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## **Low-grade gliomas (LGG) - Brief information**

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# Low-grade gliomas (LGG) - Brief information

## 1. General information on the disease

Low-grade gliomas are tumours of the central nervous system (CNS). They are solid tumours arising from malignantly transformed cells of the brain or spinal cord. Since they develop directly from CNS cells, they are also called primary CNS tumours in order to distinguish them from cancers of other body parts that have spread to the CNS (metastasis).

Low-grade gliomas can be found in all parts of the nervous system, most of them, however, are situated in the cerebellum and the central regions of the cerebrum, such as the optic pathway (optic pathway gliomas) and the hypothalamic-pituitary axis. They usually grow very slowly. Nevertheless, for a growing lesion, the space in the bony skull is limited. As a consequence, vital areas of the brain may be damaged by the space occupying, growing tumour. Therefore, low-grade gliomas can become life threatening in the course of disease.

## 2. Incidence

With a ratio of about 30 to 40 %, low-grade gliomas are the most common CNS tumours among children and adolescents. They occur at all ages with a mean age at diagnosis between five and seven years.

In Germany, about 250 children and adolescents under 18 years of age are newly diagnosed with low-grade glioma each year. This corresponds to an incidence rate of 2 to 3 per 100.000 children. There is a slight male preponderance (gender ratio: 1.2 to 1).

## 3. Types / growth patterns of low-grade gliomas

Based on their biological features, such as growth behaviour and various microscopic characteristics, the World Health Organisation (WHO) classifies the large group of low-grade gliomas either as WHO-grade I or WHO-grade II tumours.

Transformation of low-grade gliomas into high-grade (highly malignant) gliomas, as has been described in adults, appears to be overall rare in children. The relatively low incidence of such transformation in this age group has also been implied by molecular genetic analyses of low-grade gliomas, which are being performed as part of various research projects. These studies revealed that the genetic changes appearing in glioma cells of children are completely different from those found in the adult population. Besides, the age, at which adolescents start to be a risk of developing high-grade glioma, still needs to be elucidated.



The growth pattern of low-grade gliomas is unpredictable. In most patients, these tumours are localised and grow slowly. Some patients even experience phases of no tumour growth. However, low-grade gliomas may also grow fast and aggressively.

The risk of tumour cell spread (metastasis) via the cerebrospinal fluid (CSF) is generally low. Only children diagnosed with optic pathway glioma at a very young age have a slightly elevated risk of developing CSF metastases.

## 4. Causes

Low-grade gliomas originate from malignantly transformed glial cells (neuroglia). These are cells that, among other functions, provide support and protection for the brain's nerve cells (neurons). The exact cause for this malignant glia cell transformation is not completely defined yet.

It is known so far, that children with certain inherited diseases (such as Neurofibromatosis Type 1 (NF1) or tuberous sklerosis) have a higher risk of developing low-grade glioma than their healthy peers. For example, up to 20 % of patients with NF 1 develop a low-grade glioma, mostly in the area of the optic pathway.

Also, radiotherapy of the brain in childhood, 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 low grade gliomas primarily depend on the patient's age, tumour site and 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 intracranial pressure 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. Thus, a low grade glioma in the cerebellum can cause dizziness and gait disturbances, whereas such a tumour in the hemispheres can be associated with seizures and / or motor deficits and a tumour of the spinal cord with back pain and different kinds of motor and sensory deficits (like muscle weakness and numbness).

Also, impaired vision, mental and sleep problems may, although to a lesser extent, be indicative of tumour location.

**Good to know:** In most children and adolescents with low-grade glioma, health problems (symptoms) develop slowly, because the tumour usually grows slowly.

## 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.

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) and computed tomography.

These diagnostic tools help to confirm or rule out the presence of a CNS tumour as well as to assess tumour size and site and its extent with regard to the adjacent tissue. Patients with suspected optic pathway glioma additionally need a thorough eye exam performed by a specialized eye doctor. Depending on the patient's individual situation and clinical condition, additional tests may be necessary.

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. Since surgery is already part of the overall treatment concept, it should be performed by experienced paediatric neurosurgeons in a specialized treatment center. Also, the subsequent microscopic and histological analyses are complex, thus requiring an experienced pathologist to obtain the correct diagnosis.

For some patients, for example with certain optic pathway gliomas or tumours in the hypothalamic area, tumour removal might not be possible, since it carries the risk of damaging vital structures. In



these cases, the interdisciplinary team of doctors may decide that tumour diagnosis is to be made by an experienced radiologist based on special features of the lesion in diagnostic imaging.

## 7. Treatment planning

After the 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. Also, the patient's age and overall physical condition 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 low-grade glioma should take place in a children's hospital with a paediatric oncology program. Only in such a childhood cancer 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 side effects as much as possible.

Treatment usually consists of **surgical tumour removal** (neurosurgery) followed by a **controlled „watch-and-wait“-approach**. By far not all patients with low-grade gliomas need **chemotherapy** or **radiotherapy**.

### 8.1. Surgery

For patients with low grade glioma, neurosurgical intervention aiming at removing the tumour has always been the treatment of choice. Its urgency is defined by the seriousness of the clinical symptoms and the tumour location. It is well-known by now that the extent of surgical tumour removal has major impact on the subsequent course of the disease.

Therefore, the primary goal of neurosurgery is complete tumour removal. Sometimes, however, tumours are located in parts of the brain that make complete resection impossible, for such an approach would be associated with a high risk of damaging. These patients are considered to undergo incomplete removal or a biopsy of the tumour.



## 8.2. Additional treatment

If a complete removal of the tumour is not possible, the doctors will discuss whether the patient should receive non-surgical treatment, such as chemo- and radiotherapy, or not. If not, the patient will be observed by regular clinical and imaging check-ups (controlled „watch-and wait“-approach).

The experts agree that non-surgical therapy at the time of diagnosis should only be recommended for patients presenting with severe clinical symptoms.

Even after only incomplete tumour removal, many children and teenagers neither show signs of tumour growth nor any other severe health problems and their probability of survival is high. Therefore, the recommendation for these patients is, like for children after complete removal, the controlled watch-and-wait approach rather than chemo- or radiotherapy.

In case of any signs of tumour growth or if the patient presents with deteriorating clinical symptoms during one of the check-ups, the pros and cons of a second neurosurgical intervention will be evaluated, with either chemo- or radiotherapy as a non-surgical alternative.

It is well known today, that chemotherapy will not reduce the efficacy of subsequent radiotherapy. Therefore, experts from many different countries have agreed on chemotherapy as the non-surgical treatment of choice.

It is also internationally recommended that only those children whose tumour does not respond to chemotherapy should be considered to receive radiotherapy depending on their age. Chemotherapy instead of radiotherapy is particularly recommended for children and teenagers with low-grade glioma and Neurofibromatosis Type 1 (NF1), since these patients have a higher risk to develop radiotherapy-induced health problems later in life.

## 9. Therapy optimising trials and registries

In the large paediatric treatment centres, children and teenagers with low-grade glioma receive therapy according to standardised protocols. These protocols are designed by experts and provide consistent concepts for chemo- and radiotherapy based on the patient's age at diagnosis as well as concomitant diseases such as NF1.

The goal is to stop the tumour from growing while also reducing the risk of disease-related late effects (such as vision impairment by optic pathway glioma). Therefore, children and teenagers with low-grade glioma usually receive therapy according to the treatment plans of therapy optimising trials or registries.

Therapy optimising trials are standardised and controlled clinical trials that aim at steadily developing and improving treatment concepts for sick patients based on the current scientific knowledge. Registries serve to provide optimal treatment recommendations, when one trial was closed and the subsequent one is not active yet.

Between April 2004 and April 2012, children and adolescents with low-grade glioma had the option to get registered in the international therapy optimising trial SIOP-LGG 2004. Numerous children's



hospitals and treatment centres from 12 European countries participated in this long-term study. The German headquarters of the trial are located at the Children's Cancer Centre of Augsburg.

Since mid-April 2012, study SIOP-LGG 2004 has been closed for patient registration. The results of the trial are currently being analysed to serve as a basis for designing the subsequent study. Children and adolescents who, in the meantime, are diagnosed with low-grade glioma can be enrolled in the **LGG-Registry**. The study centre associated with the registry provides noncommittal therapy recommendations that correspond to the diagnostic and treatment standards of study SIOP-LGG 2004, with the current interim results being taken into account, too.

## 10. Prognosis

The prognosis for children and adolescents with low-grade glioma has significantly improved due to the standardized treatment concepts. In addition, modern diagnostic and surgical methods have contributed to improve outcome.

Most patients (90%) with low grade glioma survive their disease longterm, however, many of them with remaining tumour and/or disease- or treatment-related late effects.

Treatment options and thus prognosis are (also) markedly dependent on the tumour site and the possibilities of neurosurgical intervention. Also, potential tumour- and/or treatment related neurological, ophthalmological, endocrinological, intellectual, and psychosocial deficits can negatively affect life quality of patients with low grade glioma.

Future therapy strategies are, therefore, both aiming at improving patients' survival and reducing late-effects of tumour and therapy on conditions such as neurology, endocrinology, ophthalmology and intellectual development. The assessment of how the treatment impacts the survivors' health and quality of life is major part of current and future studies.





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