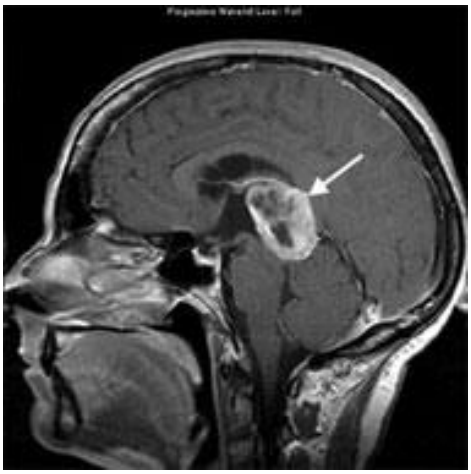
Cancer Association of South Africa (CANSA)

Fact Sheet on Pineoblastoma

Introduction

Pineoblastoma (also pinealoblastoma) is a malignant tumour of the pineal gland. Pineoblastoma may occur in patients with hereditary uni- or bilateral retinoblastoma. When retinoblastoma patients present with pineoblastoma this is characterised as 'trilateral retinoblastoma'.

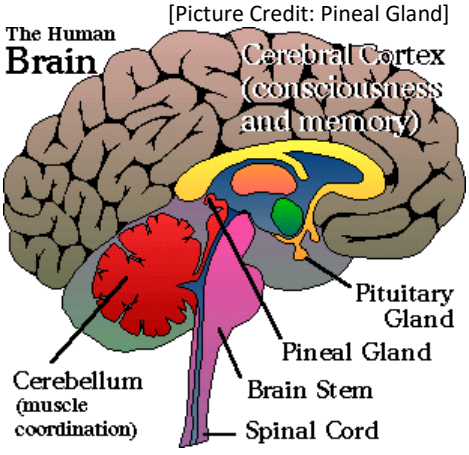


[Picture Credit: Pineoblastoma]

Pineal Tumours

These tumours originate from normal cells in the pineal gland. The pineal gland is located in the centre of the brain and is involved in the secretion of specific hormones.

[Picture Credit: Pineal Gland]



Tumour types occurring in the pineal region may or may not involve the pineal gland. Tumours that may occur in this region but are not necessarily pineal tumours include: germinoma, non-germinoma (e.g., teratoma, endodermal sinus tumour, embryonal cell tumour, choriocarcinoma, and mixed tumours), meningioma, astrocytoma, ganglioglioma, and dermoid cysts.

There are three types of pineal tumours:

- Pineocytoma: Slow-growing, grade II tumour.
- Pineoblastoma: More aggressive, grade IV, malignant tumour. A grade III intermediate form has also been described.
- Mixed Pineal Tumour: Contains a combination of cell types.

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Pineoblastoma

Pineoblastoma is one of several different types of tumours that arise in the area of the pineal gland, requiring different therapies. The exact diagnosis is critical for choosing the correct therapy. Pineal tumours typically present with hydrocephalus (a build-up of fluid pressure within the brain). A team of experts is needed for optimum therapy.

Pineal gland tumours as a group are rare, accounting for less than 1% of all primary brain tumours. Pineoblastomas represent just under half of all pineal gland tumours. Pineoblastoma usually occurs in children and young people between the ages of 20 and 40 years. It is equally common in males and females.

Pineoblastoma is more aggressive than other types of pineal gland tumours. Its fast growth usually causes cerebrospinal fluid (CSF) to build up in the brain. This condition is called hydrocephalus. While pineoblastoma may spread through the CSF in 10% to 20% of cases, most of the time the tumours do not spread to other parts of the body.

The cause of pineoblastoma is not known, although genetic abnormalities are suspected.

Li, B.K., Vasiljevic, A., Dufour, C., Yao, F., Ho, B.L.B., Lu, M., Hwang, E.I., Gururangan, S., Hansford, J.R., Fouladi, M., Nobusawa, S., Laquerriere, A., Delisle, M.B., Fangusaro, J., Forest, F., Toledano, H., Solano-Paez, P., Leary, S., Birks, D., Hoffman, L.M., Szathmari, A., Faure-Conter, C., Fan, X., Catchpoole, D., Zhou, L., Schultz, K.A.P., Ichimura, K., Gauchotte, G., Jabado, N., Jones, C., Loussouarn, D., Mokhtari, K., Rousseau, A., Ziegler, D.S., Tanaka, S., Pomeroy, S.L., Gajjar, A., Ramaswamy, V., Hawkins, C., Grundy, R.G., Hill, D.A., Bouffet, E., Huang, A. & Jouvet, A. 2020. "Pineoblastomas (PBs) are rare, aggressive pediatric brain tumors of the pineal gland with modest overall survival despite intensive therapy. We sought to define the clinical and molecular spectra of PB to inform new treatment approaches for this orphan cancer. Tumor, blood, and clinical data from 91 patients with PB or supratentorial primitive neuroectodermal tumor (sPNETs/CNS-PNETs), and 2 pineal parenchymal tumors of intermediate differentiation (PPTIDs) were collected from 29 centres in the Rare Brain Tumor Consortium. We used global DNA methylation profiling to define a core group of PB from 72/93 cases, which were delineated into five molecular sub-groups. Copy number, whole exome and targeted sequencing, and miRNA expression analyses were used to evaluate the clinico-pathologic significance of each sub-group. Tumors designated as group 1 and 2 almost exclusively exhibited deleterious homozygous loss-of-function alterations in miRNA biogenesis genes (DICER1, DROSHA, and DGCR8) in 62 and 100% of group 1 and 2 tumors, respectively. Recurrent alterations of the oncogenic MYC-miR-17/92-RB1 pathway were observed in the RB and MYC sub-group, respectively, characterized by RB1 loss with gain of miR-17/92, and recurrent gain or amplification of MYC. PB sub-groups exhibited distinct clinical features: group 1-3 arose in older children (median ages 5.2-14.0 years) and had intermediate to excellent survival (5-year OS of 68.0-100%), while Group RB and MYC PB patients were much younger (median age 1.3-1.4 years) with dismal survival (5-year OS 37.5% and 28.6%, respectively). We identified age < 3 years at diagnosis, metastatic disease, omission of upfront radiation, and chr 16q loss as significant negative prognostic factors across all PBs. Our findings demonstrate that PB exhibits substantial molecular heterogeneity with sub-group-associated clinical phenotypes and survival. In addition to revealing novel biology and therapeutics, molecular sub-grouping of PB can be exploited to reduce treatment intensity for patients with favorable biology tumors."

Jin, M.C., Prolo, L.M., Wu, A., Azad, T.D., Shi, S., Rodrigues, A.J., Soltys, S.G., Pollom, E.L., Li, G., Hiniker, S.M. & Grant, G.A. 2020.

Background: Pediatric pineoblastomas are highly aggressive tumors that portend poor outcomes despite multimodal management. Controversy remains regarding optimal disease management.

Objective: To evaluate patterns of care and optimal clinical management of pediatric pineoblastoma.

Methods: A total of 211 pediatric (age 0-17 yr) histologically confirmed pineoblastoma patients diagnosed between 2004 and 2015 were queried from the National Cancer Database. Wilcoxon rank-sum statistics and chi-squared analyses were used to compare continuous and categorical variables, respectively. Univariable and multivariable Cox regressions were used to evaluate prognostic impact of covariates. Propensity-score matching was used to balance baseline characteristics.

Results: Older patients (age ≥ 4 yr) experienced improved overall survival compared to younger patients (age < 4 yr) (hazard ratio [HR] = 0.41; 95% CI 0.25-0.66). Older patients (adjusted odds ratio [aOR] = 5.21; 95% CI 2.61-10.78) and those residing in high-income regions (aOR = 3.16; 95% CI 1.21-8.61) received radiotherapy more frequently. Radiotherapy was independently associated with improved survival in older (adjusted HR [aHR] = 0.31; 95% CI 0.12-0.87) but not younger (aHR = 0.64; 95% CI 0.20-1.90) patients. The benefits of radiotherapy were more pronounced in patients receiving surgery than in those not receiving surgery (aHR [surgical patients] = 0.23; 95% CI 0.08-0.65; aHR [nonsurgical patients] = 0.46; 95% CI 0.22-0.97). Older patients experienced improved outcomes associated with aggressive resection (P = .041); extent of resection was not associated with survival in younger patients (P = .880).

Conclusion: Aggressive tumor resection was associated with improved survival only in older pediatric patients. Radiotherapy was more effective in patients receiving surgery. Age-stratified approaches might allow for improved disease management of pediatric pineoblastoma.

Byun, H.K., Yoon, H.I., Cho, J., Shim, K-W., Han, J.W., Lyu, C.J., Kim, D-S. & Suh, C-O. 2020.

Purpose: We investigated optimal management for intracranial germinoma, including target volume and dose of radiation therapy (RT) and the combination of RT and chemotherapy (CTx).

Methods and materials: We retrospectively evaluated 213 patients with intracranial germinoma treated between 1971 and 2017. Treatment policies changed as diagnostic techniques and clinical experience improved. In the 1980s, trial RT and tumor marker study were performed, and craniospinal irradiation was performed to treat patients with presumed germinoma. CTx was introduced in 1991, and RT volume was reduced in patients showing a complete response. In 2012, the policy was changed to a "reduced volume/dose RT alone" approach, involving a smaller target volume (the whole ventricle/whole brain for localized disease) without CTx. RT doses were gradually reduced to 36 Gy for primary tumors and 18 Gy for neuraxis.

Results: The median age was 16 years. In total, 118 and 95 patients had pathologically proven and presumed germinoma, respectively, and 151 and 62 patients had localized and multifocal or metastatic diseases, respectively. With a median follow-up of 141 months, the 10-year disease-free and overall survival rates were 91.6% and 95.6%, respectively. Recurrence rates were similar for patients receiving RT-only (9 of 137, 6.6%) and those receiving CTx + RT (4 of 73, 5.5%); all patients receiving CTx-only experienced recurrences (3 of 3, 100%). Rates were the highest in the focal RT group (10 of 29, 34.5%) but were relatively low in the whole ventricle/whole brain RT (3 of 51, 5.9%) and craniospinal irradiation groups (0 of 130, 0%). Infield failure occurred in 3 patients. Fourteen patients died of recurrence (n = 4), secondary malignancy (n = 4), CTx-related toxicity (n = 2), and others (n = 4). Among the 33 patients who received "reduced volume/dose RT alone" treatment, 2 (6.1%) experienced recurrence in the spinal cord and biopsy tract, respectively.

Conclusions: The additional benefit of CTx in the treatment of intracranial germinoma seems minimal. An RT-only approach with reduced target volume and dose seems reasonable.

Incidence of Pineoblastoma in South Africa

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of Brain and Central Nervous System cancer cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	262	1:825	0,66%
Asian males	12	1:613	1,24%
Black males	92	1:2 294	0,69%
Coloured males	40	1:530	0,83%
White males	118	1:256	0,56%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	215	1:1 236	0,52%
Asian females	8	1:978	0,54%
Black females	79	1:3 413	0,41%
Coloured females	26	1:822	0,57
White females	102	1:315	0,60%

The frequency of histologically diagnosed cases of Brain and Central Nervous System cancer in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	41	23	30	36	78	46	24	4
Asian males	1	1	2	1	3	4	0	0
Black males	32	12	11	12	15	8	2	0
Coloured males	1	5	3	1	10	9	2	0
White males	7	5	14	13	30	25	20	4

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	43	12	23	29	39	37	30	4
Asian females	2	1	0	1	1	3	0	0
Black females	27	7	10	11	12	3	8	1
Coloured females	3	0	3	3	7	4	6	0
White females	9	4	10	14	19	27	16	3

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Symptoms and Diagnosis of Pineoblastoma

PNETs and pineoblastomas are aggressive tumours that tend to attach to parts of the brain that control movement, thought and sensation. Scientists have not been able to find an identifiable cause

or risk factors for these tumours. There does not appear to be a genetic predisposition, meaning that these diseases do not seem to run in families.

Symptoms depend on the location of the tumour, and each child may experience symptoms differently. Common symptoms include headache, nausea and vomiting, fatigue, lethargy, seizures, behaviour or personality changes, unexplained weight loss or gain, difficulty looking upward and weakness on one side of the body.

In addition to a physical examination, medical history and neurological examination (which tests reflexes, muscle strength, eye and mouth movement, coordination and alertness), the doctor may requests tests, including diagnostic imaging.

Since these tumours are known to spread via cerebrospinal fluid, there is a high chance that they will invade other tissues of the brain and spine, so it is essential that your child have an MRI of both the brain and spine.

After all necessary tests are complete, the best treatment options can be identified.

Because the pineal gland sits just above and behind the third ventricle and the cerebral aqueduct, fluid-filled spaces in the brain, an enlarging tumour in this region can compress the aqueduct, cutting off the normal flow of fluid within the brain. This can lead to what is known as hydrocephalus which results in enlargement of the ventricles and increased pressure in the head. This can lead to symptoms such as headache, nausea, vomiting and finally neurological deterioration as it becomes more severe.

Diagnosis and Imaging

Diagnostic imaging for paediatric cancer requires the use of specialised techniques and equipment to obtain pictures of the interior of the body, including soft tissues, organs and bones. For children with cancer, imaging studies are used to diagnose and stage tumours, evaluate and characterise masses, determine if the cancer has spread, establish which parts of a tumour are growing fastest, and – by monitoring a tumour's response to treatment – to guide state-of-the art treatment in addition to facilitating novel, experimental therapies.

Patients may require one of many different imaging procedures, including:

- X-ray – a quick, painless test that produces images of structures inside the body, especially the lungs, bones and some solid organs
- Fluoroscopy – a special X-ray technique that obtains moving, real-time images of the inside of a child's body
- Magnetic resonance imaging (MRI) – a diagnostic procedure that uses strong electromagnets, radio frequency waves and powerful computers to generate 3-D images of the body's organs, tissues and bones. MRI does not involve any ionizing radiation.
- Computed tomography (CT or CAT) – a non-invasive procedure that uses X-ray equipment and powerful computers to create detailed, cross-sectional images (slices) of a child's body
- Single Photon Emission Tomography (SPECT) and Positron emission tomography (PET) – a non-invasive diagnostic techniques that uses specific radiotracers to provide highly detailed images of the body and measures body functions such as blood flow, oxygen use and sugar

metabolism to help evaluate how a child's tissues or organs are functioning and how cancers are responding to therapy.
- Ultrasound – the use of variable frequency sound waves and their echoes to produce cross-sectional images of the inside of the body
- Nuclear medicine and molecular imaging – the use of short-lived radiopharmaceuticals (tracers) and specialised cameras to show blood flow, functional and metabolic activity within organs and lesions

Interventional radiology is routinely used to manage abnormal blood vessels, perform biopsies and as an alternative to surgery, to treat blood clots and to provide minimally invasive therapy for certain tumours.

Treatment of Pineoblastoma

Treatment for Pineoblastoma varies from patient to patient depending on specifics of each case such as age, tumour size and presenting symptoms. While other pineal tumours such as Germinoma are very sensitive to radiation, surgical removal of Pineoblastomas is often preferable. The aim of surgery can be to both obtain tumour tissue to analyse to make a definitive diagnosis and to remove as much of the tumour as possible. Various approaches to the pineal region can be used by neurosurgeons. In general, the procedures require a craniotomy (opening of the skull) in the posterior part of the head and is directed either above the cerebellum or between the occipital hemispheres to reach the pineal region.

Some patients will undergo other treatments such as radiation treatments for residual tumour or chemotherapy, particular in these malignant tumours.

Because the appropriate treatment varies considerably from patient to patient, each case should be evaluated and discussed with the patient's own treating physicians.

Chung, P.E.D., Gendoo, D.M.A., Ghanbari-Azarnier, R., Liu, J.C., Jiang, Z., Tsui, J., Wang, D.Y., Xiao, X., Li, B., Dubuc, A., Shih, D., Remke, M., Ho, B., Garzia, L., Ben-David, Y., Kang, S.G., Croul, S., Haibe-Kains, B., Huang, A., Taylor, M.D. & Zacksenhaus, E. 2020.

"Pineoblastoma is a rare pediatric cancer induced by germline mutations in the tumor suppressors RB1 or DICER1. Presence of leptomeningeal metastases is indicative of poor prognosis. Here we report that inactivation of Rb plus p53 via a WAP-Cre transgene, commonly used to target the mammary gland during pregnancy, induces metastatic pineoblastoma resembling the human disease with 100% penetrance. A stabilizing mutation rather than deletion of p53 accelerates metastatic dissemination. Deletion of Dicer1 plus p53 via WAP-Cre also predisposes to pineoblastoma, albeit with lower penetrance. In silico analysis predicts tricyclic antidepressants such as nortriptyline as potential therapeutics for both pineoblastoma models. Nortriptyline disrupts the lysosome, leading to accumulation of non-functional autophagosome, cathepsin B release and pineoblastoma cell death. Nortriptyline further synergizes with the antineoplastic drug gemcitabine to effectively suppress pineoblastoma in our preclinical models, offering new modality for this lethal childhood malignancy."

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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