Diagnostic And Treatment Principles For Low Grade Glioma Of Childhood And Adolescence

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Introduction
30 – 40 % of paediatric primary brain tumors are low grade glioma. Their annual incidence is calculated to be 10 –12 per 1,000,000 children under the age of 15 years in western countries. These tumors occur at all ages with a mean age at diagnosis or operation between 6 and 8 years. There is a slight male preponderance (1,1 – 1,2 to 1), although some diagnoses like the DIGG/DIA show a more marked male preponderance.

There is a striking association of specific variants of low grade glioma and heritable diseases which in part may serve as a model for cancer developement. 15 – 20 % of patients with neurofibromatosis type 1 develop optic pathway glioma. The occurrence of optic pathway glioma disposes to the developement of further brain tumors. Whereas optic pathway gliomas are mostly pilocytic, older age and location outside the visual system predisposes to other histologies and higher malignancy.

The distribution of low grade glioma within the CNS differs according to various published series. In young children tumors of the supratentorial midline dominate, spinal tumors occur in less than 5 %.

Histology
The clinically used term of low grade glioma confers to tumors of glial origin, usually astrocytic but oligodendrocytic as well. Their histological grade corresponds to grade I and II according to the revised system of the WHO from the year 2000 (Table 1). For clinical purpose some of the mixed glianeuronal tumors are included as well, if their glial component appears most relevant for biologic behaviour. Almost 2/3 of low grade glioma are pilocytic astrocytoma grade I, characterized by Rosenthal fibres and an often biphasic pattern with solid, Rosenthal fibre rich and a more loose, microcystic component. Even vascular proliferation is compatible with the diagnosis of pilocytic astrocytoma, which also explains why this tumor takes up contrast medium intensively. Regressive changes including calcifications, necrosis and lymphocytic infiltration are more rare. Several subgroups of pilocytic astrocytoma have been defined, their prognostic significance is not validated yet, some seem to be correlated with more aggressive clinical behaviour.

The difficulty to obtain a correct histological diagnosis is highlighted by the fact, that up to a quarter of cases have discrepant diagnoses between local and referent pathology even in large international studies. Even among high grade glioma up to 28 % have been reclassified as low grade glioma by central pathologic review.

Up to now no consistant genetic changes have been associated with low grade glioma. Although pilocytic astrocytoma, associated with NF 1, show the NF-mutation an gene 17q 11.2 regulary, sporadic pilocytic astrocytoma do not show NF 1 gene mutations, but develop rather an overexpression of neurofibromin; in some loss of 17q has been found. The comparative genomic hybridisation point towards few variable patterns. In small series only 5 of 41 analyses were abnormal and concern chromosome 9, 19 and 22. P 53 mutations are rare. Gene expression profiles show distinct patterns of pilocytic astrocytoma with and without NF 1 versus astrocytoma grade II.

The pattern of proliferation of low grade glioma cannot well be explained. They mostly show slow growth with local extension. Spontaneous regression has been reported, but is an exception definitively. Long phases of constant size have been described, explained by an increase of spontaneous apoptosis, reduction of vascular supply or a reduced growth kinetic within the tumor. Some tumors show an
aggressive growth pattern where phases of enlargement and stable disease may interchange. In adults a high proliferation rate identified by Ki 67/MIB 1 index, high levels of VEGF and vascular density or a reduction of N-CAM correlate with a higher rate of tumor progression. In small series of children these findings have been inconsistent. Chiasmatic-hypothalamic tumors did not show a correlation of MIB index and progression following chemotherapy.

A small percentage of low grade glioma may disseminate along the cranio-spinal axis, especially in chiasmatic-hypothalamic glioma of young children. Malignant transformation may be initiated by clonal expansion of cells with P53 gene mutation.

Diagnosis
The diagnostic procedure follows generally accepted guidelines for all brain tumors (Table 2).

Preoperative neurologic and ophthalmologic examination is complemented by radiological diagnosis. Pilocytic astrocytomas are hypointense in T1 with variable contrast uptake in solid parts and in the walls of cysts. These tumors are hyperintense in T2. Due to their relative paucity of cells in comparison to the cortex native CT shows a hypodense tumor. Calcifications can be found in 10%. Radiology describes different patterns of growth: cystic with one or several lateral nodules, solid with little cysts or predominantly solid tumors.

Diagnosis without biopsy appears justified in chiasmatic-hypothalamic tumors in the presence of neurofibromatosis or in the presence of extensive visual pathway involvement. Native CT has to prove a hypodense tumor. In all other cases biopsy is necessary.

Multiple cerebral tumors, ependymal or leptomeningeal deposits in the cerebral MRI, and the presence of clinical symptoms necessitate extensive neuro-radiologic diagnosis of the spinal canal. The significance of lumbar cytology has not been evaluated systematically.

Concept of therapy
The concept for the treatment of low grade glioma starts from surgical resection and histological diagnosis or from radiological diagnosis. Thereafter it has to be decided, whether a patient can be observed or whether non-surgical treatment has to follow.

Neurosurgical intervention
Neurosurgical intervention has always been the treatment of choice. The result of the primary resection determines the further course of the tumor disease. Its urgency is determined by the clinical symptoms and the tumor location. Due to the distribution of tumors the extent of resection often is limited to avoid unacceptable postoperative morbidity.

The extent of surgical resection is defined by the judgement of the surgeon and the result of the postoperative radio-imaging, with priority for the MRI-finding. In large cohorts only a 1/3 of tumors can be resected completely, a 1/3 receives subtotal or partial resection and a 1/3 is only biopsied or diagnosed clinically.

Survival in low grade glioma is not the critical endpoint. The natural history of tumors following primary surgical intervention or radiological diagnosis shows a high number of tumor progressions within the first years. The size of the residual tumor is only relevant for the time to progression, which is also determined by tumor localisation. Even the quality of complete resection differs between location of either cerebral hemisphere or cerebellum versus supratentorial midline or spinal canal.

Non-surgical therapy strategy:
To evaluate the role and impact of non-surgical therapy modalities different questions have to be answered:

- When does non-surgical therapy start – what is the indication?
- What type of treatment has to be chosen – how are the patients stratified?
- What is the ultimate goal of treatment – why shall we treat?

1. Radiotherapy
Radiotherapy of low grade glioma has been accepted as standard therapy for decades, but its optimal role has not been defined up to now. Tumors have been irradiated if they could not
be resected or following incomplete resection or relapse. For children no advantage for routine postoperative irradiation could be shown, so it often was applied at the time of progression of a residual or following incomplete resection of relapse. In small series progression rates are significantly higher if patients have been observed following incomplete surgical resection as compared to immediate irradiation. But 5 and 10 year survival rates have been identical.

The irradiation field has to comprise the clinical target volume, defined by preoperative T2 weighted tumor extension plus a safety zone corresponding to the infiltration zone which is at least 0.5 cm in pilocytic astrocytoma. The planning target volume has to consider the precision of the radiation technique and add a safety margin of 0.5 – 1.0 cm in case of conventional technique and 0.2 – 0.5 cm in case of rigid head fixation. The aim is to spare neighboring healthy brain parenchyma.

The optimal dose for irradiation of low grade glioma in children has not been determined. The choice of dose and fractionation has been influenced by age of the children, tumor location and tumor size with a tendency for lower dose in young children. Retrospective analysis of small series allows to recommend doses between 45 and 54 Gy in fractions of 1.8 Gy for older children.

To adequately evaluate the effect of radiotherapy a couple of aspects have to be considered: Tumor volume response is not directly correlated with tumor control and improvement of symptoms. The percentage of tumors with radiological regression is around 50%. There is a great variability concerning the response over time, tumor volume response is mostly delayed but continues for years. The demarcation of regressive changes from those in case of progression is sometimes difficult with a maximum size following radiotherapy occuring up to 9 – 12 months.

While radiotherapy allows for tumor volume regression and prolonged PFS its well documented late effects, especially concerning psychointellectual development, in the developing brain, make its use in small children and children with neurofibromatosis non attractive. Age at radiation and the length of follow-up are important to truly estimate the impact of radiation damage. Visual-spatial capacities are damaged by the tumor and its therapy. In all tested areas performance of children without NF1 is inferior following radiotherapy as compared to chemotherapy alone. Children with neurofibromatosis show significant neurophysiologic impairment even following chemotherapy alone. Additional late effects are endocrinopathies and vasculopathies, especially in NF1. The incidence of second malignancy has not been evaluated separately for low grade glioma. But the risk for radiotherapy induced second brain tumors is higher in young children.

2. Chemotherapy

The indication to test chemotherapy has therefore been the attempt to delay the start of an eventual radiotherapy. The claim of chemotherapy protocols has not been to replace radiotherapy but to defer its use to a higher age. It has not been evaluated yet, whether radiotherapy can be avoided in some children completely. Side-effects of chemotherapy concerning psychointellectual and endocrine development of children are less relevant.

This strategy has been accepted for small children, especially for those with large tumors, and for children with NF1 who tend to develop even more malignant brain tumors. In older children the rationale for the use of primary chemotherapy is less clear cut. But it can be sensible to treat prepubertal children with hypothalamic tumors to avoid impaired growth with chemotherapy.

Almost all chemotherapeutic agents have been tested for low grade glioma. Formal phase II studies are only available for some of the them. Combination therapy achieves response rates of 75 – 100%. For these often irregularly shaped tumors determination of response following classic patterns is often impossible. Tumor stabilisation is an adequate response for the chemotherapy strategy and is thererfore included if response rates are reported.

Chemotherapy studies focussing upon young children and upon NF1 patients

• The first CCSG study applied Carboplatin and Vincristin to 78 children with low grade glioma of all CNS localisation. Median age at
diagnosis was 37 months, 19.2 % had NF 1. After a median observation time of 30 months (range 18 – 72 months) 3 year PFS was 68 % with 76 of 78 children surviving. Younger children under 5 years achieved a more favorable PFS of 74 % +/- 7 % after 3 years as compared to older children with a PFS of 39 % +/- 21 %. NF 1 status and response to chemotherapy did not show statistical differences.

- The study of the French Society of Paediatric Oncology comprised 85 children with progressive visual pathway gliomas. The median age at start of therapy was 33 months, the percentage of NF 1 patients was 27 %. After an intensive 16 months chemotherapy with 6 drugs results have been reported following an observation time of 6,5 years (range 1.8 – 11.5 years). 5 years-PFS was 34 % and overall survival 89 %. The 5 year radiotherapy free survival was 61 %. Age under 1 year with a 3 year-PFS of 34 % was a significantly unfavorable factor as well as poor response to the first cycle of chemotherapy. Children without NF 1 fared less well in univariate analysis.

- The small series treated at the Instituto Nationale Tumori in Mailand comprised 34 children with low grade glioma of all CNS location. Median age at start of treatment was 45 months and 24 % had neurofibromatosis. The 10 – 11 months chemotherapy with Cisplatin and Etoposide was applied at growing intervals. Following a median observation time of 44 months (range 10 – 120 months) resulted in a 3 year PFS of 78 % and an overall survival of 100 %. The log rank test showed age under 1 year to be a prognostic unfavorable factor as well as poor response to the first cycle of chemotherapy. Children without NF 1 fared less well in univariate analysis.

- The first trial of the International Society for Paediatric Oncology recruited 201 patients with low grade glioma of all CNS locations. Median age at diagnosis was 35.6 months and 21.1 % had NF 1. Chemotherapy lasted 53 weeks with single high dose of Carboplatin and Vincristin. 3 year PFS was 57.5 % and 5 year PFS 45.2 %. 3 year overall survival was 89.1 %. Again age under 1 year was prognostically unfavorable, but also the necessity of an initial tumor reductive intervention. Leptomeningeal dissemination and absence of neurofibromatosis were significant only in the univariate analysis.

Taken all together the analysis of the series demonstrates that chemotherapy is effective, it produces responses and is able to delay the necessity for radiotherapy in a significant proportion of children. Long term PFS has been unsatisfactory however and in some series there is a significant number of early progressions. Up to now potential prognostic factors have not been defined prospectively, but age, NF-status, extent of primary response, start of therapy or/and histology may be some of these influential factors. One of the difficulties to compare the series has been the lack of uniform criteria for the start of non-surgical therapy, in either radiotherapy or chemotherapy trials. And there has been no uniform definition of clinical or radiological progression.

The definition of clinical or radiological indication to start non-surgical therapy is therefore crucial to the comparability of different trials. It is generally accepted that the presence of a (postoperative) tumor is no indication to therapy by itself at diagnosis. Only severe clinical, neurologic or ophthalmologic findings justify the start of non-surgical therapy, be it following partial resection or neuroradiological diagnosis. Following an observation time ophthalmologic, radiologic or neurologic progression is a sufficient indication if no tumor resection is possible. For each of the various fields clear-cut further definitions have to be defined.

**Study objectives**

Overriding aims of all studies of therapy for low grade glioma have to be:

- To provide a comprehensive standardized concept to treat children and young adults with a low grade gliom of all histologies and locations.

- To improve PFS for young children following chemotherapy. The options to achieve this goal are:
  - Improve the choice of drugs, but there has not been a chemotherapeutic agent with a specifically favorable effect.
  - Improve the intensity of therapy, but it has
not been investigated, whether more therapy improves response and whether an improved response confers a better PFS.

- Optimize the duration of therapy. Longer treatment seems to improve PFS.
- Children that have to receive radiotherapy shall be treated following modern 3-dimensional planning and by the use of modern technique in order to reduce the late effects upon normal surrounding brain.

Radiotherapy should only be applied to older children and total dose and fractionation should be maintained at 54 Gy for the brain and 50.5 Gy for the spinal canal at 1.8 Gy dose per fraction. Younger children should only be irradiated following consultation of national reference radiotherapists. For disseminated tumors a trial of cranio-spinal irradiation can be done following progression after primary chemotherapy. However in such phase II-studies the volume of irradiated tumor and metastases has to be limited.

For all low grade glioma studies the feasibility of the strategy has to be examined as well as overall survival, event free and progression free survival following diagnosis. Additionally the effects of tumor and treatments concerning neurology, endocrinology, ophthalmology and health associated factors (quality of life, health status) have to be investigated. A systematic follow-up should especially be instituted for visual function, since data for either chemotherapy or radiotherapy are totally lacking.

Due to the rarity of these tumors large international collaboration should be instituted to achieve significant results within a reasonable space of time.

References


