surgery at the time of relapse justifies an intensive surveillance imaging during follow-up.	Data from the US and Canada has indicated a significant benefit from re-irradiation. Whilst this is not conventional, considerably exceeding what is normally regarded as maximum tolerated doses, survival

resection. Local relapse is seen in 90% of patients. Neuraxis dissemination is less common and often a late event, and isolated neuraxis failure is rare.				seems to be good, with good outcomes in terms of quality of life.
Low Grade Glioma				
This includes patients with Optic pathway glioma (OPG) and hypothalamic glioma. The MDT acknowledge the importance of identifying patients with NF1. These account for the majority of paediatric tumours and most are low grade.	Currently no clinical trial exists for primrary Low Grade Glioma, except for selected NF patients - VINILO For grade 1 glioma and 2 with complete resection the MDT recommends a watch and wait strategy. For grade 1 incompletely resected tumours the MDT recommends a watch and wait strategy with further surgery as first treatment modality where possible at progression, if not feasible chemotherapy or radiotherapy	KIAA1549 –BRAF fusion (pilocytic astrocytoma) BRAFV600E mutation IDH mutations Identify if NF1	Biopsy is not required for OPG if radiological appearance and history typical. Complete resection is suggested for all sites where this would be feasible without significant neurological deficit. Biopsy is required at some stage in the course of the illness for non-NF 1 patients if considering entry into VINILO, it does not have to be performed at relapse if previously performed unless clinical and radiological suspicion	In over 8, without NF it may be appropriate to use radiotherapy in first or second line or at time of further progression and the role of radiotherapy for these tumours should be discussed in the neuro-oncology MDT.

	are options depending on age of child and presence of NF1 For Grade 2 tumours that are incompletely resected the MDT may recommend watch and wait / chemotherapy or radiotherapy depending on site and size of tumour. For central neurocytoma PCV chemotherapy (Procarbazine, CCNU and Vincristine) is preferred option For other low grade glioma in all sites where chemotherapy is recommended first line treatment would be according to the closed study UKCCSG LGG2 CNS 2004 03 with Vincristine and Carboplatin. Patients with NF1 receive only one year of treatment. In case of Carboplatin allergy (approx.. 30%) the MDT would		of a transformed tumour. In NF1 patients with OPG biopsy is recommended for entry into VINILO but not mandated.	

	support both the use of Cisplatin and Cyclophosphamide as per LGG2 but also Vincristine and Actinomycin as per Packer et al Annals of Neurology.1988: 23: 79 – 85 especially if concerns about in patient admission or hearing loss (especially relevant for those with poor vision secondary to the glioma). Relapse /progression can be treated either with a re-challenge of previous treatment (VCR and Carboplatin or VCR and Act D) or single agent Vinblastine. VINILO – phase II study of vinblastine vs vinblastine and nilotininb is recommended for the following groups (assuming no trial exclusion criteria) Refactory and recurrent low grade glioma after at least one first line therapy with pathological documentation in non-NF			

	patients. Refactory or recurrent low grade glioma after at least one first line therapy in NF patients. Low grade glioma at diagnosis in NF1 patients when the use of chemotherapy is considered for the treatment in case of threat to vision or unequivocal radiological tumor progression. Pathological documentation is advised but not mandatory. VINILO would therefore be the MDT preferred option for these groups. Third line treatment it may be possible to obtain funding for Bevacizumab. Progression can be treated with VCR and Act D, Vinblastine or Bevazicumab or TPCV. (Thioguanine, Procarbazine, CCNU [lomustine], and Vincristine)			

	Heath, J. A., C. D. Turner, et al. (2003). Pediatr Hematol Oncol 20(7): 497-504. Prados, M. D., M. S. Edwards, et al. (1997). J Neurooncol 32(3): 235-41. Hypothalamic glioma can be a particular problem with cystic formation and for a number of patients many attempts at treatment may be used over the years. For these patients individualised plans should be agreed by MDT to include paediatric oncologist, clinical oncologist and neurosurgeon.			
Mixed glial tumours				
Almost five percent of glial tumours are composed of a mixed population of glial cells, most often astrocytes-oligodendroglia or astrocytes-ependymal	Treatment should be individualised within the neuro-oncology MDT.			

cells. The management of these tumours will require detailed discussion, and usually, treatment will depend on the most malignant component.				
Medulloblastoma				
Standard risk Medulloblastoma - > 3yrs, non-metastatic Note: Metastatic disease must be excluded for all patients. Spinal imaging, preferably pre-operative MRI with contrast must be performed in all patients. Post-operative imaging (contrast enhanced MRI) must be performed in all patients within 48 hours of operation to exclude	PNET V For ineligible patients CCLG guidelines for standard risk MB – molecular analysis vital In the context of severe posterior fossa syndrome where early radiotherapy cannot be delivered the MDT recommend following the regime used in the US trial POG9031	P 53 B catenin (WNT pathway) Myc N Myc C Monosomy 6	At the outset there should be an attempt at maximal surgical resection for all tumours. In the event of a complete resection not being feasible the MDT should consider all available biological stratification before planning further surgery since extent of resection is not prognostic for WNT pathway tumours or group 3 and 4 tumours but practically this information is not currently available in the UK in a timely manner	

significant residual disease. CSF cytology is required for all patients. This should be by Lumbar Puncture, and should <u>not</u> be performed before 14 days of the last surgical resection.			to plan surgery. Residual disease at the primary site. CCG921 demonstrated that a residual of >1.5 cm^3 was associated with a worse prognosis. Although PNET 4 chemotherapy differs, the most recent analysis of this trial noted 30 patients (9.7%) out of 308 trial patients with residual disease > 1.5 cm^3. 5 year Event free survival was 64 +/- 9 % for those with residual disease, compared to 81 +/- 3 % for those with a post-operative tumour volume of < 1.5 cm^3.	

Infant medulloblastoma < 3 yrs This carries a worse prognosis than that seen in children aged >3 years, although this seems to be principally in those infants with classical medulloblastoma. The presence of desmoplasia is strongly predictive of a more favourable outcome in series from the US, Germany, France and the UK. The presence of significant residual disease was prognostic in the majority of studies. (See note above)	Many infants have desmoplastic MB or MB with extensive nodularity for which good outcomes were achieved without radiotherapy using the schedule according to HIT-2000 Von Bueren AO, von Hoff K, Pietsch T, et al. Treatment of young children with localized medulloblastoma by chemotherapy alone: Results of the prospective, multicenter trial HIT 2000 confirming the prognostic impact of histology. Neuro-Oncology. 2011;13(6):669-679. doi:10.1093/neuonc/nor025.	P 53 B catenin (WNT pathway) Myc N Myc C Monosomy 6 These patients should also be tested for Gorlin's syndrome	At the outset there should be an attempt at maximal surgical resection for all tumours. In the event of a complete resection not being feasible the MDT should consider all available biological stratification before planning further surgery since extent of resection is not prognostic for WNT pathway tumours or group 3 and 4 tumours but practically this information is not currently available in the UK in a timely manner to plan surgery.	**Avoid radiotherapy**
High risk Medulloblastoma	P53 mutation Myc N and Myc C amplified	P 53 B catenin (WNT	At the outset there should be an attempt at maximal surgical resection for all tumours. In the event of a	

	Metastatic Large residual Anaplastic large cell CCLG guidelines detail options for HR medulloblastoma. The MDT have considered these guidelines and consider an approach most similar to that which will be taken in PNET 5 using carboplatin as a radio-sensitiser and following the paper according to Jackacki et al. A local guideline documents this. In the context of severe posterior fossa syndrome where early radiotherapy can not be delivered the MDT recommend following the regime used in the US trial POG9031	pathway) Myc N Myc C	complete resection not being feasible the MDT should consider all available biological stratification before planning further surgery since extent of resection is not prognostic for WNT pathway tumours or group 3 and 4 tumours but practically this information is not currently available in the UK in a timely manner to plan surgery.	
Relapsed Medulloblastoma	CCLG guidelines – NB from 2011 Consider molecular analysis via MB feasibility study (if consent for	P 53 B catenin (WNT pathway)	Complete surgical resection is not of prognostic importance in relapse. MDT recommend surgery to obtain tissue to	

	tissue banking)	Myc N Myc C	confirm relapse and confirm biology since genetic changes may be acquired at relapse and these are prognostically important	
ATRT				
ATRT is uncommon, but increasingly recognized. It is most frequently seen in infants, and may constitute half of all tumours in this age group. There is a significant risk of a rhabdoid predisposition syndrome in very young patients, and genetic counselling is indicated for affected families.	CCLG guidelines for management of ATRT – latest update to Oct 2014. Refer also to SIOP Europe Rhabdoid Registry treatment guidelines are included with this	SMARCB1, also consider germ line mutation and type of deletion Myc	Complete surgical resection is important for long term cure in ATRT	
High Grade Glioma				

This accounts for 10-15% of paediatric CNS tumours and the prognosis is affected by the degree of surgical resection, by the administration of radiation therapy, and possibly by the administration of chemotherapy.	In the absence of an open trial for new agents in this tumour the MDT would recommend radiotherapy with adjuvant temozolomide as a radio-sensitiser as first line therapy. 75mg/m2/d for 7 days a week from the first day of radiotherapy until the last day of radiotherapy but for no longer than 49 days. It is current practice in the USA to give the temozolomide dose within 1 hour of radiotherapy due to theoretic synergy but there is not enough evidence at the moment to mandate this. After a 4 week break patients should receive up to 6 cycles of adjuvant temozolomide according to the standard 5 day schedule every 28 days. The dose should be 200mg/m^2/d. Stupp, R., W. P. Mason, et al. (2005). "Radiotherapy plus	MGMT analysis IDH mutations BRAF V600E Histone mutations	Complete cellular resection is not usually feasible owing to the infiltrative nature of the tumour but surgery where possible should aim for complete resection of the T2 change on MRI. In those cases where resective surgery is not anatomically viable then tissue for a confirmatory diagnosis and molecular studies should be obtained. Significant post-operative morbidity may be acceptable if this allows tumour resection, but this must be discussed with the patient or carers. Second look surgery (to achieve CR) must be considered whenever imaging is performed. Surgery is not usually indicated at progression.	Current CCLG guidelines recommend the use of radiotherapy (Dose 54Gy) to the clinical target volume.

	concomitant and adjuvant temozolomide for glioblastoma." N Engl J Med 352(10): 987-96. If disease is stable at the end of first line treatment it would be appropriate to commence a watch and wait strategy pursuing open trials of early phase therapies at time of disease progression and depending on clinical situation. Survival at progression is extremely rare and the role of palliative care should be discussed alongside any discussions about further therapy. If further therapies are considered then these include PCV, re-irradiation or early phase therapies.			
Infant High Grade Glioma				
Infant HGG appears to carry a better prognosis	SIOP infant high grade glioma			

than that in older patients, despite the difficulties of not being able to use radiation therapy in all patients.	schedule			
DIPG				
These tumours carry a particularly poor prognosis. Current overall survival worldwide offer less than 10% survival.	Discussions at diagnosis should include palliative care alone or alongside first line therapy with radiotherapy alone but the MDT would favour a recommendation to enter the phase 2 BIOMEDE study Re-irradiation can be considered more than a year from first line treatment. Beyond radiotherapy the MDT recommend consideration of current open experimental phase studies. Little evidence exists for the role of Temozolomide or Carboplatin	Histone 3 mutation MycN	The MDT would recommend a biopsy if considering experimental therapy (BIOMEDE)	Strategies include 54Gy in 30 fractions or 39Gy in 13 fractions, which provides no survival benefit but does confer less time in hospital. The latter should not be used if an attempt at re-irradiation is to be used to prolong palliation. Re-irradiation strategy of 30.6Gy in 17 fractions but acceptable interval between radiation episodes needs to be discussed at MDT. The MDT would favour enrolment in an early phase study above re-irradiation.

	as radio-sensitisers but the MDT would not prohibit their use currently. If disease is stable at the end of first line treatment it would be appropriate to commence a watch and wait strategy pursuing open trials of early phase therapies at time of disease progression and depending on clinical situation.			
Pineoblastoma				
Non-metastatic pineoblastoma	CCLG guidelines for non-metastatic pineoblastoma for children > 3 years			
CNS Germ cell tumour				
Intracranial germ cell tumours of any intracranial site, stage or	SIOP CNS GCTII		Non-germinomatous (Secreting) Germ Cell tumours surgery should be	Radiotherapy guidance is included in SIOP CNS GCTII

dissemination with no upper or lower age limit Compliance with diagnostic work-up and staging investigations is of great significance. This includes measurement of tumour markers (alpha-fetoprotein, AFP, and/or human chorionic gonadotrophin, HCG or β-HCG) in both cerebrospinal fluid (CSF) and serum, MRI scanning of head and spine, and CSF cytology. The implications of incomplete work-up may be profound: Unnecessary surgical interventions for non-germinomatous tumours, in which the diagnosis has been made based on			considered to remove any residual tumour after 4 cycles.	

marker elevation, have been associated with surgical toxicity, leading to death in some cases. Marker elevation in either CSF or serum is diagnostic of a secreting tumour. A diagnosis of pure germinoma is therefore unsafe, without confirmation of negative markers in both compartments, regardless of biopsy findings, as there may be undiagnosed secreting elements, giving rise to the risk of undertreatment. Failure to exclude the presence of spinal metastases by confirming a normal spinal MRI and CSF cytology risks				

undertreating nongerminomatous tumours. Diagnostic work-up If an intracranial germ cell tumour is suspected based on clinical and radiological evidence of a suprasellar or pineal mass, the following diagnostic steps must be followed: Gadolinium enhanced MRI scan of head and spine Tumour markers (AFP, ß-HCG) in both serum and CSF. For the purposes of subsequent management, elevation is defined as > 25 ng/ml for AFP and > 50 IU/l for ß-HCG in either serum or CSF.				

CSF cytology Only cases with normal markers in both compartments require biopsy for histological diagnosis. The remainder, those with elevated markers in either serum or CSF, should be treated according to the guidelines for non-germinomatous GCTs and surgical intervention limited to urgent CSF diversion procedures, where control with steroids is insufficient.				
Choroid Plexus Tumour				
Tumours of the choroid plexus epithelium are rare and account for only	CCLG guidelines recommend the use of the SIOP CPT 2009 study, although not currently open in the	P53	Patients should undergo maximal surgical resection.	

0.5% of all brain tumours. They occur mostly in infants, but have been reported in adults. All grades of choroid plexus tumour	UK as a clinical trial this provides the framework for treatment The need for and details of further treatment depends on the histopathology, the extent of surgical excision (presence of unresectable residual disease), the age of the patient, the presence of metastatic disease, and tumour response. This should be discussed in the neuro-oncology MDT			
Meningioma				
Although uncommon, meningioma does present in childhood, and may be the presenting feature of Neurofibromatosis type	Treatment in paediatric patients should be according to the document "Guidelines for the management of intracranial meningioma in children and	NF2 NF1 P53	Surgery is the mainstay of treatment for those in an accessible area.	Stereotactic radiotherapy or radiosurgery should be considered for surgically inaccessible tumours.

II.	young people (version 1.0 June 2007)"			
Endocrine tumours				
Craniopharyngioma Patients with craniopharyngioma must be managed in conjunction with the paediatric endocrinology team. The peri-operative period is particularly dangerous, and close observation of the patient according to the pituitary surgery guidelines is compulsory.			Patients with Craniopharyngioma will be discussed at the neuro-oncology MDT in conjunction with a paediatric endocrinologist and further discussion may be required with the adult pituitary surgeon specializing in Craniopharyngioma surgery (currently Mr Nelson). Good risk craniopharyngiomas, those which are no more than 4cm, no hydrocephalus, hypothalamic syndrome or breach of the III ventricular wall may be managed by radical surgical removal. If	In the event of recurrence or regrowth, further surgery may be considered. alternatively, external fractionated conformal radiotherapy is indicated. This is also the appropriate therapy for older patients with incompletely resected craniopharyngioma. Referral for proton beam radiotherapy should be considered. Recurrence after radiotherapy can be problematic, and several options may be considered, including further surgical resection, instillation of chemotherapy (bleomycin), radioactive colloid therapy

			complete surgical clearance has been achieved, close surveillance, with 6 monthly MRI is required. Poor risk tumours, those which are larger, retrochiasmal, with associated hydrocephalus, hypothalamic syndrome or breach of the III ventricle may be managed by conservative surgery. In young patients, where it is wished to avoid radiotherapy, close monitoring with 4 monthly MRI is indicated. In the event of recurrence or regrowth, further surgery may be considered.	(Yttrium), gamma knife therapy and systemic chemotherapy.
Pituitary tumour in context of MEN 1	UKCCSG and BPSED guidelines	MEN1 MEN2		

Metastatic brain lesions				
Rarely the MDT reviews cases of metastatic brain or spinal metastases of a non-CNS primary	These cases require individualised management discussed at an MDT with paediatric oncology, clinical oncology and neurosurgical presence. Attempt at surgical resection should be considered if a resection would both alleviate symptoms and prolong life expectancy.			
Cerebellar tumours				
			All patients undergoing surgery to the posterior fossa and hence at risk of cerebellar mutism are eligible for entry into the Cerebellar Mutism Study (CMS).	
RELEVANT NON-TREATMENT GUIDELINES				
Imaging guideline	CCLG imaging protocol for SIOP studies 2013			
Subfertility Consensus Document	2010			
The effects of cancer treatment on reproductive functions –	2007			

Guidance on management				
Endocrine referral	All patients with pituitary or hypothalamic tumours, with hydrocephalus or where radiotherapy involves the pituitary or hypothalamus should be referred for endocrine follow up			
Neuro psychology referral	All patients should be assessed by the neuropsychology team			
Ophthalmology referral	All patients with tumours involving the optic pathway or presenting with hydrocephalus should have ophthalmology assessment			

Appendices

Appendix 1

Treatment of Children with Radioth

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