Ependymoma in Adults

Evaluation and Treatment Protocol

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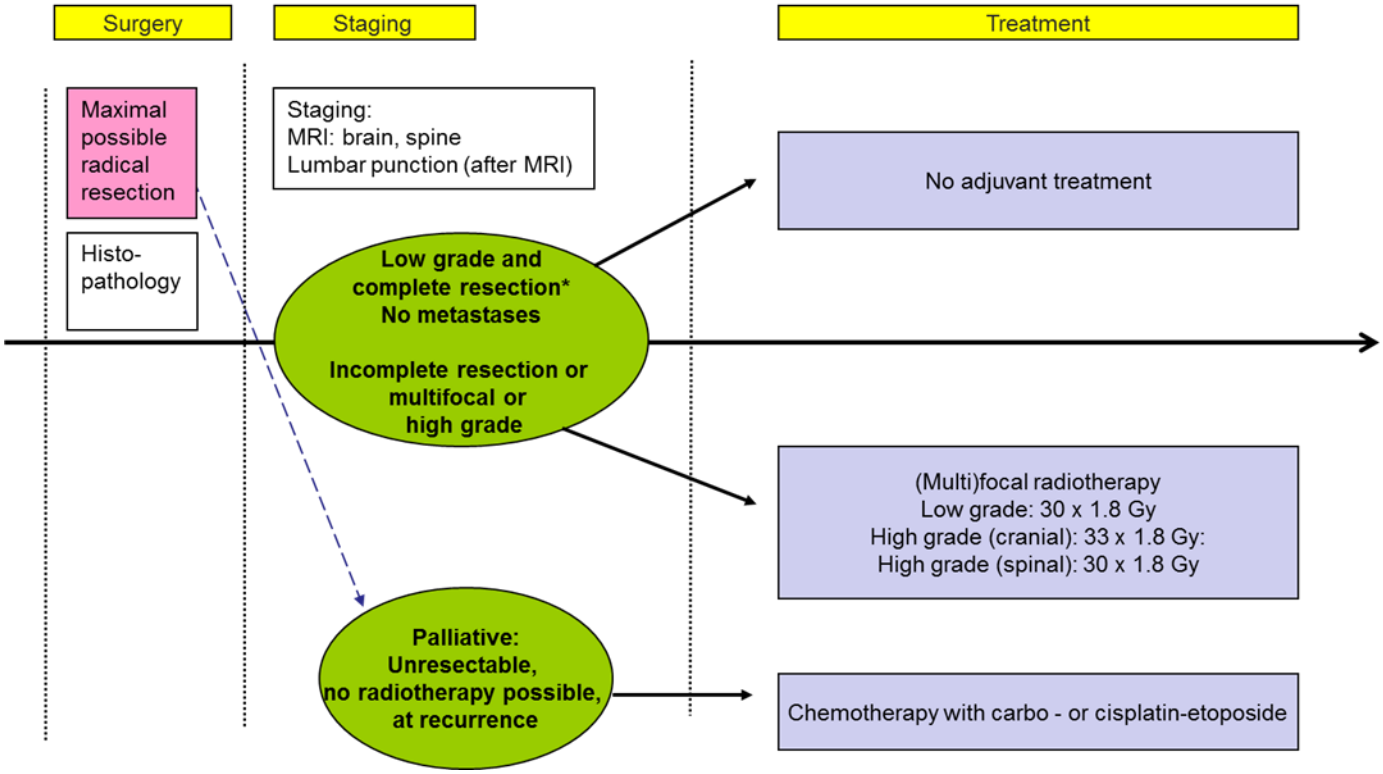
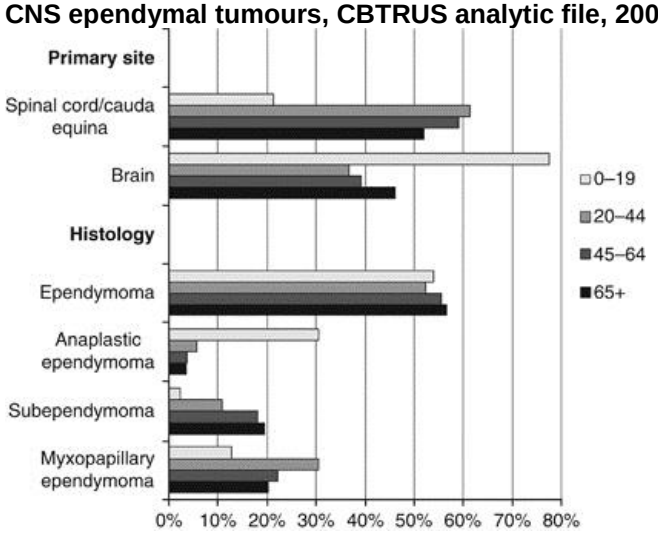

Surgery
Staging
Treatment
Maximal possible radical resection
Histo-pathology
Staging:
MRI: brain, spine
Lumbar punction (after MRI)
Low grade and complete resection*
No metastases
Incomplete resection or multifocal or high grade
Palliative:
Unresectable,
no radiotherapy possible,
at recurrence
No adjuvant treatment
(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
Chemotherapy with carbo - or cisplatin-etoposide

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.[1, 2] 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.[3, 4] 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;[5] 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.[5] Ependymoma's may occur at all ages but peak incidence is found at 0-4 years and at 55-59 years.[6] 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.[7, 8]

Figure 1. Distribution of age groups in site and histology categories for all primary brain and CNS ependymal tumours, CBTRUS analytic file, 2004–2009.[6]



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).[2] Accordingly, in adults 50-60% of ependymomas are spinal, 20-25% supratentorial and 10% infratentorial, the remainder being not otherwise specified.[1, 2, 5, 6, 9] In children intracranial location, especially infratentorially, and anaplastic histology is more frequent than in adults.[6] 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.[1, 10] Only very rarely is microscopic leptomeningeal seeding found without macroscopic metastastic disease visible on MRI.[11] 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.[12]

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.[2, 5] 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.[2, 2, 10, 10, 13, 13]
Progression free survival is reported to be 43-65% at 5 years for intracranial ependymoma and 70-75% for spinal ependymoma's.[10] Median time to progression in spinal ependymoma is 68 months (range 2-324 months).[14]

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.[7, 9] 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%).[7, 9] 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%).[9, 15]

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.[16]
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.[16]
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.[16] 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.[16]

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.[16]

7 Pathology

7.1 Definition
Ependymal tumors are glial neoplasms of the central nervous system and considered to originate from (precursors of) the 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 classified by the current WHO classification (Louis 2007)[4] as benign (WHO grade I), low-grade malignant (WHO grade II) and high-grade malignant (WHO grade III). The biological behavior of these tumors, however, depends also on the age at presentation and the location of the tumor (see below). Moreover, benign tumors (especially myxopapillary ependymoma) may show seeding within the dural compartment along cerebrospinal fluid pathways, a phenomenon that in itself does not imply malignant progression of the tumor.

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 (esp. intramedullary), 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 (Amiran 2012).[5] Tumors in the 4th ventricle may extend via the foramina of Luschka en Magendi into the subarachoid space.
Myxopapillary ependymoma occurs especially in the lumbosacral part of the spinal cord (conus medullaris and filum terminale/cauda equina)

7.4 Microscopy
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, representing intracytoplasmatic microlumina as can be identified with electron microscopy.
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). 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 2007).[4]

7.5 Prognostic factors
Prognostic factors are: completeness of tumor resection, localization, WHO grade, age, extent of disease at presentation, molecular characteristics (Kim 2013).[17] Also, the Ki-67/MIB-1 labeling index is associated with prognosis (Louis 2007).[4]

De prognostic value of the current histopathological grading of ependymal tumors as low- versus high-grade malignant is not that clear, also because the inter-observer variation in grading of these tumors is substantial (Ellison 2011).[18] Moreover, the clinical relevance of specific histopathological features may well depend on the localization of the tumor.[19, 20] (Raghunathan 2013; Godfraint 2012). Hopefully, in the near future molecular markers will guide towards a more robust and clinically relevant grading of ependymal tumors. However, molecular markers that provide unequivocal

prognostic information in daily clinical practice are not yet routinely available (Mack 2013, Kim 2013, Nagasawa 2013).[17, 21, 22]

7.6 Molecular pathology

It is increasingly clear that in the different compartments the ependymal tumors have a different genetic profile (Nagasawa 2013, Wani 2012, Witt 2012).[22-24] Supratentorial tumors are reported to show loss of the tumor suppressor P16INK4A (localised on chromosome 9p21.3) and high expression of members of the EphB-Ephrin en Notch signaling pathways.

In the posterior fossa, relatively mild genomic instability with gain of chromosome 1q en loss of 22q can be found in ependymomas in children and was associated with a poor prognosis. Furthermore, multiple cancer-related pathways can be involved in pediatric ependymomas (e.g. HIF-1a, VEGF, PDGF, MAPK, EGFR, TGF-b, tyrosine-receptor kinase, RAS, and integrin/ECM signaling), whereas in adults two other pathways (microtubule assembly/ciliogenesis and mitrochondrial/oxidative metabolism) are more often disturbed.

Both in adults and children, ependymal tumors in the spinal canal frequently show loss of chromosome 22q. In patients with Neurofibromatosis type 2 (NF2) mutations in the *NF2* gene (localized on chromosome 22q12) is often found, while in spinal ependymomas in children *NF2* gene abnormalities are often lacking. In myxopapillary ependymomas upregulation of genes of the HOX family is reported.

It is to be expected that in the near future more detailed and robust information on the molecular background of ependymal tumors will allow for improved assessment of prognosis and therapeutic decision making.

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. Thus, a gross total resection (GTR) is optimal.[1,2,19] 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.[11] Due to these factors, complete tumor removal may therefore be achieved in several stages, using "second-look" resections,[16] 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.[20]

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.[12]

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.[3,4] 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.[5] Recent publications have not been able to solve the controversy, some series advocating surgical removal as the only treatment except in selected cases,[3,4] while others argue in favour of adjuvant radiotherapy in all cases.[6,7,8]

Although there is substantial controversy about the surgical technique, resection 'en bloc' without opening the capsule versus piecemeal using ultrasonic aspiration,[9,10] 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.[21]
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.[18]
Concerning timing of surgery it is generally accepted that the surgery is performed before significant neurological deterioration occurs[22] 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.[23]

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.[12,13,14,15]
Mutism may especially occur when the tumor involves the vermis or brainstem, sometimes even weeks after surgery.[14] 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 because of a combination of patients with spinal and cerebral tumours in one study, mixture of adult and paediatric patients, inclusion of patients from different surgical and diagnostic eras, differences in radiotherapy, total dose, extent of portals (local versus craniospinal), adjuvant chemotherapy, differences in pathology, mixing grades, and 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).

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)

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) 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, OH, Akyurek, Pica). 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). Adjuvant radiotherapy was given for 58.8% (47/80) of the patients with STR and for 3.7% of the patients after GTR (Oh). 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).

Literature is more or less clear on the fact, that there is no role for prophylactic or adjuvant craniospinal irradiation (Grabenbauer, Vanuytsel). 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 2006). 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). 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 2006, 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. This observation has lead in the past to irradiate prophylactic the craniospinal axis to eradicate circulating malignant cells. But the true incidence of seeding is unknown. There are indications that spinal seeding of intracranial ependymoma depends on location of the tumour as well as the histological grade (see Figure 1). Pre-mortem cytological examination of the spinal fluid revealed circulating malignant cells in 0-15% of not selected cases (Gonzalez et al 1982, Calvo et al 1983).

Figure 1. Spinal seeding is related with grade and location

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

A review of the literature undertaken by Vanuysel and Brada in 1991 showed that spinal metastases are not prevented by prophylactic spinal irradiation, regardless of tumour grade and site.
In principal there is no role or indication for craniospinal irradiation. Tumor grade, localization, and control of the tumor at the primary site are all factors which may influence the risk of spinal seeding. Spinal metastases were not prevented by prophylactic spinal irradiation, regardless of tumor grade and site (Vanuytsel 1991).

9.3 Radiotherapy target volume
Local radiotherapy may vary from irradiation of the total posterior fossa to a treatment volume of 1-2 cm margins around the clinical target volume. The introduction of improved imaging and MRI made a more accurate definition of the tumour (gross tumour volume) possible both for intracranial and spinal tumour localizations. Interpretation of the target volume based as in older series on CT, is difficult and no longer the current standard for radiotherapy volume definition for ependymoma.

9.4 Radiotherapy dose
It is difficult to analyse 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 (Ayurek, Pica, Shaw, Schild).

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). Re-irradiation after primarily postoperative radiotherapy may be the treatment of choice for recurrent patients having less than complete resection or no surgery (Kocak). Local reirradiation with highly accurate and focal radiation techniques such as stereotactic radiosurgery for small tumours (Stafford, Jawahar), stereotactic fractionated radiotherapy for larger tumours or as a boost in high risk ependymomas (Aggarwal) or intensity-modulated radiotherapy techniques (like VMAT) are also an option 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 tumors with a lower grade (WHO grades I and II and myxopapillary spinal tumours) the treatment strategy should be complete resection without adjuvant radiotherapy. Partially resected tumours, piecemeal resection, biopsy only or no second operation possible should be followed by local radiotherapy as for subtotally resected tumors (STR) progression-free survival is longer if STR is followed by adjuvant local radiotherapy. This is independent of the primary tumor location being intracranial, supra- or infratentorial or spinal. A gross total resection (GTR) is associated with the best overall survival and progression-free survival.
High grade tumours (WHO grade III) should irradiated adjuvant and postoperatively independent of radicality of resection, either after GTR or STR.

In principle there is no role or indication for craniospinal irradiation. In case of multiple spinal lesions, also local irradiation is preferable when possible. In exceptional cases for symptomatic multifocal lesions craniospinal radiotherapy can be given.

10 Chemotherapy

Prospective data for systemic therapy in adult ependymoma are entirely lacking . A recent publication on adult ependymoma does not even mention chemotherapy. 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, 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 etoposide6. 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. 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, but it is not regarded as standard treatment. Neither is craniospinal irradiation for this indication, although it has also been reported.

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. 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. 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 . As high levels of MGMT (an enzyme that confers resistance to alkylating agents such as temozolomide) 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 . High dose chemotherapy does not seem to be effective in paediatric ependymoma , 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 .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.

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 . Bevacizumab has been tested in children with tumors refractory to platinum-containing therapy, with conflicting results. In a small retrospective study of eight heavily pretreated adult ependymoma patients, objective non-durable response was observed in six patients. One adult patient with a PDGFR-positive spinal cord ependymoma responded to imatinib, after progression on previous therapy . Current phase II studies in adult ependymoma include temozolomide and lapatinib and carboplatin-bevacizumab , 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. 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 (2013), http://dx.doi.org/10.1016/j.clon.2013.07.009

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 ≥ 18

12.2 Registration

After diagnosis and informed consent all adult patients with an ependymoma should be registered at the IKNL Trial bureau (Integraal Kankercentrum Nederland), c/o UMCU huispost F02-162 postbus 85500 3508 GA Utrecht. Tel: 088-755 6286, fax: 088-755 5462.

At least the following information should be registered for each patient:
- date of birth;
- sex;
- patient hospital registration number;
- treating physician; 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

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 postoperative MRI. This accounts 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 high grade tumors , which should include subclinical microscopic disease beyond the GTV. 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 2009, 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). The CTV is anatomically confined and limited by normal tissue structures through which tumour extension is largely unlikely like e.g. the falx or the tentorium.

For spinal locations the intravertebral foramina shall be part of the CTV.

The planning target volume (PTV) is defined as the CTV with an additional margin of to correct for movement and set-up inaccuracies and is mostly in the range of 5 mm in three dimensions for uncertainly in patient positioning and image registration.

14.2.2 Craniospinal irradiation (exceptional cases)
Whole Brain Volume
The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. In order to include the cribriform fossa within the CTV, and allowing an additional appropriate margin for PTV, the edge of the field (i.e. the geometric edge of the shielding block) would in many cases include the lenses. The geometric edge of the shield on the film should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull (paying particular attention to the margin around the inferior aspect of the temporal lobes). The margin between the shielding and the anterior border of the upper cervical vertebrae should be 0.5 cm. The lower border of the cranial fields should form a precise match with the upper border of the spinal field.
Cervical Spinal Volume
As much as possible of the cervical spinal volume is included in the lateral cranial fields with the junction between the cranial and spinal fields kept as inferior as possible. This is advised for avoidance of as much thyroid tissue irradiation as possible, by shielding this within the “cranio-cervical” volume.
Dorso-Lumbar Spine Volume
The inferior limit of the spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MR and will usually extend inferiorly to at least the lower border of the second sacral vertebra.

Metastasis boost
- The same definitions as for the primary tumour apply.

14.2.3 Dose and fractionation
Low-grade ependymoma
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

High-grade ependymoma
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

Craniospinal irradiation
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
Mainly highly conformal radiotherapy techniques should be used. Dose and fractionation can range from radiosurgery to conventionally fractionated (stereotactic) radiotherapy depending on the volume of the lesion and the time period since first radiotherapy. Radiosurgery with 1x 15 – 18 Gy, hypofractionated schemes like 3 x 8 Gy 3 x a week or 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. 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.

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, Guyotat, Metellus, Reni) .
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, Kawabata). 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, Asaid, Sayegh, McLaughlin) or 95-100% of recurrences within 10 years of follow up (Ghia, Swanson).
Intracranial ependymoma relapse occurs predominantly at the primary tumor site (Taylor, Guyotat, McLaughlin, Swanson, Metellus). Spinal relapses are rare (0-15%) and isolated spinal relapses are even more rare, especially in GII tumors (Swanson, Kawabata, Metellus, Taylor). 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).

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

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

References

References sections 4–7

1. Reni M, Gatta G, Mazza E, Vecht C. Ependymoma. Crit Rev Oncol Hematol 2007;63(1):81-89.
2. Rodriguez D, Cheung MC, Housri N, Quinones-Hinojosa A, Camphausen K, Koniaris LG. Outcomes of malignant CNS ependymomas: an examination of 2408 cases through the Surveillance, Epidemiology, and End Results (SEER) database (1973-2005). J Surg Res 2009;156(2):340-351.
3. Rushing EJ, Cooper PB, Quezado M et al. Subependymoma revisited: clinicopathological evaluation of 83 cases. J Neurooncol 2007;85(3):297-305.
4. Louis D.N., Ohgaki H. WODCWK. WHO Classification of Tumours of the Central Nervous System. 4th ed. Lyon: IARC Press; 2007.
5. Amirian ES, Armstrong TS, Aldape KD, Gilbert MR, Scheurer ME. Predictors of survival among pediatric and adult ependymoma cases: a study using Surveillance, Epidemiology, and End Results data from 1973 to 2007. Neuroepidemiology 2012;39(2):116-124.
6. Villano JL, Parker CK, Dolecek TA. Descriptive epidemiology of ependymal tumours in the United States. Br J Cancer 2013;108(11):2367-2371.
7. Oh MC, Kim JM, Kaur G et al. Prognosis by tumor location in adults with spinal ependymomas. J Neurosurg Spine 2013;18(3):226-235.
8. Engelhard HH, Villano JL, Porter KR et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equina. J Neurosurg Spine 2010;13(1):67-77.
9. Armstrong TS, Vera-Bolanos E, Bekele BN, Aldape K, Gilbert MR. Adult ependymal tumors: prognosis and the M. D. Anderson Cancer Center experience. Neuro Oncol 2010;12(8):862-870.
10. Ruda R, Gilbert M, Soffietti R. Ependymomas of the adult: molecular biology and treatment. Curr Opin Neurol 2008;21(6):754-761.
11. Fangusaro J, Van Den Berghe C, Tomita T et al. Evaluating the incidence and utility of microscopic metastatic dissemination as diagnosed by lumbar cerebro-spinal fluid (CSF) samples in children with newly diagnosed intracranial ependymoma. J Neurooncol 2011;103(3):693-698.
12. Moreno L, Pollack IF, Duffner PK et al. Utility of cerebrospinal fluid cytology in newly diagnosed childhood ependymoma. J Pediatr Hematol Oncol 2010;32(6):515-518.
13. Metellus P, Guyotat J, Chinot O et al. Adult intracranial WHO grade II ependymomas: long-term outcome and prognostic factor analysis in a series of 114 patients. Neuro Oncol 2010;12(9):976-984.
14. Gomez DR, Missett BT, Wara WM et al. High failure rate in spinal ependymomas with long-term follow-up. Neuro Oncol 2005;7(3):254-259.
15. Armstrong TS, Vera-Bolanos E, Gilbert MR. Clinical course of adult patients with ependymoma: results of the Adult Ependymoma Outcomes Project. Cancer 2011;117(22):5133-5141.
16. Yuh EL, Barkovich AJ, Gupta N. Imaging of ependymomas: MRI and CT. Childs Nerv Syst 2009;25(10):1203-1213.
17. Kim JH, Huang Y, Griffin AS, Rajappa P, Greenfield JP. Ependymoma in children: molecular considerations and therapeutic insights. Clin Transl Oncol 2013;15(10):759-765.
18. Ellison DW, Kocak M, Figarella-Branger D et al. Histopathological grading of pediatric ependymoma: reproducibility and clinical relevance in European trial cohorts. J Negat Results Biomed 2011;10:7.
19. Raghunathan A, Wani K, Armstrong TS et al. Histological predictors of outcome in ependymoma are dependent on anatomic site within the central nervous system. Brain Pathol 2013;23(5):584-594.
20. Godfraind C, Kaczmarska JM, Kocak M et al. Distinct disease-risk groups in pediatric supratentorial and posterior fossa ependymomas. Acta Neuropathol 2012;124(2):247-257.
21. Mack SC, Witt H, Wang X et al. Emerging insights into the ependymoma epigenome. Brain Pathol 2013;23(2):206-209.
22. Nagasawa DT, Trang A, Choy W et al. Genetic expression profiles of adult and pediatric ependymomas: molecular pathways, prognostic indicators, and therapeutic targets. Clin Neurol Neurosurg 2013;115(4):388-399.

23. Wani K, Armstrong TS, Vera-Bolanos E et al. A prognostic gene expression signature in infratentorial ependymoma. Acta Neuropathol 2012;123(5):727-738.
24. Witt H, Korshunov A, Pfister SM, Milde T. Molecular approaches to ependymoma: the next step(s). Curr Opin Neurol 2012;25(6):745-750.

References section 8

1. Kucia EJ, Maughan PH, Kakarla UK, Bambakidis NC, Spetzler RF. Surgical technique and outcomes in the treatment of spinal cord ependymomas: Part II: Myxopapillary ependymoma. Neurosurgery 2011;68(1 Suppl Operative):90-4.
2. Duffner PK, Krischer JP, Sanford RA, et al: Prognostic factors in infants and very young children with intracranial ependymomas. Pediatr Neurosurg 28:215–222, 1998
3. Bagley CA, Wilson S, Kothbauer KF, Bookland MJ, Epstein F, Jallo GI. Long term outcomes following surgical resection of myxopapillary ependymomas. Neurosurg Rev 2009;32:321-34
4. Kucia EJ, Maughan PH, Kakarla UK, Bambakidis NC, Spetzler RF. Surgical technique and outcomes in the treatment of spinal cord ependymomas: Part II: Myxopapillary ependymoma. Neurosurgery 2011;68(1 Suppl Operative):90-4
5. Plans G, Brell M, Cabiol J, Villà S, Torres A, Acebes JJ. Intracranial retrograde dissemination in filum terminale myxopapillary ependymomas. Acta Neurochir (Wien) 2006;148:343-6
6. Al-Halabi H, Montes JL, Atkinson J, Farmer JP, Freeman CR. Adjuvant radiotherapy in the treatment of pediatric myxopapillary ependymomas. Pediatr Blood Cancer 2010;55:639-43
7. Pica A, Miller R, Villà S, Kadish SP, Anacak Y, Abusaris H, et al. The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: A retrospective study from the rare cancer network. Int J Radiat Oncol Biol Phys 2009;74:1114-20
8. Wahab SH, Simpson JR, Michalski JM, Mansur DB. Long term outcome with post-operative radiation therapy for spinal canal ependymoma. J Neurooncol 2007;83:85-9
9. Fassett DR, Pingree J, Kestle JR. The high incidence of tumor dissemination in myxopapillary ependymoma in pediatric patients. Report of five cases and review of the literature. J Neurosurg 2005;102:59-64.
10. Nakamura M, Ishii K, Watanabe K, Tsuji T, Matsumoto M, Toyama Y, et al. Long-term surgical outcomes for myxopapillary ependymomas of the cauda equina. Spine (Phila Pa 1976) 2009;34:E756-60
11. Spagnoli D, Tomei G, Ceccarelli G, et al. Combined treatment of fourth ventricle ependymomas: report of 26 cases. Surg Neurol 2000; 54: 19-26
12. Hahn YS, Ciro E: Family and the child with a posterior fossa tumor, in Raimondi AJ, Choux M, DiRocco C (eds): Posterior Fossa Tumors. New York: Springer-Verlag, 1993, pp 201–210
13. Lyons MK, Kelly PJ: Posterior fossa ependymomas: report of 30 cases and review of the literature. Neurosurgery 28: 659–665, 1991
14. Pollack IF, Polinko P, Albright AL, et al: Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. Neurosurgery 37: 885–893, 1995
15. Sanford RA, Kun LE, Heideman RL, et al: Cerebellar pontine angle ependymoma in infants. Pediatr Neurosurg 27:84–91, 1997
16. Foreman NK, Love S, Thorne R: Intracranial ependymomas: analysis of prognostic factors in a population-based series. Pediatr Neurosurg 24:119–125, 1996
17. Dohrmann GJ: Ependymomas, in Wilkins RH, Rengachary SS, (eds): Neurosurgery, ed 2. New York: McGraw-Hill Companies, 1996, Vol 1, pp 1195–1200
18. Kucia EJ, Bambakidis NC, Chang SW, Spetzler RF. Surgical technique and outcomes in the treatment of spinal cord ependymomas, part 1: intramedullary ependymomas. Neurosurgery. 2011 Mar;68(1 Suppl Operative):57-63; discussion 63. doi: 10.1227/NEU.0b013e318208f181
19. Philippe Metellus, Dominique Figarella-Branger, Jacques Guyotat, Marylin Barrie, Roch Giorgi, Anne Jouvet, Olivier Chinot. Supratentorial Ependymomas: Prognostic Factors and Outcome Analysis in a Retrospective Series of 46 Adult Patients. Cancer July 1, 2008, Volume 113 / Number 1, 175-185
20. Schwarz TH et al. Supratentorial Ependymomas in adult patients. Neurosurgery 1999, Apr; 44 (4): 721-731

21. Lars de Jong, Frank Van Calenbergh, Johan Menten, Johannes van Loon, Steven De Vleeschouwer, Christiaan Plets, Mehrnaz Didgar, Raf Sciot, Jan Goffin. Ependymomas of the filum terminale: The role of surgery and radiotherapy, Surg Neurol Int 2012, 3:76
22. Epstein, FJ, Farmer JP, Freed D. Adult intramedullary astrocytomas of the spinal cord. J Neurosurg 1992, 77:355-359
23. Elisa J. Kucia, Nicholas C. Bambakidis, Steve W. Chang, Robert F. Spetzler. Surgical Technique and Outcomes in the Treatment of Spinal Cord Ependymomas, Part 1: Intramedullary Ependymomas. Neurosurgery, vol 68, operative neurosurgery 1, march 2011 (DOI: 10.1227/NEU.0b013e318208f181)

References section 9

Intracranial ependymoma

- Bloom HJG, Glees J, Bell J. The treatment and long-term prognosis of children with intracranial tumors. A study of 610 cases, 1950-1981 Int. J. Radiat. Oncol. Biol. Phys. 1991;18:723-745.
- Calvo FA, Hornedo J, de la Torre A, et al: Intracranial tumors with risk of dissemination in neuroaxis. Int J Radiat Oncol Biol Phys 1983 9:1297-1301,
- Dutzmann S et al. A multri-center retrospective analysis of treatmet effects and quality of life in adult patients with cranial ependymomas J Neurooncol 2013 114:319-327
- Dűtzmann S et al. A multi-centric retrospective analysis of treatment effects and quality of life in adult patients with cranial ependymomas. J. Neurooncol 2013 114:319-327
- Figarella-Branger D et al. Intracranial ependymomas in adult patients. Diagnosis and histological factors Neurochirurgie 2007 53:76-84
- Gonzalez,D Van der Schueren E, Breur K. Results of postoperative radiotherapy in intracranial ependymomas: a review of twenty-six cases. In: Hildebrand J, Gangji D, eds. Treatment of neoplastic lesions of the nervous system. New York: Pergamon Press 1982:111-115
- Kim YL Retrospective analysis of treatment outcome of pediatric ependymomas in Korea: analysis of Korean multi-institutional data. J. Neurooncol 2013 113:39-48
- Mansur et al Postoperative radiation therapy for grade II and III intracranial ependymoma Int J Radiat Oncol Biol Phys. 2005 61(2) 387-91
- Metellus et al. Multicentric French study on adult intracranial ependymomas: prognostic factors analysis and therapeutic considerations from a cohort of 152 patients. Brain 2007 130 ; 1338-49
- Metellus et al. Adult intracranial WHO grade II ependymomas: long-term outcome and prognostic factor analysis in a series 0f 114 patients Neuro Oncol. 2010 Sep;12(9):976-84
- Metellus P, et al. Intracranial ependymomas in adult patients. Retrospective analysis of 121 cases from the multicentric French study] Neurochirurgie. 2007 Jun;53 :66-75.
- Nazar GB, Hoffman HJ,BeckerJE et al: Infratentorial ependymomas in childhood: prognostic factors and treatment. J Neurosurg 1990;72:408-417.
- Paulino AC et al. Intracranial ependymomas: an analysis of prognostic factors and patterns of failure Am J Clin oncol 2002 25(2) 117-22
- Paulino AC. The local field in infratentorial ependymoma: does the entire posterior fossa need to be treated. Int J Radiat Oncol Biol Phys 2001 49(3):757-61
- Paulino AC, Radiotherapeutic management of intracranial ependymoma. Pediatr Hematol Oncol. 2002 Jul-Aug;19(5):295-308.
- Swanson et al. Intracranial ependymomas treated with radiotherapy : lonterm results from a single institute J Neurooncol. 2011 May;102(3):451-7.
- Taylor RE. Part of proceedings Review of radiotherapy Dose and volume for intracranial ependymoma Pediatr blood cancer 2004: 42:457-460
- Taylor. Review of radiotherapy dose and volume for intracranial ependymoma. Pediatr blood cancer 2004 42(5) 457-60
- Vanuytsel L, Brada M. The role of prophylactic spinal irradiation in localized intracranial ependymoma. Int J Radiat Oncol Biol Phys 1991 (21): 825-830

Spinal ependymoma

- Aggarwal R, Yeung D, Kumar P, Muhlbauer M and Kun LE. Efficacy and feasability of stereotactic radiosurgery in the primary management of unfavorable pediatriuc ependymoma. Radiother Oncol 43:269-73, 1997.

- Akyurek S, Chang EL, Yu TK, et al. Spinal myxopapillary ependymoma outcomes in patients treated with surgery and radiotherapy at M.D. Anderson Cancer Center. J Neurooncol 2006;80:177–183.
- Chao ST, Kobayashi T, Benzel E, Reddy CA, Stevens GH, Prayson RA, Kalfas I, Schlenk R, Krishnaney A, Steinmetz MP, Bingaman W, Hahn J, Suh JH. The role of adjuvant radiation therapy in the treatment of spinal myxopapillary ependymomas. J Neurosurg Spine. 2011 Jan;14(1):59-64.
- Clover LL, Hazuka MB, Kinzie JJ. Spinal cord ependymomas treated with surgery and radiation therapy. A review of 11 cases. Am J Clin Oncol. 1993 Aug;16(4):350-3.
- de Jong L, Calenbergh FV, Menten J, van Loon J, De Vleeschouwer S, Plets C, Didgar M, Sciot R, Goffin J. Ependymomas of the filum terminale: The role of surgery and radiotherapy. Surg Neurol Int. 2012;3:76.
- Feldman WB, Clark AJ, Safaee M, Ames CP, Parsa AT. Tumor control after surgery for spinal myxopapillary ependymomas: distinct outcomes in adults versus children. J Neurosurg Spine. 2013 Aug 23. [Epub ahead of print]
- Ferrante L, Mastronardi L, Celli P, Lunardi P, Acqui M, Fortuna A. Intramedullary spinal cord ependymomas--a study of 45 cases with long-term follow-up. Acta Neurochir (Wien). 1992;119(1-4):74-9.
- Gavin Quigley D, Farooqi N, Pigott TJ, et al. Outcome predictors in the management of spinal cord ependymoma. Eur Spine J 2007;16:399–404.
- Gomez DR, Missett BT, Wara WM, Lamborn KR, Prados MD, Chang S, Berger MS, Haas-Kogan DA. High failure rate in spinal ependymomas with long-term follow-up. Neuro Oncol. 2005 Jul;7(3):254-9.
- Goumnerova: Results of stereotactic radiosurgery in the management of recurrent ependymoma. Proceedings VIIth Annual Symposium Pediatric NeuroOncology, Washington, Abstract 30, 1996
- Grabenbauer GG, Barta B, Erhardt J, Buchfelder M, Thierauf P, Beck JD, Sauer R. [Prognostic factors and results after the combined surgical and radiotherapy treatment of ependymomas].Strahlenther Onkol. 1992 Dec;168(12):679-85
- Jawahar A, Kondziolka D, Flickinger JC, Lunsford LD. Adjuvant stereotactic radiosurgery for anaplastic ependymoma. Stereotact Funct Neurosurg. 73:23-30, 1999.
- Kocak Z, Garipagaoglu M, Adli M, Uzal MC, Kurtman C. Spinal cord ependymomas in adults: analysis of 15 cases. J Exp Clin Cancer Res. 2004 Jun;23(2):201-6. Review.
- Lee SH, Chung CK, Kim CH, Yoon SH, Hyun SJ, Kim KJ, Kim ES, Eoh W, Kim HJ. Long-term outcomes of surgical resection with or without adjuvant radiation therapy for treatment of spinal ependymoma: a retrospective multicenter study by the Korea Spinal Oncology Research Group. Neuro Oncol. 2013 Jul;15(7):921-9.
- Lee TT, Gromelski EB, Green BA. Surgical treatment of spinal ependymoma and post-operative radiotherapy. Acta Neurochir (Wien). 1998;140(4):309-13.
- Lin YH, Huang CI, Wong TT, Chen MH, Shiau CY, Wang LW, Ming-Tak Ho D, Yen SH. Treatment of spinal cord ependymomas by surgery with or without postoperative radiotherapy. J Neurooncol. 2005 Jan;71(2):205-10.
- Liu X, Sun B, Xu Q, Che X, Hu J, Gu S, Shou J. Outcomes in treatment for primary spinal anaplastic ependymomas: a retrospective series of 20 patients.J Neurosurg Spine. 2013 Jul;19(1):3-11.
- Merchant TE, Boop FA, Kun LE, Sanford RA. A retrospective study of surgery and reirradiation for recurrent ependymoma. Int J Radiat Oncol Biol Phys. 2008 May 1;71(1):87-97.
- Nakamura M, Ishii K, Watanabe K, Tsuji T, Matsumoto M, Toyama Y, Chiba K. Long-term surgical outcomes for myxopapillary ependymomas of the cauda equina. Spine (Phila Pa 1976). 2009 Oct 1;34(21):E756-60.
- Oh MC, Ivan ME, Sun MZ, Kaur G, Safaee M, Kim JM, Sayegh ET, Aranda D, Parsa AT. Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord ependymomas. Neuro Oncol. 2013 Feb;15(2):208-15.
- Pica A, Miller R, Villa S, Kadish SP, Anacak Y, Abusaris H, Ozygit G, Baumert BG, Zaucha R, Haller G, Weber DC. The results of surgery, with or without radiotherapy, for primary spinal myxopapillary ependymoma: a retrospective study from the Rare Cancer Network. Int J Radiat Oncol Biol Phys. 2009;74(4):1114-20
- Sakai Y, Matsuyama Y, Katayama Y, Imagama S, Ito Z, Wakao N, Kanemura T, Yoshida G, Sato K, Ando T, Nakamura H, Kato F, Yukawa Y, Ito K, Ishiguro N. Spinal myxopapillary ependymoma:

neurological deterioration in patients treated with surgery. Spine (Phila Pa 1976). 2009 Jul 1;34(15):1619-24.
- Schild SE, Wong W, Nisi K. In regard to the radiotherapy of myxopapillary ependymomas. Int J Radiat Oncol Biol Phys 2002;53:787 (update of 1998 publication of same authors)
- Sgouros S, Malluci CL, Jackowski A. Spinal ependymomas--the value of postoperative radiotherapy for residual disease control.Br J Neurosurg. 1996 Dec;10(6):559-66.
- Shaw EG, Evans RG, Scheithauer BW, Ilstrup DM, Earle JD. Radiotherapeutic management of adult intraspinal ependymomas. Int J Radiat Oncol Biol Phys. 1986 Mar;12(3):323-7.Stafford SL, Pollock BE, Foote RL, Gorman DA, Nelson DF, Schomberg PJ. Stereotactic radiosurgery for recurrent ependymoma. Cancer 88:870-5, 2000.
- Stüben G, Stuschke M, Kroll M, Havers W, Sack H. Postoperative radiotherapy of spinal and intracranial ependymomas: analysis of prognostic factors. Radiother Oncol. 1997 Oct;45(1):3-10.
- Vanuytsel L, Brada M. The role of prophylactic spinal irradiation in localized intracranial ependymoma. Int J Radiat Oncol Biol Phys 1991;21:825–830.
- Volpp PB, Han K, Kagan AR, Tome M. Outcomes in treatment for intradural spinal cord ependymomas.Int J Radiat Oncol Biol Phys. 2007 Nov 15;69(4):1199-204.
- Wahab SH, Simpson JR, Michalski JM, Mansur DB. Long term outcome with post-operative radiation therapy for spinal canal ependymoma. J Neurooncol. 2007 May;83(1):85-9. Epub 2007 Jan 6.
- Waldron JN, Laperriere NJ, Jaakkimainen L, et al. Spinal cord ependymomas: A retrospective analysis of 59 cases. Int J Radiat Oncol Biol Phys 1993;27:223–229.
- Whitaker SJ, Bessell EM, Ashley SE, Bloom HJ, Bell BA, Brada M. Postoperative radiotherapy in the management of spinal cord ependymoma.J Neurosurg. 1991 May;74(5):720-8.
- Wright KD, Gajjar A. Current treatment options for pediatric and adult patients with ependymoma. Curr Treat Options Oncol. 2012 Dec;13(4):465-77.

References section 10

- Rudà R, Gilbert M, Soffietti R. Ependymomas of the adult: molecular biology and treatment. Curr Opin Neurol 2008;21(6):754-61.
- Dützmann S, Schatlo B, Lobrinus A, Murek M, Wostrack M, Weiss C, et al. A multi-center retrospective analysis of treatment effects and quality of life in adult patients with cranial ependymomas, J Neuro-Oncol, 2013;114:319-27.
- Garvin JH Jr, Selch MT, Holmes E, Berger MS, Finlay JL, Flannery A, et al. Children's Oncology Group. Phase II study of pre-irradiation chemotherapy for childhood intracranial ependymoma. Children's Cancer Group protocol 9942: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2012;59(7):1183-9. doi: 10.1002/pbc.24274. Epub 2012 Sep 4.
- Grundy RG, Wilne SA, Weston CL, Robinson K, Lashford LS, Ironside J, et al. Children's Cancer and Leukaemia Group (formerly UKCCSG) Brain Tumour Committee. Primary postoperative chemotherapy without radiotherapy for intracranial ependymoma in children: the UKCCSG/SIOP prospective study. Lancet Oncol. 2007;8:696-705.
- Ruda R, Gilbert M, Soffietti R. Ependymoma of the adult: molecular biology and treatment. Curr Opin Neurology 2008; 21: 754-761.

- Pérez-Bovet J, Rimbau-Muñoz J, Martín-Ferrer S. Anaplastic ependymoma with holocordial and intracranial meningeal carcinomatosis and holospinal bone metastases. Neurosurg 2013;72:E497-503.
- Lassaletta A et al. Successful treatment of intracranial ependymoma with leptomenigeal spread with systemic chemotherapy and intrathecal liposomal cytarabine in a two-year old child. J Neurooncol 2007; 83: 303-306.
- Slavc I, Schuller E, Czech T, Hainfellner JA, Seidl R, Dieckmann K. Intrathecal mafosfamide therapy for pediatric brain tumors with meningeal dissemination. J Neurooncol 1998; 38: 213-218.
- Ernestus RI, Wilcke O. Spinal metastases of intracranial ependymomas. Four case reports and review of the literature. Neurosurg Rev 1990; 13: 147-154.
- Salazar OM. A better understanding of CNS seeding and a brighter outlook for postoperatively irradiated patients with ependymomas. Int J Radiat Oncol Biol Phys 1983;9:1231-1234.
- Ray GL et al. Definitive treatment of leptomeningeal spinal metastases in children. Pediatr Blood Cancer 2013; 60: 1839-41. http://onlinelibrary.wiley.com/doi/10.1002/pbc.24659/full

- Brandes AA et al. A Multicenter Retrospective Study of Chemotherapy for Recurrent Intracranial Ependymal Tumors in Adults by the Gruppo Italiano Cooperativo di Neuro-Oncologia. Cancer 2005;104:143–8.
- Gornet MK, Buckner JC, et al. Chemotherapy for advanced CNS ependymoma. J Neurooncol 1999;45:61–67.
- Rehman S, Brock C, Newlands ES. A case report of a recurrent intracranial ependymoma treated with temozolomide in remission 10 years after completing chemotherapy. Am J Clin Oncol 2006;29:106–107.
- M.C. Chamberlain, S.K. Johnston. Temozolomide for recurrent intracranial supratentorial platinum-refractory ependymoma. Cancer 2009;115:4775–4782.
- Freyschlag CF, Tuettenberg J, Lohr F, Thomé C, Schmieder K, Seiz M. Response to temozolomide in supratentorial multifocal recurrence of malignant ependymoma. Anticancer Res 2011 Mar;31(3):1023-5.
- Lombardi G, Pambuku A, Bellu L, Della Puppa A, Rumanò L, Gardiman MP, et al. Cisplatin and Temozolomide Combination in the Treatment of Supratentorial Anaplastic Ependymoma. Chemother 2013;59:176-180.
- Chamberlain MC, Johnston SK. Temozolomide for recurrent intracranial supratentorial platinum-refractory ependymoma. Cancer. 2009 Oct 15;115(20):4775-82.
- Buccoliero AM, Castiglione F, Rossi Degl'Innocenti D, et al. O6-Methylguanine-DNA-methyltransferase in recurring anaplastic ependymomas: PCR and immunohistochemistry. J Chemother 2008; 20: 263-8.
- Chamberlain MC. Etoposide for recurrent spinal cord ependymoma. Neurology 2002;58:1310–1.
- Zacharoulis S, Levy A, Chi SN, Gardner S, Rosenblum M, Miller DC, et al. Outcome for young children newly diagnosed with ependymoma, treated with intensive induction chemotherapy followed by myeloablative chemotherapy and autologous stem cell rescue. Pediatr Blood Cancer 2007;49(1):34-40.
- Iqbal MS, Lewis J. An Overview of the Management of Adult Ependymomas with Emphasis on Relapsed Disease, Clinical Oncology 2013;), http://dx.doi.org/10.1016/j.clon.2013.07.009.
- Shonka NA. Targets for therapy in ependymoma. Targ Oncol 2011; 6: 163-9.
- Lorgis V, Varbedian O, Ghiringhelli F. Metronomic cyclophosphamide with cisplatin and bevacizumab: a new chemotherapeutic regimen for refractory anaplastic ependymoma. Anticancer Res 2012;32(11):5067-70.
- Gururangan S, Fangusaro J, Young Poussaint T, Onar-Thomas A, Gilbertson RJ, et al. Lack of efficacy of bevacizumab + irinotecan in cases of pediatric recurrent ependymoma--a Pediatric Brain Tumor Consortium study. Neuro Oncol. 2012;14(11):1404-12. doi: 10.1093/neuonc/nos213. Epub 2012 Sep 26.
- Green RM, Cloughesy TF, Stupp R, DeAngelis LM, Woyshner EA, Ney DE, Lassman AB. Bevacizumab for recurrent ependymoma. Neurology 2009; 73: 1677-80.
- Fakhrai N, Neophytou P, Dieckmann K, et al. Recurrent spinal ependymoma showing partial remission under imatimib. Acta Neurochir 2004;146:1255–1258.
- Protocol IDs: CERN08-02, NCT00826241
- Protocol IDs: CERN09-02, NCT01295944
- Fouladi M, Gururangan S, Moghrabi A, Phillips P, Gronewold L, Wallace D, et al. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer 2009;115(14):3243-53.

References section 14

- Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. Lancet Oncol 2009;10:258–66.
- Beltran C, Naik M, Merchant TE. Dosimetric effect of setup motion and target volume margin reduction in pediatric ependymoma. Radiother Oncol. 2010 Aug;96(2):216-22.
- Taylor RE Review of radiotherapy dose and volume for intracranial ependymoma. Pediatr Blood Cancer. 2004 May;42(5):457-60.

References section 15

- Abdullah KG et al, Progression free survival and functional outcome after surgical resection of intramedullary ependymomas. J of Clinical Neuroscience 2015; 22: 1933-1937
- Asaid M et al, Ependymoma in adults: Local experience with an uncommon tumor. J of Clinical Neuroscience 2015; 22: 1392-1396
- Ghia AJ et al, Supratentorial gross-totally resected non-anaplastic ependymoma: population based patterns of care and outcome analysis. J Neurooncol. 2013; 115: 513-20
- Gomez DR et al, High failure rate in spinal ependymomas with long-term follow-up. Neuro Oncol. 2005 Jul;7(3):254-9.
- Guyotat J et al, Intracranial ependymomas in adult patients: analyses of prognostic factors. J Neurooncology 2002; 60(3): 255-68
- Halvorsen CM et al, Long-term outcome after resection of intraspinal ependymomas: report of 86 consecutive cases. Neurosurgery 2010; 67(6): 1622-31
- Kawabata Y et al, Long term outcome in patients harboring intracranial ependymoma. J Neurosurg 2005; 103: 31-37
- McLaughlin MP et al, EpendymomaL results, prognostic factors and treatment recommendations. IJROBP 1998; 40-4: 845-850
- Lee SH, et al, Long-term outcomes of surgical resection with or without adjuvant radiation therapy for treatment of spinal ependymoma: a retrospective multicenter study by the Korea Spinal Oncology Research Group. Neuro Oncol. 2013 Jul;15(7):921-9.
- Metellus P et al, Adult intracranial WHO grade II ependymomas: long-term outcome and prognostic factor analysis in a series 0f 114 patients Neuro Oncol. 2010 Sep;12(9):976-84
- Reni M et al, A multicenter study of the prognosis and treatment of adult brain ependymal tumors. Cancer 2004; 100(6): 1221-9
- Sayegh ET et al, Prognosis by tumor location in adults with intracranial ependymomas. J of Clinical Neuroscience 2014; 21: 2096-2101
- Swanson et al. Intracranial ependymomas treated with radiotherapy : lonterm results from a single institute J Neurooncol. 2011 May;102(3):451-7.
- Taylor RE et al, Review of radiotherapy dose and volume for intracranial ependymoma. Pediatr Blood Cancer. 2004 May;42(5):457-60
- Vera-Bolanos E et al, Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients. Neurooncology 2015; 17(3): 440-7
- Weber DC et al, Long-term outcome of patients with spinal myxopapillary ependymoma: treatment results from the MD Anderson Cancer Center and institutions from the Rare Cancer Network. Neuro-Oncology 2015; 17(4): 588-595