Cancer Association of South Africa (CANSA)

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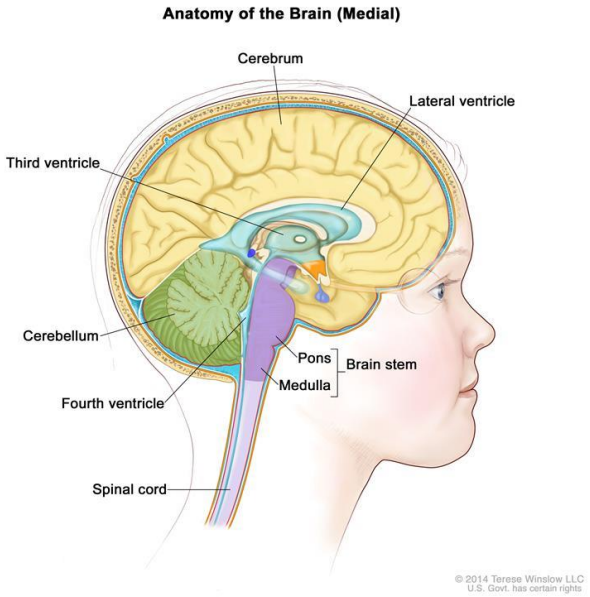
Fact Sheet on Childhood Ependymoma

Introduction

Childhood ependymoma is a disease in which malignant (cancer) cells form in the tissues of the brain and spinal cord. The brain controls vital functions such as memory and learning, emotion, and the senses (hearing, sight, smell, taste, and touch). The spinal cord is made up of bundles of nerve fibres that connect the brain with nerves in most parts of the body.

Ependymomas form from ependymal cells that line the ventricles and passageways in the brain and the spinal cord. Ependymal cells make cerebrospinal fluid (CSF). Ependymomas can form anywhere in the fluid-filled ventricles and passageways in the brain and spinal cord. Most ependymomas form in the fourth ventricle and affect the cerebellum and the brain stem (refer to diagram).



The World Health Organization (WHO) groups ependymal tumours into four main subtypes:

- Subependymoma (WHO Grade I).
- Myxopapillary ependymoma (WHO Grade I).
- Ependymoma (WHO Grade II)
- Anaplastic ependymoma (WHO Grade III).

The grade of a tumour describes how abnormal the cancer cells look under a microscope and how quickly the tumour is likely to grow and spread. Low-grade (Grade I) cancer cells look more like normal cells and tend to grow and spread more slowly than high-grade (Grade III) cancer cells.

Ependymomas tend to grow relatively slowly and displace, rather than invade adjacent brain or spinal cord tissue. They are described as plastic because they grow outside the ventricle through paths of least resistance within the brain. Some ependymomas, particularly those located in the posterior fossa, spread to other parts of the brain or spinal cord through the cerebrospinal fluid. Cerebrospinal dissemination occurred in approximately 13% of patients in one study. Ependymomas rarely metastasise to sites outside of the

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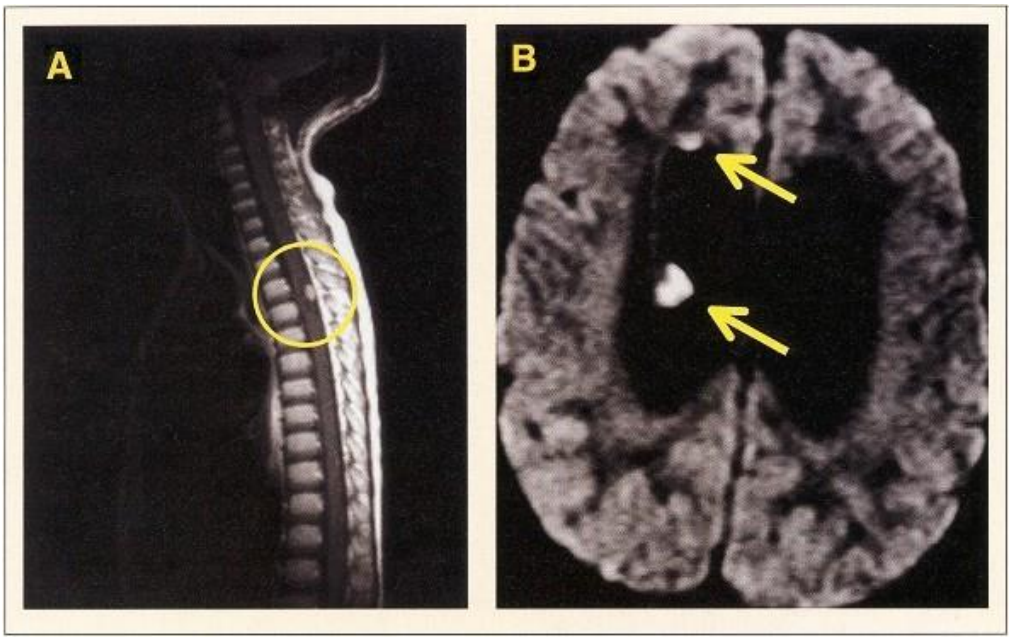
central nervous system. When ependymomas recur after treatment, they tend to grow back locally (i.e. at or near the site of the original tumour), rather than spreading to other sites.



Metastasis of Childhood Ependymoma in spinal column (A) with primary tumours in ventricles of the Brain (B)

[Picture Credit: Ependymoma]

Gillen, A.E., Riemondy, K.A., Amani, V., Griesinger, A.M., Gilani, A., Venkataraman, S., Madhavan, K., Prince, E., Sanford, B., Hankinson, T.C., Handler, M.H., Vibhakar, R., Jones, K.L., Mitra, S., Hesselberth, J.R., Foreman, N.K. & Donson, A.M. 2020.
"Ependymoma (EPN) is a brain tumor commonly presenting in childhood that remains fatal in most children. Intra-tumoral cellular heterogeneity in bulk-tumor samples significantly confounds our understanding of EPN biology, impeding development of effective therapy. We, therefore, use single-cell RNA sequencing, histology, and deconvolution to catalog cellular heterogeneity of the major childhood EPN subgroups. Analysis of PFA subgroup EPN reveals evidence of an undifferentiated progenitor subpopulation that either differentiates into subpopulations with ependymal cell characteristics or transitions into a mesenchymal subpopulation. Histological analysis reveals that progenitor and mesenchymal subpopulations co-localize in peri-necrotic zones. In conflict with current classification paradigms, relative PFA subpopulation proportions are shown to determine bulk-tumor-assigned subgroups. We provide an interactive online resource that facilitates exploration of the EPN single-cell dataset. This atlas of EPN cellular heterogeneity increases understanding of EPN biology."

PDQ Pediatric Treatment Editorial Board. 2020.
Primary brain tumors, including ependymomas, are a diverse group of diseases that together constitute the most common solid tumor of childhood. Immunohistochemical analysis, cytogenetic and molecular genetic findings, and measures of mitotic activity are increasingly used in tumor diagnosis and classification. Brain tumors are classified according to histology, but tumor location, extent of spread, molecular features, and age are important factors that affect treatment and prognosis.
According to the 2016 revision to the World Health Organization (WHO) classification of tumors of the central nervous system, ependymal tumors are classified into the following five main subtypes:[1]

- Subependymoma (WHO grade I).
- Myxopapillary ependymoma (WHO grade I).

- Ependymoma (WHO grade II).
- Ependymoma, *RELA* fusion–positive (WHO grade II or grade III).
- Anaplastic ependymoma (WHO grade III).

Donson, A.M., Amani, V., Warner, E.A., Griesinger, A.M., Witt, D.A., Levy, J.M.M., Hoffman, L.M., Hankinson, T.C., Handler, M.H., Vibhakar, R., Dorris, K. & Foreman, N.K. 2018.
"Children with ependymoma (EPN) are cured in less than 50% of cases, with little improvement in outcome over the last several decades. Chemotherapy has not affected survival in EPN, due in part to a lack of preclinical models that has precluded comprehensive drug testing. We recently developed two human EPN cell lines harboring high-risk phenotypes which provided us with an opportunity to execute translational studies. EPN and other pediatric brain tumor cell lines were subject to a large-scale comparative drug screen of FDA-approved oncology drugs for rapid clinical application. The results of this *in vitro* study were combined with *in silico* prediction of drug sensitivity to identify EPN-selective compounds, which were validated by dose curve and time course modeling. Mechanisms of EPN-selective antitumor effect were further investigated using transcriptome and proteome analyses. We identified three classes of oncology drugs that showed EPN-selective antitumor effect, namely, (i) fluorinated pyrimidines (5-fluorouracil, carmofur, and floxuridine), (ii) retinoids (bexarotene, tretinoin and isotretinoin), and (iii) a subset of small-molecule multireceptor tyrosine kinase inhibitors (axitinib, imatinib, and pazopanib). Axitinib's antitumor mechanism in EPN cell lines involved inhibition of PDGFRα and PDGFRβ and was associated with reduced mitosis-related gene expression and cellular senescence. The clinically available, EPN-selective oncology drugs identified by our study have the potential to critically inform design of upcoming clinical studies in EPN, in particular for those children with recurrent EPN who are in the greatest need of novel therapeutic approaches. *Mol Cancer Ther; 17(9); 1984-94. ©2018 AACR*."

Incidence of Childhood Ependymoma in South Africa
The National Cancer Registry (2017) does not provide any information on the incidence of Childhood Ependymoma. It only reflects information on brain and central nervous system cancers.

Causes and Risk Factors for Childhood Ependymoma
A risk factor is anything that increases a person's chance of developing cancer. Although risk factors often influence the development of cancer, most do not directly cause cancer. Some people with several risk factors never develop cancer, while others with no known risk factors do.

The causes of childhood ependymoma are unknown. There is little known about the risk factors or ways to prevent the disease.

Rarely, children with neurofibromatosis type 2 (NF2) have an increased risk of developing ependymoma. NF2 is a hereditary syndrome that causes tumours of the central nervous system that are usually noncancerous.

Signs and Symptoms of Childhood Ependymoma
Children with ependymoma may experience the following symptoms or signs. Sometimes, children with ependymoma do not show any of these symptoms. Or, these symptoms may be caused by a

medical condition that is not a tumour. If concerned about a symptom or sign on this list, please consult a paediatrician.

- Frequent headaches
- Seizures/convulsion, which is a sudden involuntary movement of a person's muscles
- Frequent nausea and vomiting
- Changes in vision, such as blurriness
- Difficulty with walking
- Loss of balance
- Swelling of the nerve at the back of the eye
- Jerky eye movements
- Neck pain

Stages of Childhood Ependymoma
The area where the primary tumour is found and the child's age are used in place of a staging system to plan cancer treatment. Staging is the process used to find out how much cancer there is and whether the cancer has spread. It is important to know the stage in order to adequately plan treatment.

There is no standard staging system for childhood ependymoma. Instead, the plan for cancer treatment after surgery depends on the following:

- Whether any cancer cells remain after surgery
- Whether the cancer has spread to other parts of the brain or spinal cord
- The age of the child

The information from tests and procedures done to detect (find) childhood ependymoma is used to plan cancer treatment. Some tests used to detect childhood ependymoma are repeated after the primary tumour is removed by surgery. This is to find out how much tumour remains after surgery. Another procedure that may be done to find out if cancer has spread is a lumbar puncture. A lumbar puncture is a procedure used to collect cerebrospinal fluid from the spinal column. This is done by placing a needle into the spinal column. This procedure is also referred to a 'spinal tap'.

Treatment of Childhood Ependymoma
Children with ependymoma should have their treatment planned by a team of health care providers who are experts in treating childhood brain tumours.

Treatment will be overseen by a paediatric oncologist, a doctor who specialises in treating children with cancer. The following health professionals may be included in the multidisciplinary team:

- Paediatric neurosurgeon
- Neurologist
- Neuropathologist
- Neuroradiologist
- Rehabilitation specialist
- Radiation oncologist

- Medical oncologist
- Endocrinologist
- Psychologist

Standard Treatment Options for Childhood Ependymoma
PDQ Pediatric Treatment Editorial Board. 2020.

Treatment Group	Standard Treatment Options
Newly diagnosed childhood myxopapillary ependymoma (WHO grade I)	Surgery with or without adjuvant radiation therapy
Newly diagnosed childhood ependymoma (WHO grade II), anaplastic ependymoma (WHO grade III), or *RELA* fusion–positive ependymoma:	Surgery
	Adjuvant therapy:
No residual disease, no disseminated disease	—Radiation therapy
Residual disease, no disseminated disease	—Second-look surgery
	—Radiation therapy
	—Preirradiation chemotherapy
Central nervous system disseminated disease	—Radiation therapy (not considered standard treatment)
	—Chemotherapy (not considered standard treatment)
Children younger than 1 year	—Chemotherapy
	—Deferred radiation therapy
Recurrent childhood ependymoma	Surgery
	Radiation therapy and/or chemotherapy

Dramatic improvements in survival have been achieved for children and adolescents with cancer. Between 1975 and 2010, childhood cancer mortality decreased by more than 50%.[1] Childhood and adolescent cancer survivors require close monitoring because cancer therapy side effects may persist or develop months or years after treatment.

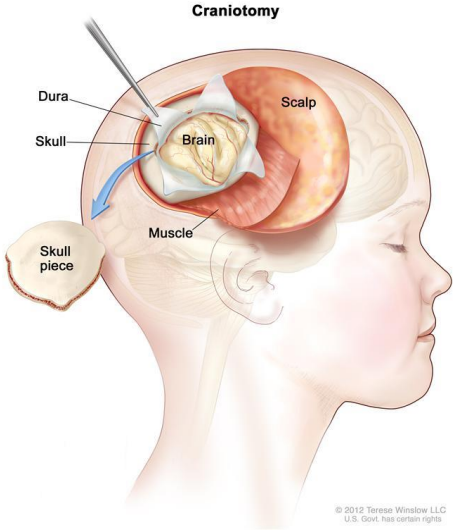
Ruangkanchanasetr, R., Swangsilpa, T., Puataweepong, P., Dhanachai, M., Hansasuta, A., Boongird, A., Sirachainan, N. & Hongeng, S. 2019.
PURPOSE: To report outcome of postoperative radiotherapy (RT) in both new and recurrent grade II and III intracranial ependymomas in children treated at Ramathibodi Hospital.
MATERIALS AND METHODS: Between 2006 and 2017, 24 pediatric intracranial ependymomas treated with postoperative RT were retrospectively reviewed. The median age at diagnosis was 44.5 months (range, 4-165 months). There were 14 (58%) males. Fourteen (58%) patients had infratentorial tumor. The median maximal diameter of tumor at diagnosis was 4.45 cm (range, 2.2-10 cm). Fourteen (58%) patients had anaplastic tumor. Gross total resections were performed in 14 (58%) patients. The median prescribed dose was 54 Gy (range, 45-60 Gy). The median total treatment time was 43 days (range, 37-78 days).

RESULTS: The median clinical follow-up time was 44.5 months (range, 1-146 months). There were nine recurrences, five of which occurred at the primary tumor site. The estimated 5-year progression-free survival rate was 56%. The estimated 5-year overall survival rate was 75%. Extent of resection was the only factor associated with improved progression-free survival and overall survival after univariate testing. Six from nine patients with recurrent diseases underwent further surgery or further RT. These six patients had better median overall survival than the three who did not. Acute complication was mostly transient and tolerable. No late radiation effect was found.
CONCLUSIONS: Postoperative radiation is an effective treatment. GTR is associated with better PFS and OS. Aggressive salvage local treatments for recurrent patients can result in good overall survival. Longer follow-up is needed in account for late relapse.

Upadhyaya, S.A., Robinson, G.W., Onar-Thomas, A., Orr, B.A., Billups, C.A., Bowers, D.C., Bendel, A.E., Hassall, T., Crawford, J.R., Partap, S., Fisher, P.G., Tatevossian, R.G., Seah, T., Qaddoumi, I.A., Vinitsky, A., Armstrong, G.T., Sabin, N.D., Tinkle, C.L., Klimo, P., Indelicato, D.J., Boop, F.A., Merchant, T.E., Ellison, D.W. & Gajjar, A. 2019.
BACKGROUND: This report documents the clinical characteristics, molecular grouping and outcome of young children with ependymomatreated prospectively on a clinical trial.
METHODS: Fifty-four children (aged ≤ 3 years) with newly diagnosed ependymoma were treated on the SJYC07 trial with maximal safe surgical resection, 4 cycles of systemic chemotherapy, consolidation therapy using focal conformal radiation therapy (RT) (5-mm clinical target volume), and 6 months of oral maintenance chemotherapy. Molecular groups were determined by tumor DNA methylation using Infinium Methylation EPIC BeadChip and profiled on DKFZ/German molecularneuropathology2.0 classifier.
RESULTS: One of the 54 study patients had metastases (CSF+) at diagnosis. Gross- or near-total resection was achieved in 48 (89%) patients prior to RT. At a median follow-up of 4.4 years (range, 0.2-10.3 years), 4-year progression-free survival (PFS) was 75.1% ± 7.2%, and overall survival was 92.6% ± 4.4%. The molecular groups showed no significant difference in PFS [4-year estimates: PF-EPN-A (42/54), 71.2% ± 8.3%; ST-EPN-RELA (8/54), 83.3% ± 17.0%; ST-EPN-YAP (4/54), 100%, p=0.22]. Subtotal resection prior to RT was associated with an inferior PFS compared to gross- or near-total resection (4-year PFS: 41.7% ± 22.5% vs. 79.0% ± 7.1%, p=0.024) as was PF-EPN-A group with 1q gain (p=0.05). Histopathologic grading was not associated with outcomes (classic vs anaplastic; p=0.89).
CONCLUSIONS: In this prospectively treated cohort of young children with ependymoma, ST-EPN-RELA tumors had a favorable outcome than reported from retrospective data. Histological grade did not impact outcome. PF-EPN-A with 1q gain, and sub-total resection were associated with inferior outcomes.

A child with newly diagnosed ependymoma has not had treatment for the tumour. The child may have had treatment to relieve symptoms caused by the tumour. The specific treatment usually is surgery to remove the tumour. Complete removal of the tumour by means of a craniotomy (see diagram below) is often not possible because of the tumour location and concerns about damaging the surrounding normal brain tissue.

Childhood ependymoma is diagnosed and removed in surgery. If the diagnostic tests show there may be a brain tumour, a biopsy is done by removing part of the skull and using a needle to remove a sample of the brain tissue. A pathologist views the tissue under a microscope to look for cancer cells. If cancer cells are found, the doctor will remove as much tumour as safely possible during the same surgery. An MRI is often done after the tumour is removed to find out whether any tumour remains. More treatment may be given after surgery.



Treatment given after surgery depends on the following:

- Age of the child
- Amount of tumour that was removed
- Whether cancer cells have spread to other parts of the brain or spinal cord

Treatment for children aged 3 and older – if the tumour is completely removed by surgery and cancer cells have not spread within the brain and spinal cord, treatment may include the following:

- Radiation therapy to the tumour bed (the area where the tumour was removed). This may be conformal radiation therapy
- A clinical trial of radiation therapy followed by chemotherapy

If a part of the tumour remains after surgery, but cancer cells have not spread within the brain and spinal cord, treatment may include the following:

- A second surgery to remove as much of the remaining tumour as possible
- Radiation therapy to the tumour bed
- A clinical trial of chemotherapy given before and after radiation therapy

If cancer cells have spread within the brain and spinal cord, treatment may include the following:

- Radiation therapy to the whole brain and spine
- A clinical trial of radiation therapy and chemotherapy

Treatment for Children Younger than 3 years of Age:

- Chemotherapy
- Radiation therapy may be given later

Subependymoma

The true incidence of subependymomas is difficult to determine, because these tumours are frequently asymptomatic and may be found incidentally at autopsy. They probably comprise less than 5% of all ependymal tumours. Occasionally, subependymomas cause ventricular obstruction and, in these cases, treatment is indicated. Spontaneous intratumoral haemorrhage has also been observed. In those cases requiring therapy, complete surgical removal is often curative.

Hou, Z., Wu, Z., Zhang, J., Zhang, L., Tian, R., Liu, B. & Wang, Z. 2013.

"Subependymoma is a rare low-grade glioma of the central nervous system that occurs most commonly in middle-aged and elderly men and rarely in children. Only a few paediatric patients with subependymomas have been reported. The authors retrospectively analysed five paediatric patients (4 males and 1 female; mean age 8.6 years; age range 5-13 years) at a single institute from July 1998 to April 2009 and summarised the clinical characteristics and management of paediatric intracranial subependymoma. The most common symptom in these five paediatric patients with subependymoma was intracranial hypertension. The tumours were located in the fourth ventricle in two patients, in the fourth ventricle with extension to the cerebellopontine angle (CPA) in one patient; in the right CPA exclusively in one patient, and intraparenchymally in the left parietal lobe in one patient, the latter two of which are rare locations for subependymoma. Surgery was performed on all five patients. The surgical approach was selected as appropriate for the tumor location. Total resection was achieved in three patients, and subtotal resection in two. All five patients had good outcomes without recurrence. We conclude that surgery is the optimal therapy for paediatric patients with intracranial subependymoma."

Myxopapillary Ependymoma

Historically, the management of myxopapillary ependymoma (WHO Grade I) consisted of an attempt at *en bloc* resection of the tumour with no further treatment in the case of a gross total resection. However, based on the finding that dissemination of these tumours to other parts of the neuraxis can occur, particularly when complete resection is not obtained and evidence that focal irradiation may improve progression-free survival, many practitioners now favour the use of irradiation following surgical resection of the primary mass.

Strojnik, T., Bujas, T. & Velnar, T. 2019.

BACKGROUND: Myxopapillary ependymomas are rare spinal tumours. Although histologically benign, they have a tendency for local recurrence.

CASE SUMMARY: We describe a patient suffering from extra- and intradural myxopapillary ependymoma with perisacral spreading. He was treated with subtotal resection and postoperative radiation therapy. After treatment, he experienced slight sphincter disorders and lumboischialgic pain with no motor or sensory disturbances. Eight months later, a tumour regression was documented. The patient is still followed-up regularly.

CONCLUSION: Lumbar myxopapillary ependymomas may present with lumbar or radicular pain, similar to more trivial lesions. Magnetic resonance imaging (MRI) is the primary modality for diagnosis. The treatment aim is to minimize both tumour and therapy-related morbidity and to involve different treatment modalities.

Pesce, A., Palmieri, M., Armocida, D., Frati, A., Miscusi, M. & Raco, A. 2019.

INTRODUCTION: Spinal Mixopapillary Ependymoma (sMPE) is an uncommon primary spinal neoplasm infiltrating the Spinal Cord(SC), Conus Medullaris(CM) and Nerve Roots associated to low

resection and a high recurrence rates. The purpose of the present extensive Literature Review is to evaluate the exact impact of the involvement of the CM and the role played by the Gross Total Resection(GTR) on Overall Survival(OS).
METHODS: The English Literature was systematically investigated using the Medline, NIH library, Pubmed and Google Scholar search engines with relevant queries. Case series reporting details concerning the OS, GTR and CM involvement rate were included, with a differential statistical weight given by the number of patients enrolled. A final cohort of 1602 clinical records was analyzed according to the three selected endpoint variables.
RESULTS: The average age was 36,44±3,41, and the CM was involved in 28.4%±28.2 of cases. The average GTR rate was 53.94±22.20%. Five and 10 years OS rates were respectively available in 1170 and 1167 cases, with an average 5 and 10 years OS rate of 94.99±3.87% and 92.31±5.73%. Through analyses performed both on aggregated and disaggregated data a strong positive statistical connection between GTR and increased OS was demonstrated despite the real clinical advantage could range as low as around 1% of increased OS rate.
CONCLUSIONS: Given the indolent sMPEs behavior it is difficult to evaluate the exact impact of GTR and CM involvement on OS although GTR could be associated to a limited survival advantage whereas the CM involvement to a survival disadvantage.

Anaplastic Ependymoma
What the research says about anaplastic ependymoma.

Komori, K., Yanaagisawa, R., Miyairi, Y., Sakashita, K., Shiohara, M., Fujihara, I., Morita, D., Nakamura, T., Ogiso, Y., Sano, K., Shirahata, M., Fukuoka, K., Ichimura, K. & Shigeta, H. 2016.
"The benefit of postoperative chemotherapy for anaplastic ependymoma remains unknown. We report two pediatric patients with refractory anaplastic ependymoma treated with temozolomide (TMZ). We did not detect O(6) -methylguanine-DNA methyltransferase (MGMT) promoter methylation in tumor samples; however, MGMT protein expression was low. With TMZ treatment, one patient had a 7-month complete remission; the other, stable disease for 15 months. Three other patients did not respond to TMZ; two had high and one low MGMT expression, and two showed no MGMT promoter methylation. These findings suggest that TMZ may be effective for pediatric refractory anaplastic ependymoma with ow MGMT protein expression."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides

information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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BACKGROUND: Myxopapillary ependymomas are rare spinal tumours. Although histologically benign, they have a tendency for local recurrence.

The Childhood Brain Tumor Foundation
http://www.childhoodbraintumor.org/medical-information/brain-tumor-types-and-imaging/item/84-ependymomas

The Ohio State University
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