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## **Medulloblastoma, CNS-PNET, Pineoblastoma (brief information)**

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Prof. Dr. med. Stefan Rutkowski, English Translation: PD Dr. med. Gesche Tallen, Last modified: 2016/11/09

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*Kinderkrebsinfo is sponsored by Deutsche Kinderkrebsstiftung*





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# Medulloblastoma, CNS-PNET, Pineoblastoma (brief information)

## 1. General information on the disease

Medulloblastoma, supratentorial primitive neuroectodermal tumours of the central nervous system (CNS-PNET), and pineoblastoma are primary tumours of the central nervous system (CNS), i. e. tumours that arise from brain tissue or spinal cord tissue.

All three tumour types are „embryonal tumours“, which means, they originate from extremely immature (undifferentiated) cells of the central nervous system, which divide at a high rate. Therefore these tumours grow very fast. Under the microscope, their cells look a lot alike.

Medulloblastoma typically develops in the cerebellum, while CNS-PNETs are usually found in the hemispheres (cerebrum), which is the part of the brain located above („supra“) the „roof“ of the cerebellum (tentorium cerebelli). That is why this type of PNET has been named supratentorial (st)PNET so far as well.

Pineoblastoma arises in the area of the pineal gland (pinealis region) in the very center of the brain. Because CNS-PNET and pineoblastoma are overall rare and the courses of the diseases as well as their treatment approaches are similar, many authors talk about them as one group.

## 2. Incidence

With a ratio of about 25 % in total, medulloblastoma and CNS-PNET are the second most common CNS tumours among children and adolescents (following low grade gliomas). Each year, about 90 children and adolescents under 15 years of age are newly diagnosed with medulloblastoma or CNS-PNET. This corresponds to an incidence rate of 7 per 1,000,000 children, 75 to 85 % of which are diagnosed with medulloblastoma.

### Medulloblastoma

Accounting for nearly 20 %, medulloblastoma is the most common malignant solid tumour occurring during childhood and adolescence. Sometimes young adults are affected, too. The patients' average age at diagnosis ranges between five and seven years. Boys are affected more often than girls (gender ratio: about 1.9 : 1).

### CNS-PNET / Pineoblastoma

Both supratentorial primitive neuroectodermal tumour (CNS-PNET) and pineoblastoma are rare. Taken together, they account for about 5 % of all CNS tumours in childhood and adolescence. In general, children with CNS-PNET or pineoblastoma are slightly younger than children with medulloblastoma. Boys and girls are almost equally affected.



### 3. Localisation and spread in the central nervous system / histological types

The major differences between medulloblastoma, CNS-PNET, and pineoblastoma are their typical locations in the CNS. In addition, their biological behaviour differs, as described in the following paragraphs.

#### Medulloblastoma

Medulloblastoma arises in the cerebellum. Depending on the microscopic (histological) features, medulloblastoma is classified into different subgroups. Their incidences and outcomes vary. Medulloblastoma spreads by uncontrolled proliferation from the cerebellum into the adjacent tissue, for example into the brain stem, but also into the cavities of the brain (ventricles of the brain) – to be precise, into the fourth ventricle, which is located within the back part of the brain (posterior fossa).

The tumour cells also spread via the cerebrospinal fluid (CSF), thereby forming metastases in the spinal canal. A total of one third of the patients with medulloblastoma already present with metastases at initial diagnosis. Metastases can be diagnosed by magnetic resonance imaging (MRI) and/or directly within the CSF obtained by spinal tap (lumbar puncture).

#### CNS-PNET / Pineoblastoma

CNS-PNET also presents as various histological subtypes, all closely resembling medulloblastoma. CNS-PNET typically arises supratentorially (see “General information on the disease”). Very rarely, they develop in other areas of the CNS. Pineoblastoma usually grows in the area of the pineal gland, a small endocrine organ in the center of the brain (pineal region).

Compared to medulloblastoma, CNS-PNET and pineoblastoma show a more aggressive growth pattern. They often spread from one cerebral hemisphere into the other and/or into the meninges, from where they invade additional CNS tissue.

Metastatisation outside the CNS, for instance to bones, bone marrow, lung, or lymph nodes, is rare for medulloblastoma as well as for CNS-PNET and pineoblastoma.

### 4. Causes

The disease is caused by a malignant transformation of nerve tissue cells. The reasons for tumour development have not been completely found out yet.

Researchers have reported that the occurrence of medulloblastoma is often associated with certain chromosomal abnormalities in the tumour cells. These may have caused problems during normal cell and tissue development, thereby transforming a healthy into a cancer cell. Since CNS-PNET are rare, only a few molecular abnormalities that might be responsible for causing the disease, have been identified yet.



It is well-known, though, that radiotherapy of the brain, for example as received by patients with certain forms of leukaemia or with eye cancer (retinoblastoma), is associated with an increased risk of developing a CNS tumour later in life.

## 5. Symptoms

Similar to those of other tumours of the central nervous system (CNS), the presenting symptoms of medulloblastoma, CNS-PNET, and pineoblastoma primarily depend on the patient's age, tumour site, size and pattern of spread within the CNS. The following general (nonspecific) and local (specific) symptoms can occur:

### General (nonspecific) symptoms

Unspecific general symptoms occur independently of the tumour's location. They may be similar to and therefore mimic other, non-CNS diseases. General symptoms of a child or adolescent with a CNS tumour may include headaches and/or back pain, dizziness, loss of appetite, nausea and vomiting (particularly after getting up in the morning), weight loss, increasing fatigue, inability to concentrate, school problems, mood swings and character changes as well as developmental delay, to name a few.

Major reason for these symptoms is the slowly but continuously increasing intracranial pressure (ICP). Elevated ICP may be caused by the growing, thus more and more space-occupying tumour within the bony skull, but also by the tumour blocking the regular flow of the cerebrospinal fluid, thereby forming hydrocephalus. In babies or small children with soft spots (open fontanelles), elevated ICP and hydrocephalus typically present with a bulging fontanelle or a larger than expected head circumference (macrocephalus), respectively.

### Local (specific) symptoms

Local symptoms may indicate the tumour location, thus, which functional regions of the CNS might be affected. For example, a tumour in the cerebellum, such as medulloblastoma, can cause dizziness and gait disturbances, whereas a tumour in the hemispheres can be associated with seizures and / or motor deficits. Also, impaired vision, mental and sleep problems may, although to a lesser extent, be indicative of tumour location.

Due to the uncontrolled and aggressive growth pattern of medulloblastoma, CNS-PNET or pineoblastoma, symptoms typically develop and deteriorate fast.

## 6. Diagnosis

If the doctor thinks that the young patient's history, physical exam and possibly even results from diagnostic imaging are suspicious of a tumour of the central nervous system (CNS), the child should immediately be referred to a childhood cancer centre where further diagnostics can be initiated and performed by childhood cancer professionals.

Very close collaboration between various specialists (such as paediatric oncologists, paediatric neurosurgeons, paediatric radiologists, to name a few) is required, both to find out whether the



patient really suffers from a malignant CNS tumour and, if so, to determine the tumour type and the extension of the disease. Knowing these details is absolutely essential for optimal treatment planning and prognosis.

The initial diagnostic procedures for a young patient presenting with a suspected CNS tumour at a childhood cancer centre include another assessment of the patient's history, a thorough physical/neurological exam and imaging diagnostics, such as magnetic resonance imaging (MRI) and, sometimes, cranial computed tomography (Cat-Scan, CCT).

These diagnostic tools help to confirm or rule out the presence of a CNS tumour as well as to determine a possible spread of the disease in other parts of the CNS, including the spinal canal. Also, tumour size and site, its extent with regard to the adjacent tissue, and hydrocephalus can be assessed by these imaging techniques.

For final diagnosis of a CNS tumour, the microscopic (histological) analysis of tumour tissue (for example obtained during surgical tumour removal or by biopsy) is required.

Because of the continuously extended knowledge of the biological tumour characteristics, the extent of histological analysis has increased rapidly during the last years. Therefore, additional tests may be applied based on the patient's individual disease's situation.

## 7. Treatment planning

After diagnosis has been confirmed, therapy is planned. In order to design a highly individual, risk-adapted treatment regimen for the patient, certain individual factors influencing the patient's prognosis (called risk factors or prognostic factors) are being considered during treatment planning (risk-adapted treatment strategy).

Important prognostic factors are the type, the localization, size and spread of the tumour. In addition, certain biological tumour markers are increasingly considered while determining optimal treatment options.

Also, the patient's age and overall physical condition at diagnosis play a prognostic role. All these factors are included in treatment planning in order to achieve the best outcome possible for each patient.

## 8. Treatment

Treatment of children and adolescents with medulloblastoma, CNS-PNET, or pineoblastoma, respectively, should take place in a children's hospital with a paediatric oncology program. Only such a childhood cancer centre provides highly experienced and qualified staff (doctors, nurses and many more), since they are specialised and focussed on the diagnostics and treatment of children and teenagers with cancer according to the internationally most advanced treatment concepts.

The doctors in these centres collaborate closely with each other. Together, they treat their patients according to treatment plans (protocols) that are continuously optimised. The goal of the treatment is to achieve high cure rates while avoiding side effects as much as possible.



Current treatment concepts involve **neurosurgical tumour removal**, **radiotherapy** of the brain and / or spinal cord, and **chemotherapy**.

## 8.1. Neurosurgery

The primary aim of surgery is the complete removal of the tumour by microsurgical techniques. This means that a special microscope is used during the procedure, by which the neurosurgeon can also rule out any visible remaining tumour tissue after tumour removal. Due to these microsurgical techniques, total tumour resection can be achieved for more than 50 % of patients with medulloblastoma today, but for less with CNS-PNET or pineoblastoma.

Tumour removal may also result in normalising cerebrospinal fluid (CSF) flow in some patients initially presenting with hydrocephalus. Others may need a transient hydrocephalus drainage prior to tumour removal or even a permanent drainage system later.

## 8.2. Additional treatment

Following neurosurgical tumour removal, chemo- and/or radiotherapy are additional options in current treatment strategies. Decision upon which therapy is to be applied is primarily based on the patient's age, the histological subtype of the tumour, certain biological risk factors as well as the extent of both metastases and surgical tumour removal.

Some patients may also benefit from high-dose chemotherapy followed by autologous stem cell transplantation to increase their chances of survival. Current treatment regimens particularly consider this option for children with CNS-PNET, pineoblastoma or metastasised medulloblastoma, who are younger than four years, as well as for certain patients with recurrent disease (relapse).

The treatment regimens for patients with relapse are generally considering the patient's overall condition, the intensity of prior treatment, and the initial response to chemotherapy.

## 9. Therapy optimising trials and registries

In Germany, treatment of almost all children and adolescents with first diagnosis or relapse of medulloblastoma, CNS-PNET, or pineoblastoma are treated according to the treatment plans (protocols) of "therapy optimising trials" or registries .

The term "therapy optimising trial" refers to a form of controlled clinical trial, which aims at improving current treatment concepts for sick patients based on the current scientific knowledge.

Patients who can not participate in any study, for example because none is available or open for them at that time, or since they do not meet the required inclusion criteria, respectively, may be included in a so-called **registry**. Such a registry pools scarce data in order to help with the planning of appropriate future clinical trials. To ensure optimal treatment for patients not registered in a study, experts from assigned trial panels usually provide recommendations and advice to the local caregiver team.



In Germany, a long-term therapy optimising trial (trial “HIT 2000”) for the treatment of children and adolescents with medulloblastoma, CNS-PNET or pineoblastoma was closed in 2011. Many children’s cancer centres in Germany and Austria had participated in this trial. A subsequent trial for patients with medulloblastoma has already been established based on the experiences with HIT 2000 (*see below*). Additional studies are currently underway.

#### Currently open trials and registries:

- **TRIAL SIOP-PNET 5 MB for patients with medulloblastoma:** Since April 2014, patients with medulloblastoma, who are at a „low“ or „standard“ risk of recurrent disease and who are older than three years (or five years, depending on the tumour subtype) at diagnosis, can participate in this European-wide conducted study. The headquarters of the trial are located in the Children’s Cancer Centre at the University of Hamburg, Germany. The head of the trial is Prof. Dr. med. Stefan Rutkowski.
- **I-HIT-MED Registry:** (in Kürze I-HIT-MED Register) Patients with medulloblastoma, CNS-PNET or pineoblastoma, who, for different reasons, cannot or do not want to participate in any currently available or open trial, can be enrolled in this registry, regardless of the treatment given. These patients will receive treatment as per individually designed treatment plans. The goal of the registry is not to assess the feasibility of an ongoing trial, safety or efficacy of a certain treatment. It rather aims at collecting individual patient data for future analysis. The headquarters of the registry are located in the Children’s Cancer Centre at the University of Hamburg, Germany (head of the study: Prof. Dr. med. Stefan Rutkowski).
- **HIT-REZ Registry:** Patients, whose disease does not respond to current treatments (therapy-resistant, progressive medulloblastoma, CNS-PNET, or pineoblastoma) or with recurrent disease (relapse), respectively, can be enrolled in this registry, which has been open since January 2015. This registry does not serve to test new treatment regimens or drugs. However, the experts running the registry are providing treatment recommendations based on the most recent results obtained from national trials (for example from the HIT-REZ 2005 trial, which was closed in 2016) as well as international relapse trials. The headquarters of the registry are located in the Children’s Cancer Centre at the University of Essen, Germany. The head of the study is Prof. Dr. med. Gudrun Fleischhack.

## 10. Prognosis

The chances of cure mainly depend on the type of tumour.

#### Medulloblastoma

The overall outcome for children and adolescents with medulloblastoma improved considerably during the last thirty years. Whereas in the 1960s the survival rate for patients was only 3% after five years, it is higher than 60 % today. Children with a favourable risk profile regarding tumour biology as well as extent of tumour removal or metastases have an over 80 % chance of survival.



### CNS-PNET / Pineoblastoma

Patients with CNS-PNET or pineoblastoma show less favourable survival rates. Despite the current treatment regimens, which include a combination of surgery, chemo- and radiotherapy, long-term survival rates do still not exceed 20 to 30 %, especially not for young children. Older patients may expect an about 60 % chance of long-term survival. Overall, CNS-PNET and pineoblastoma are a very heterogeneous group of cancers and individual outcomes may strongly vary within this group.

**Note:** The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with these types of tumours. They do not predict individual outcomes.

In the context of cancer, the term „cure“ should rather be referred to as „free of cancer“, because current treatment regimens may help getting rid of the tumour, but they are also frequently associated with numerous late-effects. Early detection and appropriate management of these long-term secondary effects typically require intensive rehabilitation and thorough long-term follow-up care, although a patient may have been „cured“ from the cancer.



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