Ependymoma in Adults

Evaluation and Treatment Protocol

**Dutch Neuro-Oncology Society
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1   Working group

Chairman
J.E.C. Bromberg, MD, PhD, neurologist, Erasmus University Medical Center, Rotterdam, j.bromberg@erasmusmc.nl

Working group members
- J.M.M. Gijtenbeek, MD, PhD, neurologist, Radboud University Nijmegen Medical Centre, Nijmegen, anja.gijtenbeek@radboudumc.nl
- E. Kurt, MD, neurosurgeon, Radboud University Nijmegen Medical Centre, Nijmegen, erkan.kurt@radboudumc.nl
- M. van Linde, MD, medical oncologist, Amsterdam University Medical Centre, m.vanlinde@amsterdamumc.nl
- A.T. Swaak-Kragten, MD, radiation oncologist, Erasmus University Medical Center, Rotterdam, a.swaak@erasmusmc.nl
- W. Taal, MD, PhD, neurologist, Erasmus University Medical Center, Rotterdam, w.taal@erasmusmc.nl
- F.Y. de Vos, MD, PhD, medical oncologist, University Medical Centre Utrecht, Utrecht, f.devos@umcutrecht.nl
- H.L. van der Weide, MD, radiation oncologist, University Medical Centre Groningen, h.l.van.der.weide@umcg.nl
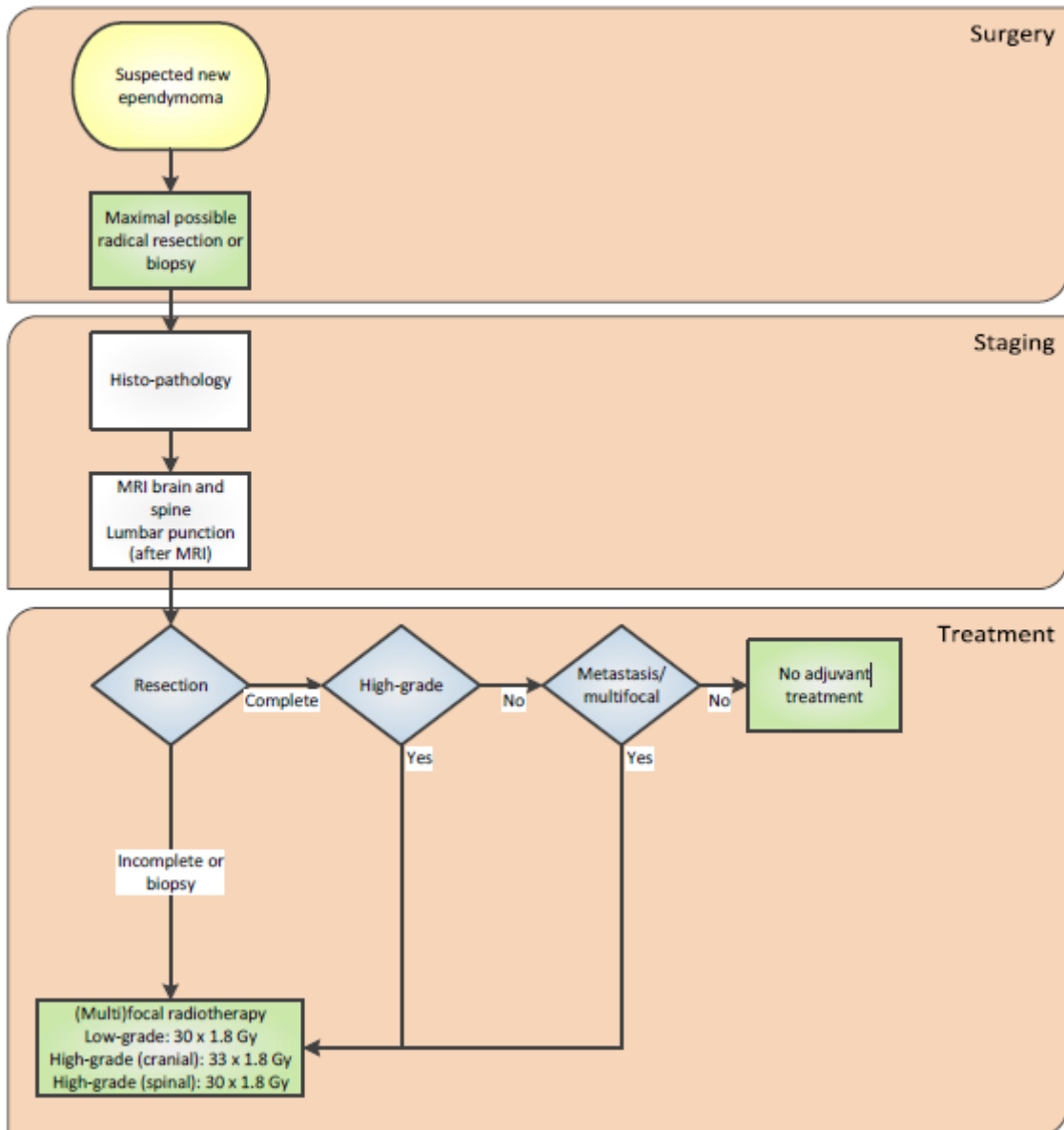- P. Wesseling, MD, PhD, neuropathologist, Radboud University Nijmegen Medical Centre, Nijmegen, p.wesseling@pathol.umcn.nl

Advisor
- V.K.Y. Ho, MSc, epidemiologist, Netherlands Comprehensive Cancer Organisation (IKNL), Utrecht, v.ho@iknl.nl

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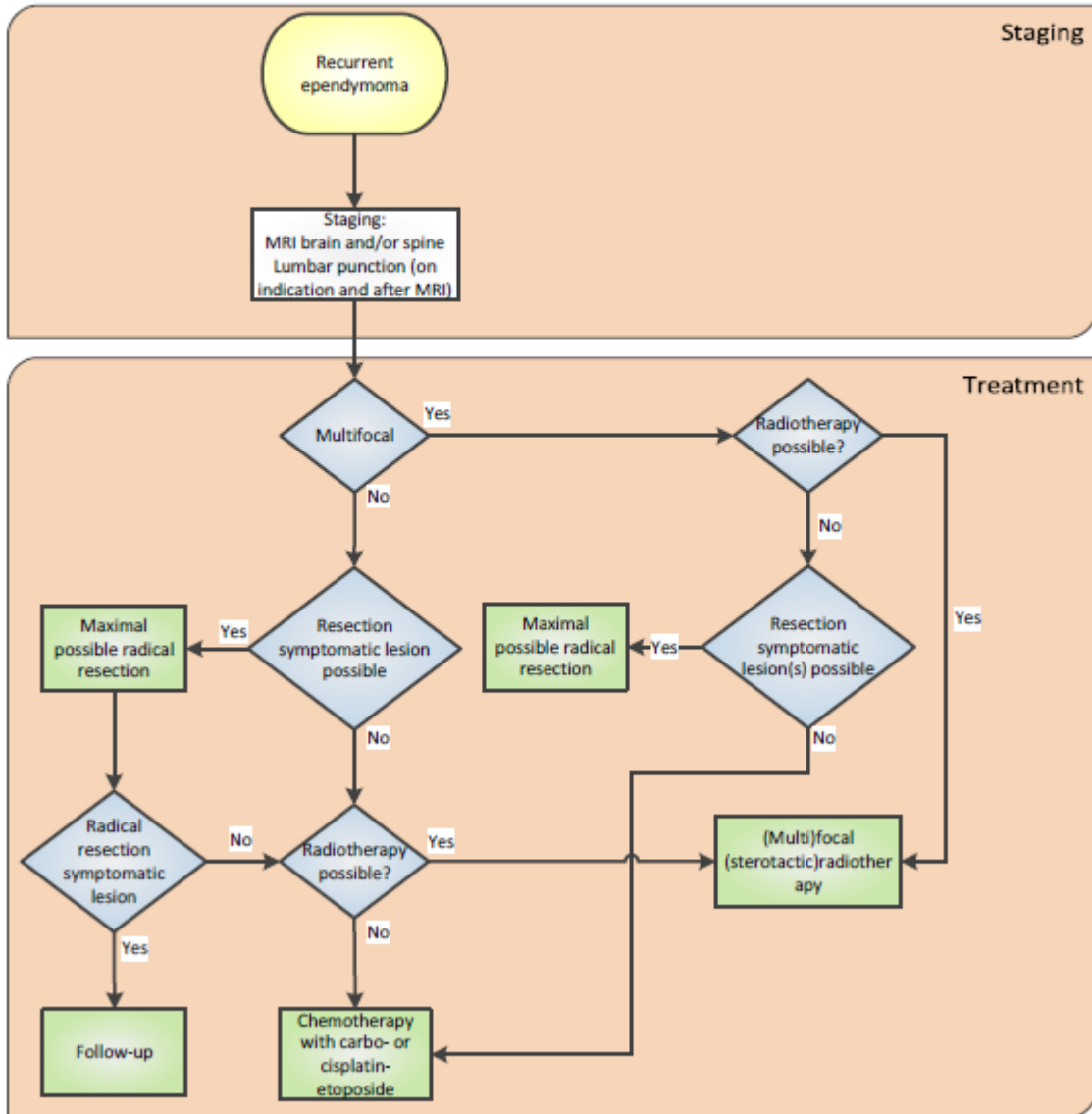## Flowchart newly diagnosed ependymoma

Surgery

Suspected new ependymoma

Maximal possible radical resection or biopsy

Staging

Histo-pathology

MRI brain and spine
Lumbar punction (after MRI)

Treatment

Resection — Complete → High-grade — No → Metastasis/ multifocal — No → No adjuvant treatment

High-grade — Yes

Metastasis/ multifocal — Yes

Resection — Incomplete or biopsy

(Multi)focal radiotherapy
Low-grade: 30 x 1.8 Gy
High-grade (cranial): 33 x 1.8 Gy
High-grade (spinal): 30 x 1.8 Gy

Flowchart recurrent ependymoma

Recurrent ependymoma

Staging:
MRI brain and/or spine
Lumbar punction (on indication and after MRI)

Multifocal

Yes → Radiotherapy possible?

No

Resection symptomatic lesion possible

Yes → Maximal possible radical resection

No

Radiotherapy possible? — No → Radiotherapy possible?

Radical resection symptomatic lesion

Yes → Follow-up

No

Radiotherapy possible?

Yes

No → Chemotherapy with carbo- or cisplatin-etoposide

Maximal possible radical resection ← Yes — Resection symptomatic lesion(s) possible

No

(Multi)focal (sterotactic)radiotherapy

Yes

4   Epidemiology

Ependymoma's are neuroepithelial tumours arising from the ependymal lining of cerebral ventricles, the choroid plexus or the central canal of medulla, spinal cord or filum terminale. Additionally they may arise from foetal rests of ependymal cells in the brain parenchyma (Reni 2007, Rodriquez 2009). No known risk factors exist.[1] Ependymomas are classified according to the WHO into grade I tumours (subependymoma, found mostly in the posterior fossa and lateral ventricles, and myxopapillary ependymoma found in the conus, cauda and filum terminale), and malignant grade II (ependymoma) and grade III (anaplastic ependymoma) tumours (Rushing 2007, Louis 2007). Ependymoblastoma, a grade IV tumour, is classified under the Primitive Neuro-Epithelial Tumours (PNET) and is not regarded as an ependymoma.

Ependymomas are rare tumours with an annual incidence in the US of 2-4 per million (Amirian 2012), in The Netherlands they are diagnosed approximately 52 times per year.(data IKNL) They constitute 3-5% of adult intracranial glioma's and 8-10% of childhood tumours of the central nervous system (Amirian 2012). Ependymoma's may occur at all ages but peak incidence is found at 0-4 years and at 55-59 years (Villano 2013)
Spinal ependymoma's make up 24-40% of all spinal tumours depending on the age at diagnosis, are the most common spinal glial tumour and occur especially in adults (Oh 2014, Engelhard 2010).

Figure 1. Distribution of age groups in site and histology categories for all primary brain and CNS ependymal tumours, CBTRUS analytic file, 2004–2009. (Villano 2013)
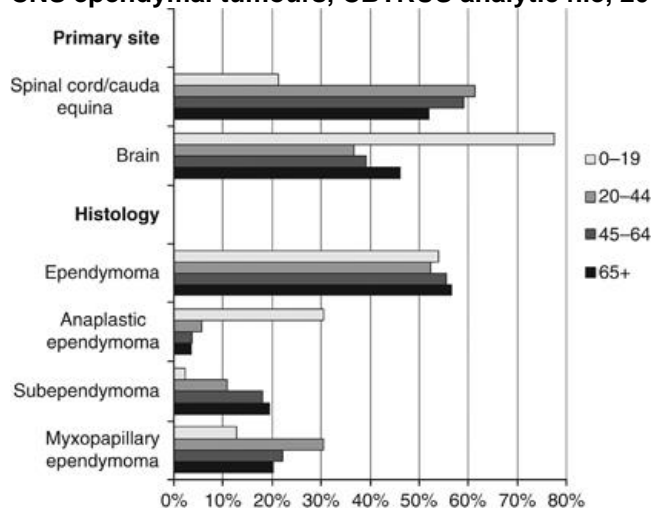
The median age at diagnosis is 35 years but varies according to the localization of the tumour: supratentorial ependymomas occur at a younger age (median 20 yrs) than spinal tumours (median 45 yrs) with infratentorial tumours in between (median 24 yrs) (Rodriguez 2009). Accordingly, in adults 50-60% of ependymomas are spinal, 20-25% supratentorial and 10% infratentorial, the remainder being not otherwise specified (Reni 2007, Rodriquez 2009, Amirian 2007, Villano 2013, Armstrong 2010). In children intracranial location, especially infratentorially, and anaplastic histology is more frequent than in adults (Villano 2013). Of the supratentorial tumours approximately half are localized in the ventricles the remainder being parenchymal.

CSF dissemination develops in 3-15% of all ependymomas and is more frequent in infratentorial and anaplastic tumours, though only in 5% is dissemination present at the time of presentation (Reni 2007, Ruda 2008). Only very rarely is microscopic leptomeningeal seeding found without macroscopic metastatic disease visible on MRI (Fangusaro 2011). However prognosis seems similar in

microscopic and macroscopic metastatic disease, therefore CSF evaluation should be an integral part of the evaluation of patients with radiologically non-metastatic ependymoma (Moreno 2010).

Prognosis depends on several factors and is worse in young children and older adults (age ≥ 60), anaplastic ependymoma (occurring in 3-5% of adults and 30% of children), intracranial rather than spinal localization and, in most studies, if no total resection was performed (Rodriquez 2009, Amirian 2012). Median survival is reported to be approximately 20 years; 7.8 years for supratentorial, 11.4 years for infratentorial and 25 years for spinal tumours. Overall survival is 70% at 5 years; 55.6%, 64% and 90% for respectively supratentorial, infratentorial and spinal localizations (Rodriquez 2009, Ruda 2008, Metellus 2010).
Progression free survival is reported to be 43-65% at 5 years for intracranial ependymoma and 70-75% for spinal ependymoma's (Ruda 2008). Median time to progression in spinal ependymoma is 68 months (range 2-324 months) (Gomez 2005).

5   Clinical Features

Clinical presentation depends on the localization of the tumour. Patients with ependymoma present with pain in 50-73% of intracranial tumours and in 60-85% of tumours in the conus or cauda equina (Oh 2013(1), Armstrong 2010). Other common symptoms in spinal tumours are sensory deficits (30-70%), weakness (45-70% in spinal cord, 23% in cauda tumours) and bowel or bladder dysfunction (16-25%) (Oh 2013(1), Armstrong 2010). In intracranial tumours other common symptoms are weakness (33%), sensory deficits (33%), visual disturbances or mental status changes (46-50%), impaired coordination (45%) and nausea or vomiting (30-40%) (Armstrong 2010, Armstrong 2011).

6   Imaging Features

6.1 Intracranial ependymoma
MRI is the imaging modality of choice. On CT an ependymoma is generally isodense or mildly hyperdense compared with normal brain parenchyma. In 50% of pediatric patients calcifications are found and in approximately 10% signs of haemorrhage. Enhancement is heterogeneous (Yuh 2009). On MRI ependymomas are generally hypointense on T1 and hyperintense on T2-weighted images but signal intensity is heterogeneous, especially in supratentorial ependymomas in which cyst formation is frequently encountered. Both calcifications and old haemorrhages are generally of low signal intensity on all MRI sequences. The soft tissue components of the tumour generally enhance somewhat irregularly with gadolinium. Diffusion weighted imaging shows reduced diffusivity in some components of the tumour but is unreliable in making the diagnosis. Perfusion imaging usually demonstrates remarkably increased cerebral blood volume (rCBV) and poor return to baseline after treatment, contrary to most other glial neoplasms (Yuh 2009).
Infratentorial ependymomas frequently fill and distend the 4th ventricle at diagnosis resulting in hydrocephalus. A typical though not entirely pathognomonic feature of ependymomas is fingerlike extension through the foramina of Luschka and/or Magendie to the upper spinal cord or cerebellopontine angle. Furthermore ependymomas may encase vessels or nerves causing cranial neuropathies or alternatively present within the cerebellopontine angle.
Supratentorial ependymomas arise in the brain parenchyma rather than the ventricles in approximately two-thirds of patients (Yuh 2009). Radiologically the distinction between grade II and anaplastic ependymomas is troublesome.

6.2 Spinal ependymoma
As in intracranial ependymomas, spinal ependymomas usually show a heterogeneous signal with low signal intensity on T1 and high intensity on T2 and some heterogeneous enhancement with gadolinium is often seen with a sharp boundary at the edge of the tumour. Ependymomas tend to lie more centrally in the spinal cord than astrocytomas. In approximately 20% haemorrhage has occurred leading to a rim with low signal intensity on T2 usually at the border of the tumor (Yuh 2009).

6.3 Leptomeningeal spread
As in leptomeningeal seeding by other malignancies MRI can show smooth or nodular enhancement and thickening of the spinal cord surface, intradural extramedullary enhancing foci or nerve root thickening and additional macroscopic tumours. The lumbar region, especially the caudal sac, is the most common region for drop metastases. Intracranially leptomeningeal nodules, enhancing nerve roots or communicating hydrocephalus can be found. Intraventricular nodules and masses often demonstrate little or no enhancement (Yuh 2009).

7   Pathology

7.1 Definition
Ependymal tumors are glial neoplasms (gliomas) of the central nervous system considered to originate from (precursors of) ependymal cells covering the walls of the ventricular system (including the central canal in the spinal cord).

7.2 Biological features
Based on microscopic features, ependymomas are traditionally graded as benign (WHO grade I), low-grade malignant (WHO grade II) or high-grade malignant (WHO grade III) (Louis 2016). However, especially for grade II and III ependymomas the prognostic value of histopathological grade is limited. The biological behavior of ependymomas also depends on the age at presentation, location of the tumor, and extent of resection (see below). Of note, myxopapillary ependymomas (WHO grade I) may show seeding within the (spinal) dural compartment, but this in itself does not imply malignant progression.

7.3 Localization/macroscopy
Ependymal tumors may occur at any site along the ventricular system and in the spinal canal. In children, they most commonly occur in the 4th ventricle and spinal canal, followed by localization in the supratentorial compartment (more often in/near the lateral ventricles than in the 3rd ventricle, sometimes in the brain parenchyma). In adults, infratentorial and spinal ependymomas arise with almost equal frequency. About fifty percent of all intramedullary tumors are ependymomas. Tumors in the 4th ventricle may extend via the foramina of Luschka en Magendi into the subarachoid space. Myxopapillary ependymoma typically occur in the lumbosacral part of the spinal cord (conus medullaris and filum terminale/cauda equina).

7.4 Pathology
Classic histopathological features of ependymal tumors are the presence of 'true rosettes' (ring of tumor cells radially oriented around a central lumen) and/or of 'perivascular pseudorosettes' (ring of tumor cells radially oriented around a blood vessel with a zone free of tumor cell nuclei immediately around the vessel). Immunohistochemically, ependymomas show expression of glial fibrillary acidic protein (GFAP), corroborating the glial nature of the tumor cells. In the true rosettes, the apical part of the cells shows staining for epithelial membrane antigen (EMA). Furthermore, in many ependymomas 'dot like' EMA staining is present in the cytoplasm of dispersed tumor cells (in fact representing intracytoplasmatic microlumina as can be identified with electron microscopy).
Traditionally, two distinct types of WHO grade I ependymal tumors are recognized: subependymoma (paucicellular lesion with clustering of tumor cells and often without marked formation of true or pseudo-rosettes) and myxopapillary ependymoma (with papillary formations of tumor cells and abundant accumulation of mucoid material in the stroma of these papillae).
The low- and high-grade malignant ependymomas (WHO grade II en III) form a histological spectrum (ependymoma vs. malignant/anaplastic ependymoma), but prognostic value of grading for these tumors is limited. Microscopic features of higher grade of malignancy are high mitotic activity, florid microvascular proliferation and/or pseudopalisading necrosis. Histological variants are the cellular, papillary, clear cell and tanycytic subtype (Louis 2016).
Based on detailed molecular analyses combined with clinicopathological information, a recent large study identified nine subgroups of ependymal tumors, three in each of the following compartments: supratentorial, posterior fossa and spinal (Pajtler 2015). Some of these subgroups largely correspond to entities that were already recognized in previous WHO classifications, especially subependymoma, WHO grade I (generally presenting in adult patients and occurring in all three compartments) and myxopapillary ependymoma, WHO grade I (in the spinal compartment of both adults and children). Another subgroup, ependymoma, RELA fusion-positive, typically is an aggressive, supratentorial tumor occurring in children and (less frequently) adults. This subgroup was found to be distinct enough to be incorporated as a separate entity in the WHO 2016 Classification (Louis 2016).

Immunohistochemical L1CAM and cyclin D1 staining are reported as promising surrogate markers for recognition of this ependymoma subtype.

Most likely, more genetically defined subgroups of ependymal tumors will be introduced in the near future. Examples are ependymoma, YAP1 fusion-positive (supratentorial tumours in infancy/childhood associated with a relatively good prognosis) and ependymomas with particular methylation profiles (posterior fossa type A, typically found in young children, with a balanced genome and poor prognosis; posterior fossa type B, occurring in childhood to adulthood, with genome-wide polyploidy and good prognosis) (Wesseling 2018).

Key characteristics of nine molecular groups of ependymoma (Pajtler 2015, Louis 2016)

Anatomical location	Group	Genetic characteristic	Dominant pathology	Age at presentation	Outcome
Supratentorial	ST-EPN-*RELA*	*RELA* fusion gene	Classic/anaplastic	Infancy to adulthood	Poor
	ST-EPN-*YAP1*	*YAP1* fusion gene	Classic/anaplastic	Infancy to childhood	Good
	ST-SE	Balanced genome	Subependymoma	Adulthood	Good
Posterior fossa	PF-EPN-A	Balanced genome	Classic/anaplastic	Infancy	Poor
	PF-EPN-B	Genome-wide polyploidy	Classic/anaplastic	Childhood to adulthood	Good
	PF-SE	Balanced genome	Subependymoma	Adulthood	Good
Spinal	SP-EPN	*NF2* mutation	Classic/anaplastic	Childhood to adulthood	Good
	SP-MPE	Genome-wide polyploidy	Myxopapillary	Adulthood	Good
	SP-SE	6q deletion	Subependymoma	Adulthood	Good

EPN = ependymoma, MPE = myxopapillary ependymoma; NF2 = Neurofibromatosis type 2; PF-EPN-A/B = posterior fossa ependymoma type A/B, RELA = V-rel avian reticuloendotheliosis viral oncogene homolog A, SE = subependymoma, ST = supratentorial, YAP = Yes-associated protein 1

7.5 Molecular pathology
Apart from the molecular aberrations already mentioned above, ependymomas display a broad range of cytogenetic aberrations, most commonly gains of chromosomes 1q, 5, 7, 9, 11, 18, and 20 and losses of chromosomes 1p, 3, 6q, 6, 9p, 13q, 17, and 22. Loss of chromosome 9, and in particular homozygous deletion of CDKN2A has been recurrently demonstrated in supratentorial ependymomas. Monosomy 22 and deletions or translocations of chromosome 22q are particularly common in spinal cord tumors and tumors associated with neurofibromatosis type 2. The *NF2* gene (localized on chromosome 22q12) is involved in ependymoma tumorigenesis, and *NF2* mutations occur frequently in spinal ependymomas.

7.6 Prognostic and predictive factors
Supratentorial ependymomas are associated with better survival rates than are posterior fossa neoplasms, especially in children. Spinal ependymomas have a significantly better outcome than do intracranial tumours, although late recurrences (> 5 years after surgery) can occur. Children with ependymoma fare worse than adults. This difference may reflect the more frequent occurrence of pediatric tumors in the posterior fossa versus the predominantly spinal location for adult tumors. Extent of surgical resection is consistently reported to be a reliable indicator of outcome; gross total resection is associated with significantly improved survival. Especially for WHO grade II and III

ependymomas the clinical utility of individual histopathological features or tumor grade is highly controversial. Gain of chromosome 1q has been reported as a reproducible prognostic marker for poor outcome in posterior fossa tumors. Molecular characterization of ependymal tumors is very promising for improved assessment of prognosis for individual patients with ependymoma.

7.7 Pathological diagnosis in daily clinical practice
For optimal patient care, in most cases with a clear-cut histological diagnosis of subependymoma or myxopapillary ependymoma additional molecular testing is not necessary. Similarly, in adult patients with a classic ependymoma of the spinal cord without histological signs of high-grade malignancy additional molecular testing can be omitted. However, ependymomas in the supratentorial or posterior fossa compartment are ideally characterized in more detail by molecular diagnostics (or with immunohistochemistry for surrogate markers). Methylation profiling analysis is a very helpful molecular tool in this respect, as it allows for unequivocal designation of a particular molecular type in most of these tumors (Capper, Nature 2018; Capper, Acta Neuropathol 2018). Alternatively, for the supratentorial ependymomas RELA fusion or YAP fusion may be demonstrated by e.g. RT-PCR, and RELA fusion-positive status is indicated by immunohistochemical staining for L1CAM and CyclinD1 (Parker 2014). For recognition of the posterior fossa type A group of ependymomas, immunohistochemistry is very helpful as well as these tumors (in contrast to posterior fossa type B tumors) lack nuclear H3 K27me3 staining (Panwalker 2017).

8   Neurosurgery

8.1 General
The extent of tumor resection is the most important prognostic factor associated with long-term survival for patients with ependymoma, regardless of location (Ruda 2018). Thus, a gross total resection (GTR) is optimal (Kucia 2001, Duffner 1998, Philippe Metellus 2008). The surgery is classified as Gross Total Removal (GTR) if the surgeon describes a complete removal of the tumor, and the postoperative scan confirms this. This postoperative scan may be performed within 72 hours after surgery, but 3 months after surgery is accepted as well in case pathologic examination shows a myxopapillary ependymoma (and the surgeon describes GTR). The surgery is classified as Subtotal Resection (STR) if the surgeon observes unresected tumor in the operative field, and postoperative MRI confirms this.
Complete resectability depends not only on the skill of the operator, but also on the characteristics of the tumor itself: in more than 50% of the infratentorial ependymomas the tumor involves the cerebello pontine angle and the cranial nerves. Furthermore, resectability may also reflect a favorable tumor biology determining a non-infiltrating growth pattern (Spagnoli 2000). Due to these factors, complete tumor removal may therefore be achieved in several stages, using "second-look" resections (Foreman 1996), for example after an early postoperative scan. The degree of difficulty of second interventions depends on where the rest or regrowth is located and whether it is easily identifiable as tumorous tissue.
Complication rates show large variation in literature, mainly due to biased data that are based on inhomogenous patient selection.
Hydrocephalus can be managed with a perioperative external ventricular drain, ventriculoperitoneal shunt, or even third ventriculostomy (depends on the location and extension of the tumor).

8.2 Supratentorial Ependymomas
The approach to supratentorial lesions varies according to location, the goal of gross total resection is the same as in infratentorial surgery. In most cases the surgery is less challenging when compared with ependymomas of the infratentorial region, and the outcomes are good despite frequent recurrences. Association with the third ventricle and metastasis seem to have a negative impact on survival (Schwarz 1999).

8.3 Infratentorial Ependymomas
The approach depends on the exact localization of the tumor and may be via a midline suboccipital approach, lateral suboccipital approach or a modified approach. In case of hydrocephalus drainage may be necessary prior to surgery.
Ependymomas in the posterior fossa are in close proximity to critical structures such as cranial nerves, brainstem and vasculature making GTR risky with the possibility if long-term dysfunction and disability. Posterior fossa syndrome, also referred to as cerebellar mutism, is a recognized complication of posterior fossa surgery and most common when brainstem or vermis invasion is involved. Although mutism generally resolves over time, consideration must be given to the balance between improved survival with GTR and potential postoperative morbidity. A complete resection is not feasible in approximately 50% of patients (Hahn 1993).

8.4 Spinal Ependymomas
8.4.1. Ependymoma of the filum terminale (EFT)
EFT form a specific and relatively uncommon subtype of spinal cord ependymomas: in contrast to the more common intramedullary ependymomas, EFT present macroscopically as an intradural extramedullary tumor that may be surrounded by the cauda equina nerve roots. Compared to intramedullary ependymomas, most frequently seen in childhood and adolescence, EFT generally occur at a later age. Complete resection of EFT can lead to permanent cure (Bagley 2009, Kucia 2011). However, there is a significant risk of local relapse and of dissemination through CSF pathways leading to spinal cord compression above the level of the cauda equina and even of brain

metastasis (Plans 2006). Recent publications have not been able to solve the controversy, some series advocating surgical removal as the only treatment except in selected cases (Bagley 2009, Kucia 2011), while others argue in favour of adjuvant radiotherapy in all cases (Al-Halabi 2010, Pica 2009, Wahab 2007).

Although there is substantial controversy about the surgical technique, resection 'en bloc' without opening the capsule versus piecemeal using ultrasonic aspiration (Fassett 2005, Nakamura 2009), it is believed that internal decompression may increase the risk of CSF dissemination, while recurrences following successful en bloc resection are rare. So the advocated technique is straightforward, resection "en bloc" after dissecting the tumor from the surrounding cauda equine nerve roots by separating the tumor capsule by an arachnoid plane. Transsection of the filum terminale then allows removal of the tumor without opening the tumor capsule. Unfortunately, in case of larger tumors and mass effect, it is usually necessary to open the tumor capsule and debulk the mass using ultrasound aspiration before one can safely dissect the nerve roots from the capsule (Blars de Jong 2012).

In some cases the cauda equine nerve roots are situated within the tumor, and it is impossible to achieve GTR (without causing neurological deficits). In these cases we advise to perform adjuvant local radiotherapy, because a surgical procedure in the future will not change this situation and the tumor will stay unresectable.

On the other hand, if GTR is achieved we advocate to withhold radiotherapy, and perform a wait and scan policy. In case tumor recurrence is observed in the follow up phase, reoperation will be the first choice of treatment, while radiotherapy still can be an option after the reoperation.

8.4.2. Intramedullary ependymoma

The strategies for intramedullary tumor removal depend upon the relationship of the tumor to the spinal cord. Most tumors are totally intramedullary and are not apparent upon inspection of the surface. Therefore, intraoperative ultrasound may be used to localize the tumor and to determine the rostrocaudal tumor borders. The plane between the ependymoma and surrounding spinal cord is usually well defined and easily developed. Large tumors may require internal decompression with an ultrasonic aspirator or laser. Although somatosensory evoked potentials and direct motor evoked potentials are employed routinely, only rarely do they influence surgical decisions or technique. If GTR can be achieved, overall outcomes are excellent and the recurrence rate is very low (Kucia 2011).

Concerning timing of surgery it is generally accepted that the surgery is performed before significant neurological deterioration occurs (Epstein 1992) in order to obtain the optimal post-operative functional recovery of the patient.

Complication rates vary, in larger series an overall complication rate of 34% is reported, with wound infections and CSF leaks being the primary complications (Elisia 2011).

8.5 Complications of surgery

Postoperative complications are related to tumor location and have been reported to include cranial nerve palsies, increased ataxia, mutism, and (rarely) death (Hahn 1993, Lyons 1991, Pollack 1995, Sanford 1997).

Mutism may especially occur when the tumor involves the vermis or brainstem, sometimes even weeks after surgery (Sanford 1997). Although cerebellar mutism is an infrequent complication, it might occur and generally resolves over a period of months.

9   Radiotherapy

9.1 Intracranial ependymoma
Traditionally radiotherapy has an important role in the treatment of intracranial ependymoma. Due to the rarity of this brain tumour the majority of the clinical studies on adult patients with cerebral ependymomas are difficult to interpret. Studies combine patients with spinal and cerebral tumours in one study, include a mixture of adult and paediatric patients, include patients from different surgical and diagnostic eras, include differences in radiotherapy, both total dose, extent of portals (local versus craniospinal), adjuvant chemotherapy, differences in pathology, mixing grades, and furthermore most studies are retrospective and multi-centric. There are no randomised studies and the evidence for the benefit of radiotherapy after surgery is based only on retrospective studies (Bloom 1991, Nazar 1990, Metellus 2010, Kim 2013). Last but not least, almost all studies have been performed in the era before molecular classification of ependymoma.

In patients with WHO grade II ependymomas and incompletely resected tumours postoperative local radiotherapy was significantly associated with better PFS and OS (Metellus 2010). 10-year OS rate was increased from 78.3 % ± 5.4 to 87.3% ± 6.9 (P=.005).
In patients with anaplastic ependymoma there is a predominant pattern of local relapse. The extent of resection improves survival, but there is no evidence that postoperative radiotherapy improves the outcome. However, post-operative radiotherapy is generally accepted and applied in these cases (Dűtzmann 2013, Ruda 2018).

9.2 Spinal ependymoma
9.2.1 Primary spinal ependymoma
Currently, there are no prospective data available and data summarized here are derived mainly from retrospective cohort series. In adults the recurrence rate of spinal ependymoma is lower than in the paediatric population (Feldman 2013). A radical resection is not possible in approximately a quarter of cases (Clover 1993). Postoperative local radiotherapy is reported not to have an influence on overall survival (Oh 2013(2)) and therefore, some recommend radiotherapy as salvage therapy at recurrence only (Chao 2011).
Overall, the role of postoperative local adjuvant radiotherapy is still unclear, although it is favoured for subtotally resected ependymoma. Adjuvant radiotherapy is reported to prolong progression-free survival as well as the recurrence-free interval if resection is not complete (Gomez 2005, Oh 2013(2), Akyurek 2006, Pica 2009). In a review of 348 patients with spinal cord ependymomas who underwent resection, GTR was obtained in 77.0% (268/348) and STR in 23% of patients (Oh 2013(2)). Adjuvant radiotherapy was given for 58.8% (47/80) of the patients with STR and for 3.7% of the patients after GTR (Oh 2013(2)). PFS was significantly prolonged with adjuvant radiotherapy after STR (p < 0,001) and remained significant in multivariate Cox regression analysis) after correcting for tumour grade and tumor location in the upper and lower spine (Oh 2013(2)).
Literature is more or less clear on the fact, that there is no role for prophylactic or adjuvant craniospinal irradiation (Grabenbauer 1992, Vanuytsel 1991). There is even no evidence that craniospinal radiotherapy prevents the development of spinal metastases (Vanuytsel 1991).

For myxopapillary ependymomas of the spine a 100% survival rate of 5-years was reported compared with 76% for patients with other subtypes when treated with adjuvant radiotherapy independent of extent of resection (Schild 1998, Schild 2002, Akyurek 2006, Pica 2009). Results are different for local control or progression-free survival: patients with gross total resection had a better outcome than those without a complete resection. A trend towards significance was reported for the 5-year PFS with ca. 81% in the gross total resection group (n = 47) versus 59% (p = 0.11) in patients with subtotal resection and biopsy (n = 53)(Pica 2006). Akyurek et al reported regardless of the extent of resection (n = 14 GTR, n =13 STR) that adjuvant RT appears to significantly reduce the rate of tumour progression (Akyurek 2006). In this subgroup of myxopapillary ependymoma adjuvant radiotherapy with a higher dose than 50 Gy significantly reduced the rate of local progression (Akyurek 2006, Pica

2009, Schild 2002).
Not only gross total resection but also the operation technique defines whether radiotherapy should be added: a "piecemeal" resection where the tumour capsule is violated, can cause a CSF dissemination (Nakamura 2009, Volpp 2007). The latter is reported for all low-grade ependymoma including myxopapillary ependymoma.
Therefore, it may be recommended to defer radiotherapy until recurrence in those patients having undergone radical resection if patients are followed closely clinically and with imaging.

9.2.2 Spinal metastases of intracranial ependymoma
Ependymoma cells have the potential to seed into the cerebro-spinal fluid. Pre-mortem cytological examination of the spinal fluid revealed circulating malignant cells in 0-15% of unselected cases (Gonzalez et al 1982, Calvo et al 1983). Tumor grade, localization, and control of the tumor at the primary site are all factors which may influence the risk of spinal seeding (see Figure 1).

Figure 1. Spinal seeding is related to grade and location

Grade	III	I or II
Location	infratentorial	supratentorial
	III + supratent.	0% seeding
	III + infratent .	15% seeding

Although the true incidence of seeding is unknown, this possibility has led in the past to prophylactically irradiating the craniospinal axis to eradicate circulating malignant cells. However, a review of the literature undertaken by Vanuytsel and Brada in1991 showed that spinal metastases are not prevented by prophylactic spinal irradiation, regardless of tumour grade and site.
In principal there is, therefore, no role or indication for craniospinal irradiation.

9.3 Radiotherapy target volume

Local radiotherapy is given to the resection area and residual tumor. CTV margins depend on the tumor grade (see below). For selected patients with very diffuse metastases, (cranio)spinal radiotherapy can be considered. Reduction of the treatment volume was the goal of a more recent cooperative group trial for pediatric ependymoma and has been published: a reduction of a CTV margin from 2 cm to 1 cm appears to have reduced toxicity without affecting tumor control rates (Merchant 2008, Taylor 2004). To further reduce toxicity future protocols will use a margin of 5 mm which has been shown in a first dosimetry study (Beltran 2010).

9.4 Radiotherapy dose
It is difficult to analyze literature on the effect of dose on response due to a pre-selection for a lower treatment dose for younger patients and larger target volumes. Taylor (95) presented data of 11 series and concluded that there is some evidence for dose-response effect either for >45 Gy versus < 45 Gy and >50 Gy versus<50 Gy. The same is true for spinal ependymoma, where, independent of the histologic subtype, a higher total radiation dose than 50.4 Gy seems to be needed to reach long-term local control (Akyurek 2006, Pica 2009, Shaw 2000, Schild 2002).

9.5 Radiotherapy at recurrence
At recurrence there are different indications for radiotherapy. Radiation therapy may have a role as salvage therapy in delaying recurrences, as the use of radiotherapy as salvage therapy after initial recurrence has been reported to correlate significantly with longer times to a second recurrence

(Chao). The median recurrence-free survival time before the second recurrence was 9.6 years for those who received radiotherapy versus 1.1 years for those who did not (p = 0.0093) (Chao 2011). Re-irradiation after primary postoperative radiotherapy may be the treatment of choice for recurrent patients having less than complete resection or no surgery (Kocak 2004). Local re-irradiation with highly accurate and focal radiation techniques such as stereotactic radiosurgery for small tumours (Stafford, Jawahar), stereotactic fractionated radiotherapy for larger tumours (Aggarwal) or intensity-modulated radiotherapy techniques (like VMAT) are also options for intracranial recurrences. Twelve out of 36 recurrent ependymomas could be controlled with stereotactic radiotherapy with a median survival time of 30 months (Goumnerova 1996).

9.6 Summary of indications for irradiation
For grade I tumours the treatment strategy should be gross total resection without adjuvant radiotherapy as this type of resection is associated with the best PFS and OS. Independent of the primary tumor location (intracranial or spinal), all other extent of surgery i.e. partial resection, piecemeal resection or biopsy (only if no second operation is possible), should be followed by local radiotherapy.
Grade II ependymomas should receive postoperative radiotherapy in case of less than complete resection.
High grade tumours (WHO grade III) should be irradiated postoperatively independent of extent of resection.

10   Chemotherapy

Prospective data for systemic therapy in adult ependymoma are entirely lacking (Ruda 2008) . A recent publication on adult ependymoma does not even mention chemotherapy (Dützmann 2013). Resectable tumors have not been treated with chemotherapy. Even in children, the data on neo-adjuvant or adjuvant therapy are scarce. Systemic therapy is mostly employed in young children in order to avoid radiotherapy in curative setting (Garvin 2012, Grundy 2007), or else in palliative setting. For patients with spinal cord ependymoma, no evidence supporting treatment with chemotherapy exists, with the exception of minor responses documented with oral etoposide. Irresectable or metastatic intracranial ependymomas that are not amenable to radiotherapy have been treated with a variety of platinum and non-platinum regimens. Macroscopic leptomeningeal dissemination is rare in intracranial ependymomas (less than 5%), but a 20% rate of positive CSF cytology at initial diagnosis has been reported in pediatric cases of intracranial anaplastic ependymoma (Ruda 2008). Macroscopic leptomeningeal dissemination is an indication for chemotherapy if radiotherapy is not feasible. Although positive CSF cytology is associated with worse prognosis, controversy exists as to consequences for treatment. Chemotherapy has been described as a treatment option in paediatric case reports (Pérez 2013, Lassaletta 2007, Slavc 1998), but it is not regarded as standard treatment. Neither is craniospinal irradiation for this indication, although it has also been reported (Ernestus 1990, Salazar 1983, Ray 2013).

The (retrospective) data suggest a higher response rate for platinum-containing therapy, although that has not been shown to translate into improved progression free or overall survival (Brandes 2005, Gornet 1999). A variety of agents have been tried, ranging from platinum analogues, etoposide, nitrosureas to temozolomide, both as single agents and in combination protocols such as PCV, CEV and platinum-containing doublets (Rehman 2006, Chamberlain 2009, Freyschlag 2011, Lombardi 2013). Platinum-based chemotherapy regimens have better response rates (31-67%) than non-platinum-based regimens (11-13%), including nitrosurea-based regimens (25%). The wide range of response rates reflects the selection bias and small sample size of these data. Platinum-refractory ependymoma has a particularly poor prognosis, with a 6-months PFS of just 2% with temozolomide (Chamberlain 2009). As high levels of MGMT (an enzyme that confers resistance to alkylating agents such as temozolomide (Buccoliero 2008) have been observed in ependymoma, use of alkylators is not recommended (unless MGMT silencing can be documented). Oral etoposide is reasonably well tolerated even in patients with poorer condition, and has led to durable progression-free survival (median 15 months) in recurrent and metastatic disease (Chamberlain 2002). High dose chemotherapy does not seem to be effective in paediatric ependymoma (Zacharoulis 2007), and has not been reported in adults.

The data on chemotherapy in adult ependymoma were recently reviewed, which led to no new conclusions but that a guideline would be helpful in view of the many different regimens currently in use (Iqbal 2013). The authors carried out an email-based simple survey across the cancer centres of the UK asking their choice of chemotherapy regimen in recurrent/metastatic ependymomas in adults. Of the 30 centres approached, replies were returned from about 80% of those surveyed. A trend towards favouring oral based regimens was observed. A minority stated they would not offer systemic therapy for recurrent ependymoma.

A recent EANO guideline concludes that temozolomide is also an option as first line chemotherapy agent, based on the more favourable toxicity profile (Ruda 2018). The committee still regards platinum-based chemotherapy as the systemic therapy of choice based on higher efficacy outcomes in larger study populations as opposed to temozolomide chemotherapy studies. However, temozolomide, regardless of MGMT status, could be discussed between treating physician and chemotherapy-naive patients with supratentiorial ependymoma as an alternative, bearing in mind the lesser data and outcome parameters.

The use of agents that target signal transduction or angiogenesis has not been fully investigated. Targets for therapy ranges from blocking the ErbB2, PDGFR α and αvβ3 integrin pathways to PKC and COX-2 inhibition (Shonka 2011). Bevacizumab has been tested in children with tumors refractory to platinum-containing therapy, with conflicting results (Lorgis 2012, Gururangan 2012). In a small retrospective study of eight heavily pretreated adult ependymoma patients, objective non-durable response was observed in six patients (Green 2009). One adult patient with a PDGFR-positive spinal cord ependymoma responded to imatinib, after progression on previous therapy (Fakhrai 2004). Current phase II studies in adult ependymoma include temozolomide and lapatinib (CERN08-02) and carboplatin-bevacizumab (CERN09-02), both for recurrent ependymoma.

In conclusion, systemic therapy in adult ependymoma is only used for tumors for which no surgery or radiotherapy is available, i.e. in palliative setting. Although no one regimen is demonstrably more effective than any other, it seems reasonable to advocate the treatment with the highest response rate, even in the absence of a proven survival effect. The suggested preferred first line systemic treatment for adults with irresectable, recurrent and/or metastatic ependymoma that are not amenable to radiotherapy, is a platinum compound with etoposide. Alternatively oral temozolomide can be used. In children with ependymomas, carboplatin-based regimens performed similarly to cisplatin-based regimens . Based on local preference and experience, either carboplatin-etoposide or cisplatin-etoposide is acceptable. The toxicity of these regimens is manageable and predictable, and they have been well tested in a variety of tumors. Alternatively, for patients with recurrent spinal cord ependymoma, oral etoposide can be considered. Oral etoposide may also be prescribed for patients with lesser performance status. The use of targeted therapy and biologicals is recommended only in clinical trials that identify molecular and clinical profiles for selection of optimal treatment regimens.

From Iqbal MS, Lewis J, An Overview of the Management of Adult Ependymomas with Emphasis on Relapsed Disease, Clinical Oncology (Iqbal 2013)

Table 1

Summary of chemotherapy in advanced/recurrent ependymomas in adults

Study	Number of cases	Number responding (%)	Number stable (%)	Median time to progression (months)
[45] Platinum-based regimens (cisplatin + etoposide and cisplatin + etoposide + cyclophosphamide)	6	4 (67%)	2 (33%)	6
[45] Nitrosureas-based regimens (various combinations of lomustine, carmustine, procarbazine, vincristine, L-aspartate, dianhydrogalactitol)	8	2 (25%)	4 (50%)	10
[46] Cisplatin-based chemotherapy (cisplatin + etoposide + cyclophosphamide; cisplatin + temozolomide; carboplatin + etoposide)	13 including 2 (15.4%) CR	4 (31%)	7 (53.8%)	9.9
Non-cisplatin-based chemotherapy (PCV, CEV, temozolomide, MOPP)	15 No CR	2 (13.3%)	11 (73.3%)	10.9
[47] Chronic oral etoposide (for recurrent spinal cord ependymoma)	10 No CR	2 (20%)	5 (50%)	15
[48] Temozolomide (platinum-refractory ependymoma)	25	1 (4%)	9 (36%)	5.5
[18] Bevacizumab-containing chemotherapy (bevacizumab alone 2, with irinotecan 3, carboplatin 2 and temozolomide 1)	8	6 (75%)	1 (12.5%)	6.4

Survey results

Regimen	First line	Second line	Third line	Totals
Platinum-based regimen	6	2	2	10
Temozolomide	5	7	0	12
PCV	7	2	1	10
Oral etoposide	2	0	0	2
No chemotherapy				2

PCV, procarbazine, Lomustine (CCNU) and vincristine.

11   Objectives

The objectives of the current protocol are to:
1)   treat all adult patients with an ependymoma in The Netherlands in a uniform manner through a comprehensive protocol;
2)   document the feasibility of this treatment protocol by recording side-effects and actually administered treatment in a standardized fashion;
3)   document the outcome of adult ependymoma in EFS and OS after treatment in this standardized treatment protocol;

To this end, all patients will be prospectively registered in a central database.

12   Eligibility and registration

12.1 Inclusion criteria
Diagnosis of ependymoma

- diagnosis should be pathologically verified and be confirmed by central review whenever possible.
  Central review will be done by:

  Prof. dr. J.M. Kros, neuropathologist,
  Erasmus Medical Centre/location Centrum
  Dr. Molewaterplein 40
  3015 GD ROTTERDAM,
  email: j.m.kros@erasmusmc.nl

- Age $\geq$ 18

12.2 Registration
After diagnosis and informed consent patients should be notified by email to neuro-onco-trials@erasmusmc.nl

At least the following information should be registered for each patient: date of birth, sex, patient hospital registration number, treating physician, date of diagnosis and date of registration.

13   Diagnostic work-up

Because of the risk of dissemination of the ependymoma complete assessment of the extent of disease using MR imaging of brain and spine, and investigation of CSF for leptomeningeal dissemination is essential to determine optimal treatment. Diagnostic investigations are summarized in the flow-chart.

Imaging
Cranial MRI should be performed in all cases pre-operatively and within 48 hours following surgery if resection is performed (not required after biopsy only). Spinal MRI should ideally be performed before lumbar puncture and surgery and should include the full spine (C0–S3). Pre-contrast T1 sequences are mandatory, especially after surgery.

CSF examination
Ependymomas may disseminate through the CSF, although the risk is relatively low in the absence of macroscopic visible tumour on MR imaging, and it is of utmost importance to stage patients completely before starting treatment.

14   Practical treatment guidelines

14.1 Neurosurgery
See section 8.

14.2 Radiotherapy

In short, radiotherapy is indicated:
- **for grade I ependymomas: only after subtotal resection**
- **for grade II ependymomas: after subtotal resection.**
- **for grade III ependymomas: irrespective of extent of resection.**

14.2.1 Radiotherapy treatment volume – local treatment
The gross total volume (GTV) contains the tumour bed (resection cavity) and/or the visual residual tumor on recent MRI. The pre-operative tumour extension should be taken in to account when delineating the tumour bed. This is the case for both the primary tumor and the metastases.
The clinical target volume (CTV) includes subclinical microscopic disease and is defined as the GTV plus an added margin of 5 mm for low grade tumour and 10 mm for grade III tumours, which should include subclinical microscopic disease beyond the GTV. The CTV is anatomically confined and limited by normal tissue structures through which tumour extension is largely unlikely like e.g. the bone, falx or the tentorium.

For spinal locations the intravertebral foramina shall be part of the CTV.
For multifocal myxopapillary epenymoma confined to the conus/cauda region, the radiotherapy volume should encompass the entire cauda (conus till the caudal end of the thecal sac),

14.2.2 Craniospinal irradiation (exceptional cases)
the entire subarachnoid space is included. Specific attention should be given to inclusion of the cribiform plate, temporal fossa, optic nerves, Meckel's cave and other cranial nerve foramina, the lateral extensions of the spinal nerves and the inclusion of the entire thecal sack caudally as visible on MRI.
<u>Metastasis boost</u>
– The same definitions as for the primary tumour apply.

14.2.3 Dose and fractionation
<u>Low-grade ependymoma</u>
After incomplete (intracranial and spinal) or piecemeal (spinal tumours) resection

Volume	Total dose	Fraction dose	No. fractions
Tumour bed (cranial, spinal)(+ 5 mm)	54	1.8	30

<u>High-grade ependymoma</u>
After resection independent of radicality

Volume	Total dose	Fraction dose	No. fractions
Tumour bed (intracranial)(+10 mm)	59.4	1.8	33
Tumour bed or metastasis (spinal) (+ 10 mm)	54	1.8	30

<u>Craniospinal irradiation</u>
In case of multiple symptomatic spinal metastasis and seeding and multifocal craniospinal lesions

Volume	Total dose	Fraction dose	No. fractions
Cranio-spinal irradiation (CSI)	36	1.8	20
Boost to tumour bed and metastases (Tumour + 5 mm)	18	1.8	10
Tumour bed total	54	1.8	30

14.2.4 At recurrence
The use of highly conformal radiotherapy techniques, i.e. stereotactic radiotherapy, is strongly recommended. Dose and fractionation can range from single fraction radiosurgery to conventionally fractionated (stereotactic) radiotherapy depending on the volume of the lesion and the time interval since first radiotherapy. Radiosurgery with 1 x 15 – 18 Gy, hypofractionated schemes like 3 x 8 Gy 3 x a week or conventional schemes like 25 - 30 x 1.8 Gy could be applied.

14.3 Chemotherapy – dose and administration guidelines
Patients with irresectable, recurrent and/or metastatic ependymoma that are not amenable to radiotherapy can be treated with palliative chemotherapy consisting of cisplatin and etoposide, provided that adequate performance status is present (at the discretion of the physician). Unfit patients may be treated with oral etoposide or temozolomide. Chemotherapy is not indicated for adults with resectable ependymomas, or when radiotherapy is possible.

14.3.1. Cisplatin-etoposide courses
Schedule
One cycle consists of:
Cisplatin 20 mg/m^2 d.1-5 IV
Etoposide 100 mg/m^2 d.1-5 IV
Repeat cycle after 21 days. Courses maybe continued in the absence of progression, in the presence of good tolerance and clinical condition. Generally 4-6 cycles is a maximum, mainly because of hematological, neuro- or nephrotoxicity.

Administration of cisplatin-etoposide
Cisplatin will be dissolved in 1000 ml NaCl 0.9% and administered over four hours.
Etoposide will be administered in 500 ml NaCl 0.9% and administered over one hour.

Suggested premedication and supportive care of cisplatin-etoposide
Anti-emetics:
Aprepitant 125 mg PO day 1, 80 mg PO days 2-5.
Dexamethasone 10 mg IV prior to infusion of cytostatic drugs.
5HT3 antagonist (e.g. ondansetron 8 mg PO or IV or granisetron 1 mg PO or IV) prior to infusion of cytostatic drugs, to be repeated in the evening.
Metoclopramide 10-20 mg up to 3 dd in case of nausea/vomiting.

Hydration: a minimum of 2000 mL NaCl 0.9% hydration per 24 h is warranted on days of cisplatin administration, with potassium-, magnesium- and calciumsupplementation.
Growth factors: only in case of febrile neutropenia in the first course or prolonged delay due to hematological toxicity (see hematological toxicity) if it is decided to continue on 100% dose rather than apply a dose reduction.

Toxicity and dose modifications of cisplatin-etoposide
Hematological toxicity
At the start of each cycle of chemotherapy the absolute neutrophil count (ANC) should be ≥ 1 x 10^9/L, and platelets ≥ 100,000 x 10^9/L. In case count recovery is delayed, monitor counts on a twice weekly

basis. As soon as counts recover (but within 2 weeks), the second cycle is administered *at the original dose*. If courses have to be delayed for less than 2 weeks more than once, a dose reduction to 80% is advised. If febrile neutropenia has occurred, the next course may either be delivered at the original dose with PEGfilgrastim support the day after the last chemotherapy administration, or a dose reduction to 80% may be applied . In case chemotherapy has to be delayed for 2 weeks or more, the next course will be delivered at 80% of the original dose for both agents. In the 5-day schedule, an 80% dose reduction is most conveniently carried out by dosing 4 rather than 5 days, at the original daily dose for each drug.

Premenopausal females may be prescribed orgametril in case of grade 3-4 thrombopenia (i.e. platelets < 50 x 10^9/l) during treatment, in order to minimize menstrual blood loss. Because the majority of female patients will be on either oral contraceptives or LH-RH agonists, the chances of heavy menstrual bleeding seem remote.

Non-hematological toxicity
For grade 3 or 4 mucositis, the next course will be delayed until recovery to grade 0 or 1. The second cycle may be administered at 80% of the etoposide dose (i.e. 120 mg/m^2 d.1 and 2), with 100% of the cisplatin dose.
All other toxicities (save alopecia) should resolve until grade 1 or 0 before the second course is started. In case of dose delay of 2 or more weeks, the next course will be delivered at 80% of the original dose for both agents.

14.3.2. Oral etoposide courses
Schedule
One cycle consists of:
Etoposide 50 mg/m^2/day orally for 21 consecutive days followed by a 14-day break. The next cycle starts at day 36.

Courses maybe continued in the absence of progression, in the presence of good tolerance and clinical condition. There is no absolute maximum to the duration of treatment.

Suggested premedication and supportive care of oral etoposide
Anti-emetics: Although no initial anti-emetic schedule is advised, metoclopramide 10mg up to 6 dd in case of nausea/vomiting is usually prescribed. If that is not effective, 5HT3 antagonist (e.g. 1-2 DD ondansetron 8 mg PO or granisetron 1 mg PO) may be prescribed.
Hydration: no specific hydration schedule required.
Growth factors: not advised.

Toxicity and dose modifications of oral etoposide

Hematological toxicity
At the start of each cycle of chemotherapy the absolute neutrophil count (ANC) should be ≥ 1 x 10^9/L, and platelets ≥ 100,000 x 10^9/L. In case count recovery is delayed then monitor counts on a weekly basis. As soon as counts recover, the next cycle is administered at 80% of the original dose.
Premenopausal females may be prescribed orgametril in case of grade 3-4 thrombopenia (i.e. platelets < 50 x 10^9/l) during treatment, in order to minimize menstrual blood loss. Because the majority of female patients will be on either oral contraceptives or LH-RH agonists, the chances of heavy menstrual bleeding seem remote.

Non-hematological toxicity
For grade 3 or 4 mucositis, the next course will be delayed until recovery to grade 0 or 1. The second cycle may be administered at 80% of the etoposide dose (i.e. 40 mg/m^2).

All other toxicities (save alopecia) should resolve until grade 1 or 0 before the second course is started. In case of dose delay of 1 or more weeks, the next course will be delivered at 80% of the original dose.
Since this is palliative chemotherapy for unfit patients, in case of considerable side-effects the treatment plan should be re-evaluated, and stopping chemotherapy should be strongly considered.

14.3.3. Temozolomide courses
Schedule
One cycle consists of:
Temozolomide 150 mg/m2/day (200 mg/m2/day in chemotherapy-naïve patients) orally for 5 consecutive days every 4 weeks. The next cycle starts at day 29. If the first cycle was tolerated well, the following cycles can be dosed at 200 mg/m2/day.
There is a maximum of 12 cycles for the duration of treatment.

Suggested premedication and supportive care of temozolomide
Anti-emetics: Ondansetron 8 mg one hour prior to temozolomide administration on days 1 and 2 of every cycle as standard prophylactic anti-emetic scheme. Furthermore, metoclopramide 10mg up to 6 dd in case of nausea/vomiting is usually prescribed. If that is not effective, 5HT3 antagonist (e.g. 1-2 DD ondansetron 8 mg PO or granisetron 1 mg PO) may be prescribed.
Hydration: no specific hydration schedule required.
Growth factors: not advised.

Toxicity and dose modifications of temozolomide
Hematological toxicity
At the start of each cycle of chemotherapy the absolute neutrophil count (ANC) should be ≥ 1.5 x 109/L, and platelets ≥ 100,000 x 109/L. In case count recovery is delayed then monitor counts on a weekly basis. As soon as counts recover, the next cycle is administered at 75% of the original dose. Premenopausal females may be prescribed orgametril in case of grade 3-4 thrombopenia (i.e. platelets < 50 x 109/l) during treatment, in order to minimize menstrual blood loss. Because the majority of female patients will be on either oral contraceptives or LH-RH agonists, the chances of heavy menstrual bleeding seem remote.
Non-hematological toxicity
All other toxicities should resolve until grade 1 or 0 before the next course is started. In case of dose delay of 1 or more weeks, the next course will be delivered at 75% of the original dose.

15   Follow up

The interval between primary disease and recurrence varies greatly in the literature, depending on patient characteristics (age, tumor grade, location), extent of surgery and length of follow up.

Intracranial:
Recurrences occur in 15-66% of patients and PFS ranges from 43-84% at 5 years to 24-78% at 10 years (Ghia 2013, Guyotat 2002, Metellus 2010, Reni 2004) .
In published retrospective series on adult patients, most recurrences (up to 86%) were reported within the first 5 years of follow up, with median intervals ranging from 12-18 months (Guyotat 2002, Kawabata 2005). Still, frequent recurrences have been reported from 5-10 years of follow up. Most study describe 86-89% of recurrences within the first 5 years (Kabawata 2005, Asaid 2015, Sayegh 2014, McLaughlin 1998) or 95-100% of recurrences within 10 years of follow up (Ghia 2013, Swanson 2011).
Intracranial ependymoma relapse occurs predominantly at the primary tumor site (Taylor 2004, Guyotat 2002, McLaughlin 1998, Swanson 2011, Metellus 2010). Spinal relapses are rare (0-15%) and isolated spinal relapses are even more rare, especially in GII tumors (Swanson 2011, Kawabata 2005, Metellus 2010, Taylor 2004). Routine spinal imaging therefore seems unnecessary unless symptoms are present. If a recurrence is found, MRI of the entire craniospinal axis should be performed as combined local and distal recurrences occur in 10-50% (McLaughlin 1998).

Spinal:
Reccurrences occur in 11-57% and PFS ranges from 40-87% at 5 years to 48-80% at 10 years (Gomez 2005, Lee 2013, Weber 2015, Abdullah 2015, Halvorsen).
Median time to recurrence is 26-82 months (range 2-324 months), with most relapses occurring within 10 years (Gomez 2005, Weber 2015, Halvorsen 2010, Asaid 2015). In some articles however, the median time to progression is > 10 years (Lee 2013, Vera-Bolanos 2015)

Suggested follow-up:
It seems reasonable to perform surveillance imaging most intensively in the first year after treatment, reducing frequency after this time and continuing surveillance until 10 years after treatment. For spinal ependymoma, this period should be extended to 15 years due to some very late recurrences.

Intracranial ependymoma
MRI brain only
-    year 1: every 3 months
-    year 2-5: every 6 months
-    year 5-10: every 12 months
At time of recurrence, MRI of the entire craniospinal axis is performed
NB patients should be referred to an endocrinologist, if radiation dose to pituitary gland exceeds 20 Gy. First referral should take place 1 year after radiation treatment.

Spinal ependymoma
MRI local site only
First MRI 3 months after surgery
If no residual tumor present:
-    year 1: every 6 months
-    year 2-10: every 12 months
-    year 10-15: every 24 months

If residual tumor present:
-    follow-up as in intracranial ependymoma, after 10 years MRI every 24 months

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