



**kinderkrebsinfo.de**

Informationsportal zu Krebs- und Bluterkrankungen bei Kindern und Jugendlichen

## High-Grade Glioma (HGG) – Brief Information

Copyright © 2020 Competence Network Paediatric Oncology and Haematology

Author: Maria Yiallourous, created 2007/03/09, Editor: Maria Yiallourous, Release: Prof. Dr. med.

Christof Kramm, English Translation: Dr. med. habil. Gesche Tallen, Last modified: 2020/09/16

***Kinderkrebsinfo is sponsored by Deutsche Kinderkrebsstiftung***





## Table of Content

1. General information on the disease .....	3
2. Incidence .....	3
3. Types of high-grade gliomas .....	3
4. Causes .....	4
5. Symptoms .....	5
5.1. General (unspecific) symptoms .....	5
5.2. Local (specific) symptoms .....	5
6. Diagnosis .....	5
6.1. Tests to secure diagnosis .....	6
6.2. Tests before treatment begins .....	6
7. Treatment planning .....	7
8. Treatment .....	8
8.1. Treatment methods .....	8
8.2. Course of treatment (standard therapy for patients from 3 years of age) .....	9
8.2.1. Induction phase .....	9
8.2.2. Consolidation phase .....	10
8.2.3. Treatment options after this therapy .....	10
8.3. Treatment according to therapy optimising trial HIT-HGG 2007 .....	10
9. Therapy optimising trials .....	10
10. Treatment according to therapy optimising trial HIT-HGG 2013 .....	11
11. Prognosis .....	12
Bibliography .....	14

# High-Grade Glioma (HGG) – Brief Information

## 1. General information on the disease

Highly malignant or high-grade gliomas (HGG) are tumours of the central nervous system (CNS). They are solid tumours arising from transformed cells of the brain and/or the spinal cord. Since they directly originate from the central nervous system, they are also called primary CNS tumours, thereby differentiating them from malignant tumours of other organs that have spread (metastasised) to the CNS.

High-grade gliomas in children and adolescents are rare. However, they show considerably malignant behaviour since they usually grow fast and frequently destroy healthy brain tissue. By being able to migrate within the central nervous system for various centimetres, high-grade gliomas can induce the development of new tumours. Without the appropriate therapy, high-grade gliomas can be lethal within only a few months. Due to their usually rapid and infiltrating growth, treatment is difficult.

## 2. Incidence

High-grade gliomas account for approximately 15 to 20 % of CNS tumours in children and adolescents. They appear in all age groups; yet, children aged younger than three years are rarely affected. Each year, about 60 to 80 children and adolescents younger than 15 years of age are newly diagnosed with a high-grade glioma in Germany. This corresponds to an incidence rate of 5 to 10 new diagnoses per 1.000.000 children per year. Boys and girls are almost equally affected.

## 3. Types of high-grade gliomas

Various types of high-grade gliomas (HGG) have been identified based on their localization within the central nervous system (CNS), the cell of origin and the degree of malignancy.

### High-grade gliomas of the brainstem

High-grade gliomas of the brainstem, such as "typical diffuse intrinsic pontine glioma" (as well as histologically and genetically diagnosed "diffuse midline gliomas HR K27M mutated WHO-grade IV", as long as they are located in the brainstem), account for about one third of all HGG in children and teenagers. Due to their localization within the pons – an area of the brainstem, through which all important nerve tracts between extremities and brain are passing –, they can cause various severe neurological deficits and also result in a rapid and fatal course of the disease, even when they are small in size.

### Gliomas in other parts of the central nervous system



About two thirds of high-grade gliomas are usually found in other parts of the CNS, especially in the cerebral cortex. These gliomas can be further subgrouped based on their histological and molecular characteristics, which provide insight into their origin and degree of malignancy. In general, these are tumours that are classified as WHO-grade III or WHO-grade IV according to the grading system of the World Health Organization (WHO classification).

In children and adolescents, the most common among HGG are anaplastic astrocytomas (WHO grade III) and glioblastoma multiforme (WHO grade IV). Other tumour types are rather rare. These include the gliomatosis cerebri, a type of tumour that is typically characterised by a particularly extended infiltration and spread into adjacent tissue. Although its cells are frequently of low-grade malignancy, this tumour is classified as a highly malignant glioma because of its distinct growth pattern.

**Good to know:** The various types of HGG differ in frequency and show different growth characteristics, different courses of the disease, different responses to treatment, and thus different outcomes (prognoses).

**Note with regards to typical diffuse intrinsic pons glioma (DIPG):** DIPG, which are usually diagnosed by imaging, frequently turn out as "diffuse midline gliomas histone 3 K27M-mutated (WHO-grade III)" based on their histology and molecular biological characteristics and are, therefore, classified by the WHO as an entity of their own. However, despite their different terminology based on underlying diagnostics, they represent the same tumour type after all.

## 4. Causes

High-grade gliomas originate from a malignant transformation of glial cells (glia). These are cells that, among other functions, provide support and protection for the brain's nerve cells (neurons). Why glia cells become malignant in some individuals is not completely known yet.

It is known so far that children with certain inherited diseases (such as Li-Fraumeni syndrome or Turcot syndrome) have a higher risk of developing high-grade gliomas than their healthy peers. Because these genetic conditions are associated with an elevated risk for tumour development, they are also known as cancer predisposition syndromes. In addition, it has been shown that malignant glial cell transformation can be associated with genetic alterations and/or chromosomal aberrations in these cells. In general, these genetic alterations in tumor tissue are not relatively and most certainly developed early in development.

Also, irradiation of the skull (cranial irradiation), for example during treatment of leukaemia or retinoblastoma, a malignant tumour of the eye, increases the risk of developing a CNS tumour. Although not as frequently, chemotherapy can also promote the development of a high-grade glioma. However, for most children and adolescents, no specific cause for the development of high-grade glioma has been identified so far.

## 5. Symptoms

Due to the tumours' rapid growth, symptoms of children and adolescents with high-grade glioma usually develop within a few weeks or months. Similar to those of other tumours of the central nervous system (CNS), the presenting symptoms of high-grade gliomas primarily depend on the patient's age, tumour site and size, and pattern of spread within the central nervous system. The following general (nonspecific) and local (specific) symptoms can occur.

### 5.1. General (unspecific) 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 intracranial pressure may be caused by the growing, thus more and more space-occupying tumour within the bony skull (or spinal canal), 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 intracranial pressure and hydrocephalus typically present with a bulging fontanelle or a larger than expected head circumference (macrocephalus), respectively.

### 5.2. Local (specific) symptoms

Local symptoms may indicate the tumour location, thus, which functional regions of the central nervous system may be affected. Thus, a high-grade glioma in the cerebellum can cause dizziness and gait disturbances, whereas such a tumour in the hemispheres can be associated with seizures, and a tumour of the spinal cord with different kinds of motor and sensory deficits (like muscle weakness and numbness), to name a few. Also, impaired vision or mental and sleep problems may be indicative of tumour location.

**Good to know:** Not all patients presenting with one or more of the symptoms mentioned above do have a high-grade glioma or another type of brain tumour. Many of these symptoms may also occur with other, harmless diseases that are not associated with a brain tumour at all. However, if certain symptoms persist or get worse (for example repetitive headaches or rapid increase of head circumference in a young child), a doctor should be seen to find the underlying reason. In case it is a brain tumour, treatment should be started as soon as possible.

## 6. Diagnosis

If the paediatrician 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 hospital with a childhood cancer program (paediatric oncology unit), 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.

## 6.1. Tests to secure diagnosis

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 diagnostic, such as magnetic resonance imaging (MRI) or (less often) computed tomography (CT). These tests help find out exactly whether the patient has a tumour of the central nervous system. Also, localisation and extent of the tumor, its demarcation regarding adjacent tissue as well as a potential hydrocephalus can be diagnosed by these imaging techniques very well.

In children with a suspected tumour of the visual tract, an assessment by an experienced eye specialist (ophthalmologist) is also performed. Depending on the patient's individual situation with regards to disease and treatment, additional tests may be required. For example, investigation of the cerebral spinal fluid might be needed in order to identify or rule out, respectively, a spread of tumour cells into the spinal canal.

For most patients, final diagnosis is backed up by microscopic (histological) examination of tumour tissue that has been neurosurgically removed (biopsy). An exception, however, are children with pontine glioma or gliomatosis cerebri, respectively, diagnosis of which can usually be confirmed based on typical MRI characteristics and clinical symptoms. An additional biopsy may contribute to a better characterisation of these tumours and may therefore be recommendable, but not ultimately required for treatment planning.

## 6.2. Tests before treatment begins

In preparation for the intensive treatment of the brain tumour, further investigations are performed, such as electrocardiography (ECG) and echocardiography to check cardio function. An electroencephalogram (EEG) helps identify potential areas in the brain that the tumour might have made susceptible to cause seizures. In addition, an ophthalmological exam as well as various electrophysiological investigations to assess vision, hearing, motor and sensory functions (evoked potentials) may be required.

Furthermore, additional blood tests are needed to assess the patient's general health condition and to check whether the function of certain organs (such as liver and kidneys) is affected by the disease and whether there are any metabolic disorders to be considered prior or during therapy. Condition and function of the hormonal glands will be checked in order to detect and manage potential tumour- and/or treatment-associated endocrinological impairments as early as possible. For the same reason, neuropsychological testing might be done prior to cancer treatment. Any changes occurring during the course of treatment can be assessed and managed better based on



the results of those initial tests, which thus help to keep the risk of certain treatment-related side effects as low as possible.

Also, the patient's blood group needs to be determined in case a transfusion is required during treatment. In sexually mature females (which means after they have experienced their first menstrual bleeding), a pregnancy test is recommended prior to treatment as well.

**Good to know:** Not every patient needs the complete check-up. On the other hand, tests might be added that haven't been mentioned here, depending on the individual situation of the patient. Your caregivers will inform you and your child, which diagnostic procedures are individually required in your case and why.

## 7. Treatment planning

Once the diagnosis of a malignant glioma has been confirmed, treatment planning starts. In order to provide the patient with the best possible individual and risk-adapted therapy, the treatment team considers specific factors that are known to have an impact on the prognosis (so-called prognostic factors).

Important prognostic factors are the type of malignant glioma, its size, localization, and spread in the central nervous system. Detailed knowledge about the type of tumour allows conclusions regarding its growth pattern and grade of malignancy (WHO-grade, see chapter "Types of malignant gliomas"), whereas the tumour site and size determine its operability. Both factors have immediate impact on the patient's chances of survival and, therefore, are a major basis when choosing the optimal treatment strategy. Additionally, response to treatment, age, and the patient's health status at the time point of diagnosis play an important role. Age at diagnosis, for example, determines whether the patient will receive radiotherapy or not.

All these risk factors are considered when planning the treatment. The goal is to achieve the best possible results for every patient. Hence, the individual disease situation determines how the patient should be treated best.

Patients (at the age of three or older) who have been diagnosed with a high-grade glioma [such as glioblastoma multiforme WHO-grade IV (GBM), diffuse midline glioma histone 3K 27M-mutated WHO-grade IV (DMG), anaplastic astrocytoma WHO-grade III (AA), diffuse intrinsic pons glioma (DIPG), and gliomatosis cerebri (GC)] receive an intensive treatment, in the framework of a therapy optimising study (see chapter "Treatment" and "Therapy optimising trials").

The treatment plans for patients with less frequent grade III gliomas (such as anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, or anaplastic pleomorphic xanthoastrocytoma) usually include a less intensive therapy due to the relatively favourable prognosis of these tumours. Children under the age of three years are treated as per so-called infant protocol, which does not include radiotherapy.

## 8. Treatment

If high-grade glioma has been diagnosed, treatment should be started as soon as possible in a children's hospital with a paediatric oncology program. Only in such a treatment centre, highly experienced and qualified staff (doctors, nurses and many more) is guaranteed, since they are specialized and focus on the diagnostics and treatment of children and teenagers with cancer according to the 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 acute or long-term side effects as much as possible.

Treatment strategies for patients with high-grade glioma include **surgical tumour removal** as well as **radiotherapy** and **chemotherapy**. The choice of treatment strategy depends primarily on the site and extent of the tumour (thus, its removability) as well as on the patient's age at diagnosis and the individual health situation.

### 8.1. Treatment methods

The most effective treatment for children and adolescents with high-grade glioma is a combination of neurosurgery, radiotherapy, and chemotherapy. Neurosurgery is performed first, followed by chemo- and radiotherapy, which are usually applied during the same phase of treatment (simultaneously). Neurosurgery is of highest impact, since the extent of tumour removal significantly determines the further course of the disease. The more radically the tumour can be resected, the higher are the chances of survival. According to the current standard of knowledge, surgery and radiation have proven to extend the life span of a young patient with high-grade glioma.

Neurosurgery is of highest impact, since the extent of tumour removal significantly determines the further course of the disease. The more radical the tumour can be resected, the higher are the chances of survival. According to the current standard of knowledge, surgery and radiation have proven to extend the life-span of a young patient with high-grade glioma.

Yet, surgery or radiation cannot be performed in every child. Many tumours of the brain stem, such as diffuse intrinsic pontine gliomas, are neurosurgically not accessible. Also, radiotherapy of the brain or spinal cord is not recommended for children aged younger than three years. In addition, the possible, still justifiable extent of tumour removal can vary: tumours that are located very centrally in the brain (for example tumours of the diencephalon or the midbrain) usually cannot be completely removed or approached surgically at all, since this would result in a substantial damage of healthy brain tissue and associated deficits.

Previous therapy optimising clinical trials have shown that additional (adjuvant) chemotherapy can improve treatment results. However, no treatment approach ensuring that the tumour will not start growing again after a short while has been developed so far. The most crucial step prior to any treatment is the decision whether the patient should receive therapy, and if so, which goal the treatment should have: either cure (curative treatment) or management of disease-related





symptoms, such as pain (palliative care). Regardless of the goal setting, treatment and care in the framework of a trial is always recommended.

## 8.2. Course of treatment (standard therapy for patients from 3 years of age)

The following paragraphs introduce the current recommendations for standard therapy for children and adolescents (from 3 years of age) with high-grade glioma (grade-IV glioma, anaplastic glioma grade III, pontine glioma, gliomatosis cerebri). Treatment recommendation for children younger than three years of age is different, in particular, it doesn't include radiotherapy. Information on treatment as per therapy optimising study "HIT-HGG 2013", which has been open for recruitment since spring 2018, can be found in the chapter „Treatment according to trial HIT-HGG 2013“.

First step when treating a patient with high-grade glioma is maximal neurosurgical tumour removal, with the exception of pontine glioma and gliomatosis cerebri, which are surgically not accessible due to their localisation or growth pattern, respectively.

Surgery is followed by radiotherapy and chemotherapy, which are also recommended for patients with inoperable tumours. Treatment consists of two major parts: the induction phase at the beginning (induction therapy) and the subsequent consolidation phase (consolidation therapy). Both phases include various treatment blocks.

### 8.2.1. Induction phase

Induction therapy starts about two to four weeks after surgery or directly after an MRI-based diagnosis, respectively. It takes six to seven weeks and either aims at further reducing the size of a tumour that could not be completely removed or at eliminating potentially remaining tumour cells after complete tumour removal. The major approach includes simultaneous radio- and chemotherapy.

Radiotherapy is given to the tumour region over a period of six to seven weeks with daily doses of 1.8 Gy. The total radiation dose depends on the patient's age and the site of the tumour: For children between three and five years of age, the total dose is 54 Gy, for children from the age of six it is 59.4 Gy. For patients with pontine glioma, limitation of the total dose to 54 Gy is recommended. Radiotherapy is given five days a week, sparing the weekends.

Chemotherapy includes treatment with the agent temozolomide (Temodal®), which is taken as a pill every evening from day one to the last day of radiation. This also applies to weekends, although there is no radiotherapy on weekends. Radiotherapy and simultaneous chemotherapy are followed



by a four weeks' break. This gives the patient some time to recover before consolidation phase starts.

### 8.2.2. Consolidation phase

Consolidation therapy begins about four weeks after cessation of induction, that means, after the recovery phase. Consolidation consists of chemotherapy only and takes about a year. Its goal is to maintain the results achieved by induction treatment or to even improve them.

For chemotherapy, temozolomide is given again, but with its dosage usually twice as high compared to induction therapy. If tolerated well, it can even be increased further. Treatment is given for five days in a row, followed by a 23 day recovery phase. This results in a repetition of treatment every 28 days (four weeks) for a total of 12 courses. The efficacy of treatment is monitored by regular MRI controls.

### 8.2.3. Treatment options after this therapy

In some patients, the tumour size shrinks, thereby becoming surgically accessible and possibly completely removable after induction, or after both induction and consolidation therapy, respectively. Other patients suffer progressive disease despite treatment and, thus, may not benefit from standard therapy any more. Depending on their individual situation, treatment recommendations focusing on progressive or recurrent disease may be considered for subsequent management.

## 8.3. Treatment according to therapy optimising trial HIT-HGG 2007

Treatment according to protocol HIT-HGG 2007 (*see below*) involves neurosurgical tumour resection followed by combined radio- and chemotherapy.

Chemotherapy consists of five to six weeks of daily treatment with the anticancer agent Temozolomid. Major goal of the intensive treatment is to either shrink residual tumour tissue after incomplete resection or to fight those cancer cells that may have remained in the body even after radical surgery.

The intensive treatment phase is usually followed by a less intense though longer-lasting therapy (maintenance therapy) which aims at further improving the patient's outcome. This therapy phase consists of treatments with Temozolomid given on five consecutive days once a month. Total treatment duration is one year.

## 9. Therapy optimising trials

In Germany, diagnostics and treatment of almost all children and adolescents with first diagnosis of high-grade glioma (HGG) are performed according to the treatment plans (protocols) of "therapy optimising trials", so named because the treatment concepts of such trials are continuously being optimised based on the latest medical knowledge and the experience with former protocols.

In Germany (with international participation), the following therapy optimising trials or treatment recommendations, respectively, are currently active for patients with malignant glioma, pontine glioma or with gliomatosis cerebri:

- **Trial HIT-HGG 2013:** Since July 2018, children and adolescents between the age of 3 to 17 years who have been newly diagnosed with high-grade glioma (grade-IV glioma, anaplastic astrocytoma grade III), pontine glioma or gliomatosis cerebri, can be recruited into this trial. HIT-HGG 2013 represents the subsequent study of the HIT-HGG 2007 trial, which was closed for recruitment by the end of 2016 and is currently being analysed. Numerous childhood cancer centres throughout Germany, Switzerland, Austria, and Belgium participate in this trial. The German trial centre is located at the Department of Paediatric Oncology/Haematology, University Hospital Göttingen (principal investigator: Prof. Dr. med. Christof Kramm).
- **Therapy recommendations for infants according to the future trial HIT-SKK:** Infants and toddlers (aged younger than three years at diagnosis, which is rare), are currently treated according to the recommendations which will form part of the future trial for infants, HIT-SKK (treatment without radiotherapy). A proposal for a separate registry has been submitted (see *below*). Treatment according to the future registry will be based on the recommendations given in the HIT-SKK protocol. The registry centre will stay at the University Hospital Göttingen, supervised by Prof. Dr. med Christof Kramm.
- **Trial HIT-HGG-REZ-Immunovac:** Since February 2018, patients with relapsed high-grade glioma can be recruited to the trial HIT-HGG-REZ-Immunovac. This study investigates whether giving a vaccine after relapse surgery improves patient survival (immunotherapy). The trial is currently active in one German treatment centre (University Children's Hospitals in Würzburg) with Prof. Dr. med. Matthias Eyrich (Universitätsklinik Würzburg) as the principal investigator.

**Future registry:** Opening a registry for children under three years of age as well as for all patients who won't receive treatment as per trial HIT-HGG 2013, is planned for 2020. The latter also include children and adolescents with the less frequent grade-III tumours (such as anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ganglioglioma, anaplastic xanthoastrocytoma). For this registry, the study centre will also offer treatment recommendations based on the most recent scientific knowledge. Hence, the spectrum of recommendations provided by the trial centre will consider patients of all age groups, regardless of their diagnosis.

## 10. Treatment according to therapy optimising trial HIT-HGG 2013

Treatment according to trial HIT-HGG 2013 is based on the current standard therapy, which consists of neurosurgical tumour removal (if applicable) followed by a combined radio-/chemotherapy (with temozolomide). This strategy was previously introduced to children and adolescents in trial HIT-HGG 2007, and its efficacy has proven to be comparable to that achieved by conventional multi-agent chemotherapy regimens, but with less treatment-induced adverse effects and long-term secondary damages (sequelae).

Since overall treatment results for patients with high-grade glioma (including pontine glioma and gliomatosis cerebri) are still unsatisfactory, the new trial was initially designed to test two new agents in addition to the standard regimen and compare their efficacy by conducting a trial with two treatment "arms": one of them using valproic acid, which is also used as an anti-epileptic drug, the other one chloroquin, which is known as an anti-malaria agent. As indicated, both substances have been used to treat other diseases over decades, but have most recently also shown anti-tumour effects. Patients were assigned to the two different trial arms in a randomised manner. Unfortunately, the use of chloroquin was ceased in July 2019. Therefore, the chloroquin arm in the trial was closed, while treatment with valproic acid has been continued. Randomisation has become redundant since.

The trial is supposed to find out whether the additional agent significantly improves the efficacy of the current radio- and chemotherapy and, thus, probability of survival.

Treatment with valproic acid starts as soon as possible, which means immediately after confirmation of diagnosis (either histologically after surgery, or, if surgery is not an option, immediately after confirming diagnosis by MRI). The agent is given as pills or suspension on a daily basis, without any break, over a total of 58 weeks (or longer).

About two to four weeks after histological or radiological diagnosis (defined as week 0), standard therapy begins, comprising radiotherapy and simultaneous chemotherapy with temozolomide for six to seven weeks (induction therapy) and a subsequent treatment phase with temozolomide alone for about a year (consolidation therapy). *Information on standard therapy is provided in chapter "Course of treatment (standard therapy for patients from 3 years of age)".*

## 11. Prognosis

Despite improved methods in diagnosis and therapy, prognosis for children and adolescents with high-grade glioma is still unfavourable. The overall probability to survive 5 years after the initial diagnosis was made is currently about 10 to 19 %. However, overall survival rates significantly depend on the localization and type of high-grade glioma as well as on the extent of tumour removal by surgery. Therefore, they may vary between 50 % for patients after complete resection and 0 % for those children for whom no anticancer therapy is possible at all.

In general, the possibility to develop recurrent disease (relapse) after successful first-line treatment is high for young patients with a high-grade glioma and prognosis for patients with relapsed disease is even worse. A new treatment approach has to be considered carefully to maintain appropriate quality of life for the patient. Current therapy optimising clinical studies aim at further improving the treatment options and reducing the side effects for patients with childhood (relapsed) HGG. Further specific knowledge of the disease is intensified by associated research projects, the results of which will determine future treatment protocols.



**Note:** The survival rates mentioned in the text above are statistical values. Therefore, they only provide information on the total cohort of patients with childhood high-grade gliomas. They do not predict individual outcomes. High-grade gliomas can show unpredictable courses, in both patients with favourable and patients with unfavourable preconditions.

In the context of cancer, the term „cure“ should rather be referred to as „free of cancer“, because current treatment regimens may help to destroy 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.

# Bibliography

- [1] Broniscer A, Gajjar A „Supratentorial high-grade astrocytoma and diffuse brainstem glioma: two challenges for the pediatric oncologist“, *Oncologist* 2004;9:197-206. Review, 15047924 pubmed
- [2] Cohen KJ, Pollack IF, Zhou T, Buxton A, Holmes EJ, Burger PC, Brat DJ, Rosenblum MK, Hamilton RL, Lavey RS, Heideman RL „Temozolomide in the treatment of high-grade gliomas in children: a report from the Children's Oncology Group.“, *Neuro-oncology* 2011 Mar;13(3):317-23, 21339192 pubmed
- [3] Eyrich M „Immuntherapie rezidivierter Gliome – ein individualisierter Therapieansatz“, *WIR - die Zeitschrift der Deutschen Leukämie-Forschungshilfe e.V. und der Deutschen Kinderkrebsstiftung* 2/2018, [https://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift\\_Wir/2018\\_2/Immuntherapie.pdf](https://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift_Wir/2018_2/Immuntherapie.pdf) uri
- [4] Fleischhack G, Rutkowski S, Pfister SM, Pietsch T, Tippelt S, Warmuth-Metz M, Bison B, van Velthoven-Wurster V, Messing-Jünger M, Kortmann RD, Timmermann B, Slavc I, Witt O, Gnekow A, Hernáiz Driever P, Kramm C, Benesch M, Frühwald MC, Hasselblatt M, Müller HL, Sörensen N, Kordes U, Calaminus G. „ZNS-Tumoren“, in: *Niemeyer C, Eggert A (Hrsg.): Pädiatrische Hämatologie und Onkologie. Springer-Verlag GmbH Deutschland, 2. vollständig überarbeitete Auflage* 2018: 359, 978-3-662-43685-1 isbn
- [5] Howe GR, Burch JD, Chiarelli AM, Risch HA, Choi BC „An exploratory case-control study of brain tumors in children“, *Cancer Res* 1989;49(15):4349-52, 2743324 pubmed
- [6] Karremann M, Gielen GH, Hoffmann M, Wiese M, Colditz N, Warmuth-Metz M, Bison B, Claviez A, van Vuurden DG, von Bueren AO, Gessi M, Kühnle I, Hans VH, Benesch M, Sturm D, Kortmann RD, Waha A, Pietsch T, Kramm CM „Diffuse high-grade gliomas with H3 K27M mutations carry a dismal prognosis independent of tumor location.“, *Neuro-oncology* 2018 Jan 10;20(1):123-131, 29016894 pubmed
- [7] Kramm C „Die neue HIT-HGG-2013-Studie“, *WIR - Zeitschrift der Deutschen Kinderkrebsstiftung und der Deutschen Leukämie-Forschungshilfe e.V.* 3/17, [https://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift\\_Wir/2017\\_3/HIT.pdf](https://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift_Wir/2017_3/HIT.pdf) uri
- [8] Kramm C „Die HIT-HGG-Studiengruppe - Beratung und Protokolle für alle Behandlungssituationen bei hochmalignen Gliomen im Kindes- und Jugendalter“, *WIR - die Zeitschrift der Deutschen Leukämie-Forschungshilfe e.V. und der Deutschen Kinderkrebsstiftung* 1/2010, [http://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift\\_Wir/2010\\_1/WIR\\_1\\_10\\_klinik\\_01.pdf](http://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Zeitschrift_Wir/2010_1/WIR_1_10_klinik_01.pdf) uri
- [9] Kramm C, Wolff J.E.A. „Hochgradig maligne Gliome und Ponsgliome im Kindes- und Jugendalter“, *Interdisziplinäre Leitlinie der Deutschen Krebsgesellschaft und der Deutschen Gesellschaft für Pädiatrische Onkologie und Hämatologie* 2008, [http://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Leitlinien/2008/Leitlinie\\_HGG\\_Ponsgliome.pdf](http://www.kinderkrebsstiftung.de/fileadmin/Redaktion/Leitlinien/2008/Leitlinie_HGG_Ponsgliome.pdf) uri

[www.awmf.org/uploads/tx\\_szleitlinien/025-024I\\_S1\\_Gliome\\_niedrigen\\_Malignitätsgrades\\_Kindesalter\\_Jugendalter\\_2013-06.pdf](http://www.awmf.org/uploads/tx_szleitlinien/025-024I_S1_Gliome_niedrigen_Malignitätsgrades_Kindesalter_Jugendalter_2013-06.pdf) uri

- [10] Kramm C, Rausche U, Butenhoff S, Kühnöl C, Kunze C, Kortmann R, Wolff J, van Gool S „Hochmaligne Gliome im Kindes- und Jugendalter“, *Monatsschr Kinderheilkd.* 2008, 156:1201-1207, 10.1007/s00112-008-1799-3 doi
- [11] Kramm CM, Wagner S, Van Gool S, Schmid H, Strater R, Gnekow A, Rutkowski S, Wolff JE „Improved survival after gross total resection of malignant gliomas in pediatric patients from the HIT-GBM studies“, *Anticancer Res* 2006;26:3773-9, 17094400 pubmed
- [12] Kühl J, Korinthenberg R „ZNS-Tumoren. In: Gadner H, Gaedicke G, Niemeyer CH, Ritter J (Hrsg.): Pädiatrische Hämatologie und Onkologie“, *Springer-Verlag* 2006: 777-822, 3540037020 isbn
- [13] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW „The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary.“, *Acta neuropathologica* 2016 Jun;131(6):803-20, 27157931 pubmed
- [14] MacDonald TJ, Aguilera D, Kramm CM. „Treatment of high-grade glioma in children and adolescents.“, *Neuro Oncol* 2011, [Epub ahead of print], 21784756 pubmed
- [15] Ripperger T, Bielack SS, Borkhardt A, Brecht IB, Burkhardt B, Calaminus G, Debatin KM, Deubzer H, Dirksen U, Eckert C, Eggert A, Erlacher M, Fleischhack G, Frühwald MC, Gnekow A, Goehring G, Graf N, Hanenberg H, Hauer J, Hero B, Hettmer S, von Hoff K, Horstmann M, Hoyer J, Illig T, Kaatsch P, Kappler R, Kerl K, Klingebiel T, Kontny U, Kordes U, Köhrholz D, Koscielniak E, Kramm CM, Kuhlen M, Kulozik AE, Lamottke B, Leuschner I, Lohmann DR, Meinhardt A, Metzler M, Meyer LH, Moser O, Nathrath M, Niemeyer CM, Nustede R, Pajtler KW, Paret C, Rasche M, Reinhardt D, Rieß O, Russo A, Rutkowski S, Schlegelberger B, Schneider D, Schneppenheim R, Schrappe M, Schroeder C, von Schweinitz D, Simon T, Sparber-Sauer M, Spix C, Stanulla M, Steinemann D, Strahm B, Temming P, Thomay K, von Bueren AO, Vorwerk P, Witt O, Wlodarski M, Wälchli W, Zenker M, Zimmermann S, Pfister SM, Kratz CP „Childhood cancer predisposition syndromes-A concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology.“, *American journal of medical genetics. Part A* 2017;173(4):1017-1037, 28168833 pubmed
- [16] Rutkowski S, Trollmann R, Korinthenberg R, Warmuth-Metz M, Weckesser M, Krauss J, Pietsch T „Leitsymptome und Diagnostik der ZNS-Tumoren im Kindes- und Jugendalter“, *Gemeinsame Leitlinie der Gesellschaft für Neuropädiatrie und der Gesellschaft für Pädiatrische Onkologie und Hämatologie* 2016, [http://www.awmf.org/uploads/tx\\_szleitlinien/025-022I\\_S1\\_ZNS-Tumoren\\_Kinder\\_Jugendliche\\_2016-09.pdf](http://www.awmf.org/uploads/tx_szleitlinien/025-022I_S1_ZNS-Tumoren_Kinder_Jugendliche_2016-09.pdf) uri
- [17] Seidel C, von Bueren AO, Bojko S, Hoffmann M, Pietsch T, Gielen GH, Warmuth-Metz M, Bison B, Kortmann RD, Kramm CM „Concurrent radiotherapy with temozolomide vs. concurrent radiotherapy with a cisplatin-based polychemotherapy regimen : Acute



toxicity in pediatric high-grade glioma patients.“, *Strahlentherapie und Onkologie* 2018 Mar;194(3):215-224, 29022050 pubmed

- [18] Wagner S „Therapie von hochgradig malignen Gliomen im Kindes- und Jugendalter“, *WIR Informationsschrift der Aktion für krebskranke Kinder e.V. (Bonn)* 2003,1:13, [http://www.kinderkrebsstiftung.de/fileadmin/KKS/files/zeitschriftWIR/2003\\_1/behaltungsnetzwerk09.pdf](http://www.kinderkrebsstiftung.de/fileadmin/KKS/files/zeitschriftWIR/2003_1/behaltungsnetzwerk09.pdf) uri
- [19] Wolff JE,Driever PH,Erdlenbruch B,Kortmann RD,Rutkowski S,Pietsch T,Parker C,Metz MW,Gnekow A,Kramm CM „Intensive chemotherapy improves survival in pediatric high-grade glioma after gross total resection: results of the HIT-GBM-C protocol.“, *Cancer* 2010;116(3):705-12, 19957326 pubmed