International Consortium on Low Grade Glioma - ICLGG
of the International Society of Pediatric Oncology - SIOP

Cooperative multicenter Study for Children and Adolescents with Low Grade Glioma

SIOP - LGG 2004

(RG_09-201)

EudraCT number 2005-005377-29

Version 3.0_a, 14 September 2010

Please destroy previous versions

UK Start Date: 1st September 2004

Children's Cancer Trials Team (CCTT)
Cancer Research UK Clinical Trials Unit (CRCTU)
School of Cancer Sciences
University of Birmingham
Edgbaston
Birmingham, B15 2TT

Tel: 0121 415 8578/ 0121 415 8572
Fax: 0121 414 3700

Amendment - CNS 2004 03 A1

List of changes made to the protocol-Version 1 - 14th April 2003, includes formal corrections, which were necessary following the review process through the Deutsche Krebsgesellschaft (German Cancer Society), or were corrections of mistakes within the text, updates of changes of persons in charge etc. This protocol corresponds to the German Master Protocol Version I April 2004 (corrected January 2006). All changes are listed in the following table.

Entire protocol	Study abbreviation: SIOP-LGG 2004, after consulting the finance sponsors, the Deutsche Kinderkrebsstiftung (German childhood cancer foundation) and the Deutsche Krebsgesellschaft (German Cancer Society), Mrs. Inga Rossion
P1	Protocol ref/version number updated in header and on front cover Removal of text 'The content of this protocol is confidential and may only be passed on to members of the respective national study committees.'
P. 1,4,18	EudraCT number 2005-005377-29 inserted
P. 4	The Belgian study group BSPHO entered the participating study groups Update of the timing of protocol phases NCI - PDQ Database ID code: SIOP-LGG 2004 EU20555 inserted SIOP Statement inserted
P. 5-6	Update of the list with names of the international study committee
P. 7	Addition of Trial Management Committee signatures
P. 8	Amendment of text to: The consortium emphasizes that even following approval from the national and/or local ethics committees no legal responsibility for possible consequences resulting from the application of recommendations from this protocol will be taken by the members of the consortium.
P. 17	Reference to the pilot phase of the protocol was removed, because a pilot phase was not performed. Amendment of address: Department of Radiotherapy Leipzig Amendment of address: Roger Taylor
P.18	National trial coordinators representating participating national oncology groups: Sue Picton replaces David Walker as UK Chief Investigator Amendment of address: International Data Center, Clinical Trials & Biostatistic Unit
P. 18	1.3.2 Chemotherapy arm - addition of text 'Common consolidation for all children with alternative in case of early progression or allergy' and deletion of 'Offer of two treatment options for consolidation'
P. 19	Amendment of the ICD O-Code for pilocytic Astrocytoma °I from 9241/3 to 9421/1 and Desmoplastic Infantile Ganglioma °I from 9505/0 to 9412/1
P. 59	3. Tumours All Locations - Chemotherapy Group – deletion of the text 'Option A' from the sentence 'All children receive Standard induction and Consolidation 'Option A' with Vincristin and Carboplatin'
P. 61	Chapter 6.4: changing "Histopathology" to "Pathology" and adding "Tumor type" and "WHO-Grade"
P. 63	Inserting the sentence: Pregnancy has to be excluded by HCG-determination in fertile adolescent girls
P. 67	Director of the Hirntumorreferenzzentrums (national brain tumor reference center): Amended from .Dr O.D.Weistler to Prof. Dr. T. Pietsch
P. 77-79	Amendment to Colour Vision and Contrast Sensitivity tables + additional instructions

P. 80	Frequency of examinations: amendment of text from 'the frequency will need to increse' to 'the frequency will need to be increased'
P. 82	Amendment of the ICD O-Code for pilocytic Astrocytoma °I from 9241/3 to 9421/1 and Desmoplastic Infantile Ganglioma °I from 9505/0 to 9412/1
P. 87	New address for the International Data Centre
P. 87/88	Additional information on Patient Randomisation into the Cineca database
P. 134	Adding the information "Contraception: Pregnancy has to be prevented in fertile adolescent girls during chemotherapy by reliable anticonceptive methods, e. g. by hormonal anticonception".
P. 135	Address change German reference center for RT Address change: Roger Taylor
P. 143	15.1.5 Reference amendment 'Merchant (2000b)' amended to 'Merchant 2002b'
P. 144	15.1.6 Typing errors amended 'oragans' to 'organs' and 'Radiation induced growth hormone deficiencies seems' amended to '…seem'
P. 158	Definition: Extent of resection Addition of possibilities R2 -S1 for near total resection and R3 – S1 for partial resection. R2 corrected to R3 for partial resection in the text
P. 163	Addition of address of the International Randomisation center Amendment of text in Design of Trial 'primary tumour site pure chiasmatic tumors (Dodge II)' to 'primary tumour site chiasmatic tumors (Dodge II and III)'
P. 166	Amendment of text in Statistical Analysis 'pure chiasmatic tumors (Dodge II)' to 'chiasmatic tumors (Dodge II and III)'
P. 180	18.2 Amendment of Study period to remove pilot phase - Study activated on April 1st 2004
P. 181	18.5. Documentation and data handling – amendment of International Data Centre address and addition of RDE information
P. 181	18.7. Data-quality-control: adding the information that "correction can only be made using query forms"
P. 183	18.12. more detailed description and emphasizing of the role of the ethics committees
P. 205	Wrong specification in common toxicity criteria - leucocytes Grade 2 change from ≥ 2000 - < 2000 to ≥ 2000 - < 3000, and granulocytes Grade 1 from ≥1500 - < 1500 to ≥ LLN - 1500

Amendments- 14 September 2010

Front Cover	Version updated to 3.0, 14 September 2010, study code update to RG_09-201 from CNS 2004 03. CCLG contact details replaced by CRCTU contact details Version number updated on all headers and study code added to all headers
P. 3	Amendments list added
P. 4/81	'Former' added to UKCCSG
P. 6/7	Reference to CCSG replaced by CRCTU
P.7	UK Chief Investigator signature added
P.10	Table of contents updated
P.17	Dr changed to Prof for David Walker

	Non Substantial Amendment
Front Cover	Version updated to 3.0_a, 14th September 2010
Headers	All headers updated to reflect change to 3.0_a, 14th September 2010
Contents Pages	Page numbers updated

Cooperative multicenter Study for Children and Adolescents with low grade glioma SIOP - LGG 2004

Participating Societies:

Gesellschaft für Pädiatrische Onkologie und Hämatologie – GPOH, Germany
Gesellschaft für Pädiatrische Onkologie und Hämatologie – GPOH, Austria
Associazione Italiana Ematologia e Oncologia Pediatrica - AIEOP
Former United Kingdom Children's Cancer Study Group – UKCCSG
Société Francaise des Cancers d'Enfants - SFCE
Sociedad Espanola de Oncologìa Pediátrica – SEOP
Nordic Organisation of Pediatric Hematology and Oncology – NOPHO
Belgian Society of Pediatric Hemato-Oncology - BSPHO

Protocol activated: 01.04.2004

Recruitment phase 01.04.2004 – 31.03.2010
Observation phase 01.04.2010 – 31.03.2012

EudraCT - Nr: 2005-005377-29
NCI - PDQ Database ID code: SIOP-LGG 2004 EU20555

SIOP-Statement for the SIOP-LGG 2004 Cooperative multicenter Study for Children and Adolescents with Low Grade Glioma

The Scientific Committee of SIOP has reviewed this protocol for scientific validity and has deemed the hypotheses being addressed are scientifically valid. However, SIOP is not the sponsor, as defined by the ICH Harmonised Tripartite Guidelines, of this study, and accepts no legal responsibility for the conduct of this study. In addition, neither the Board nor the Scientific Committee of SIOP accepts responsibility for the overall conduct of this study and has specifically pointed out that implementation of this study requires the approval of the Research Ethics Committee/Institutional Review Board of each participating institution. The responsibility for the management of any individual patient treated with this protocol rests with the treating physician.

The protocol is compiled from contributions of members of the International Consortium on low grade glioma of the SIOP. The master-protocol has been written in Augsburg with the secretarial assistance of Silvia Soellner.

I. International Study Committee SIOP LGG 2004

PEDIATRIC ONCOLOGY
Germany – GPOH: Astrid K. Gnekow
Austria – GPOH: Irene Slavc
Italy – AIEOP: Giorgio Perilongo
UK –: Sue Picton, David Walker
Nordic Countries - NOPHO: Tore Stokland, Per Erik Sandstrom, Niels Clausen, Mikko Arola, Olafur Gisli Jonsson
Spain - SEOP: Ofelia Cruz, Aurora Navajas, Anna Teijeiro
France – SFCE: Jacques Grill, Chantal Kalifa, Marie-Anne Raquin
Belgium - BSPHO: Joris Verlooy

PATHOLOGY AND MOLECULAR BIOLOGY
Germany – GPOH: Volkmar Hans, Torsten Pietsch, Wolfram Scheurlen
Austria – GPOH: Johannes Hainfellner
Italy – AIEOP: Felice Giangaspero
UK –: James Ironside, Keith Robson
Nordic Countries - NOPHO: Kari Skullerud, David Scheie
Spain - SEOP: NN
France – SFCE: Marie-Madeleine Ruchoux, Anne Jouvet, Dominique Figarella-Branger, Arielle Lellouch-Toubiana
Belgium -

RADIOLOGY
Germany – GPOH: Monika Warmuth-Metz
Austria – GPOH: Daniela Prayer
Italy – AIEOP: Milena Calderone
UK –: Tim Jaspan
Nordic Countries – NOPHO: Soren Jacob Bakke
Spain – SEOP: Eli Vazquez
France – SFCE: Dominique Couanet
Belgium -

RADIOTHERAPY
Germany – GPOH: Rolf D. Kortmann
Austria – GPOH: Karin Diekmann
Italy – AIEOP: Giovanni Scarzello
UK –: Roger Taylor
Nordic Countries – NOPHO: Knut Lote
Spain – SEOP: Jordi Giralt
France – SFCE: Christian Carrie, Jean Louis Habrand
Belgium -

NEUROSURGERY
Germany – GPOH: Niels Soerensen
Austria – GPOH: Thomas Czech
Italy – AIEOP: NN
UK –: Paul Chumas
Nordic Countries – NOPHO: Bengt Gustavson
Spain – SEOP: NN
France – SFCE: Michel Zerah
Belgium -

OPHTHALMOLOGY
Germany – GPOH: Bettina Wabbels
Austria – GPOH: NN
Italy – AIEOP: Maria Luisa Pinello
UK – : Alistair Fielder, Ian Simmons
Nordic Countries – NOPHO: Terje Christoffersen
Spain – SEOP: NN
France – SFCE: NN
Belgium -

NEUROPEDIATRICS, HEALTH STATUS /QUALITY OF LIFE
Germany – GPOH: Gabriele Calaminus, Knut Brockmann, Ronald Straeter, Friedrich Ebinger, Pablo Hernaiz-Driever
Austria – GPOH: Herwig Lackner
Italy – AIEOP: NN
UK - : Colin Kennedy, Adam Glaser
Nordic Countries – NOPHO: Bo Stromberg
Spain SEOP: Jose Mª Indiano
France – SFCE: Chantal Rodary
Belgium -

ASSOCIATED RESEARCH, PHASE II – STUDIES
Eric Bouffet, Toronto, Canada
Didier Frappaz, Lyon, France

BIOSTATISTICS
Germany - GPOH: Andreas Faldum, Angela Emser
Italy - AIEOP: Gian Luca De Salvo
UK - : Suzanne Stephens, David Machin
France - SFCE: Marie-Cécile Le Deley
Nordic Countries – NOPHO: Thore Egeland
Belgium -

DATA MONITORING AND SAFETY COMMITTEE
Carolyn Freemann, Montreal, Canada
Martin Schrappe, Kiel, Germany
Richard Sposto, Arcadia, Ca., USA

II. Signatures
Trial Management Committee

SIOP-LGG 2004

Gnekow, Astrid, GPOH

Grill, Jacques, SFCE

Date: 29/04/04

Perilongo, Giorgio, AIEOP

29-4-2004

Sandstrom, Per-Erik

Date: 29.04.04

Stokland, Tore

29 April 2004

Walker, David, CCSG

Date: 29.4.04

Kortmann, Rolf D., GPOH

19.05.04

Scarzello, Giovanni, AIEOP

Date: 30.4.04

Taylor, Roger, CCSG

19.05.04

De Salvo, Gian Luca, AIEOP

5.5.04

Faldum, Andreas, GPOH

Version 3.0, 14 September 2010

This Protocol is approved by :

Dr Sue Picton **Signature :** **Date :** 16/9/10.

Chief Investigator

III. Important Note SIOP LGG 2004

With this protocol the International Consortium on low grade glioma research presents the second trial for the treatment of low grade glioma in children and adolescents.

The consortium emphasizes that even following approval from the national and/or local ethics committees no legal responsibility for possible consequences resulting from the application of recommendations from this protocol will be taken by the members of the consortium. Treatment and follow-up of patients with low grade glioma requires a high degree of medical competence and humane presence existing only in hospitals with adequate infra-structure. A state of emergency due to complications from the underlying disease or from its treatment can develop in every patient at any time and may require all resources mentioned. In such circumstances increased efforts can not compensate for a lack of experience. Children with brain tumors – even when of "low" grade malignancy only – should thus be treated by an experienced team and interdisciplinary cooperation is a prerequisite for such a team comprising neurosurgeons, neuropathologists, neuroradiologists, radiotherapists, ophthalmologists and pediatricians. Sufficient experience concerning the treatment of pediatric brain tumors and of extracranial malignant tumors in cooperative multicenter trials is implied, as well.

The protocol describes a multicenter study for the treatment of pediatric brain tumors of low grade malignancy in children and adolescents. It contains information regarding registration to the study. The protocol was not written for patients who do not participate in this study. Possible changes or amendments to the protocol will be communicated to participating institutions. Additionally, participating centers are requested to ensure validity and actuality of their available protocols regularly. Before entering patients into the study institutions have to obtain ethical approval of the protocol according to local regulations.

This concerted research action is run by the International Consortium on Childhood LGG which represents the LGG strategy group of the Brain Tumor Sub-Committee of the International Society of Pediatric Oncology (SIOP). This is the second generation of clinical trials run by this consortium.
The contribution of the major European Pediatric Neuro-oncology Groups – e.g. the ones from France, Germany, Italy, the Scandinavian countries, Spain and the United Kingdom – to the study has made possible to conceive a prospective randomised trial as part of the protocol. This is the first prospective randomised trial ever run in Europe on childhood LGG and the second in the world.

IV. Table of contents SIOP LGG 2004

V. Abbreviations SIOP LGG 2004

ACTH	Corticotropin
ADH	Antidiuretic hormone
AIEOP	Associazione Italiana Ematologia e Oncologia Pediatrica
AML	Acute myeloic leukemia
BEAR	Brainstem evoked auditory response
BSA	Body surface area
Carbo	Carboplatin
CCSG	Children's Cancer Study Group (USA)
CDDP	Cisplatin
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete remission and/or response
CRCTU	Cancer Research UK Clinical Trials Unit
CSF	Cerebrospinal fluid
CS-RT	Cranio-spinal radiotherapy
CT	Chemotherapy
CTC	Common toxicity criteria
CT-scan	Computer tomography
CTV	Clinical target volume
DIGG/DIA	Desmoplastic infantile ganglioglioma /-astrocytoma
DLGG	Disseminated low grade glioma
DS	Diencephalic syndrome
EEG	Electro-encephalo-gramm
EFS	Event free survival
EORTC	European Organisation for Research and Treatment of Cancer
FSH	Follicle stimulating hormone
F-U	Follow-up
GCS	Glasgow coma scale
G-CSF	Granulocyte-Colony stimulating factor
GFR	Glomerular filtration rate
GH	Growth hormone
GnRH	Gonadotrophin releasing hormone (= LHRH)
GPOH	(German and Austrian) Society of Pediatric Oncology and Hematology
Gy	Gray
HCG	Hypothalamic-chiasmatic glioma
HS	Health status
HUI	Health utility index
iv	Intra-venous
ICD-O	International classification of diseases - Oncology
ICRU	International Commission for Radiation Units, Washington, D. C.
IDMC	International Data Monitoring Committe
IGF BP 3	Insulin-like growth factor binding protein 3
IGF I	Insulin-like growth factor 1
JPA	Juvenile pilocytic astrocytoma

LGG	Low grade glioma
LH	Luteinising releasing hormone
MDS	Myelodysplastic syndrome
MR	Minor response
MR(I)	Magnetic resonance imaging, magnetic resonance tomography
NCI	National Cancer Institute
NF I	Neurofibromatosis type NF I
NOPHO	Nordic Organisation of Pediatric Hematology and Oncology
OAR	Organs at risk
OP	Operation, surgery
OPG	Optic pathway glioma
OR	Objective response
OS	Overall survival
p.o.	per os
PA	Pilocytic astrocytoma
PD	Progressive disease
PF	Posterior fossa
PFS	Progression free survival
PNET	Primitive neuroectodermal tumor
POG	Pediatric Oncology Group
PR	Partial remission and/or response
PTV	Planning target volume
Qol	Quality of life
R	Randomisation
RDE	Remote data entry
RFS	Radiotherapy free survival
RT	Radiotherapy
s.c.	Subcutaneously
SAE	Severe adverse event
SD	Stable disease
SDQ	Strengths and difficulties questionnaire
SEOP	Sociedad Espanola de Oncología Pediátrica
SFCE	Societé Francaise Cancers Enfants
SFOP	Societé Francaise d'Oncologie Pediatrique
SIADH	Syndrome of inadequate secretion of ADH
SIOP	International Society of Pediatric Oncology
SMN	Second malignant neoplasm
SSD	Source to skin distance
TPDCV	Thioguanin-Procarbazin-Dibromodulcitol-CCNU-Vincristin
TR	Tumor response
TRE	Tumor related event
TSH	Thyroid stimulating hormone
UK-CCSG	United Kingdom Children's Cancer Study Group
VCR	Vincristin
VEP	Visual evoked potential
VP 16	Etoposide
WHO°	Degree of malignancy according to world health organisation grading

1. Preamble SIOP LGG 2004

The protocol SIOP - LGG 2004 attempts to offer a comprehensive treatment strategy to all children and adolescents up to an age of 16 years, who are affected by a low grade glioma arising in any part of the central nervous system. Results of the preceding SIOP - LGG trial as well as results from national trials and reports in the literature form the basis of the recommendations and the randomized part(s) of the study.

Considering tumor location and the absence or presence of the associated genetic disorder Neurofibromatosis (NF I) patients are divided into three strategic groups. Within each group the extent of primary resection, the presence or absence of severe neurologic symptoms and the presence or absence of tumor progression determines whether children are to be observed following diagnosis and resection or treated with either chemo- or radiotherapy. Thus, there are basically 9 distinct groups of patients. Differences between histologic entities among the totality of low grade glial tumors and their biologic behavior in different regions of the brain may add to the complexity of the treatment recommendations.

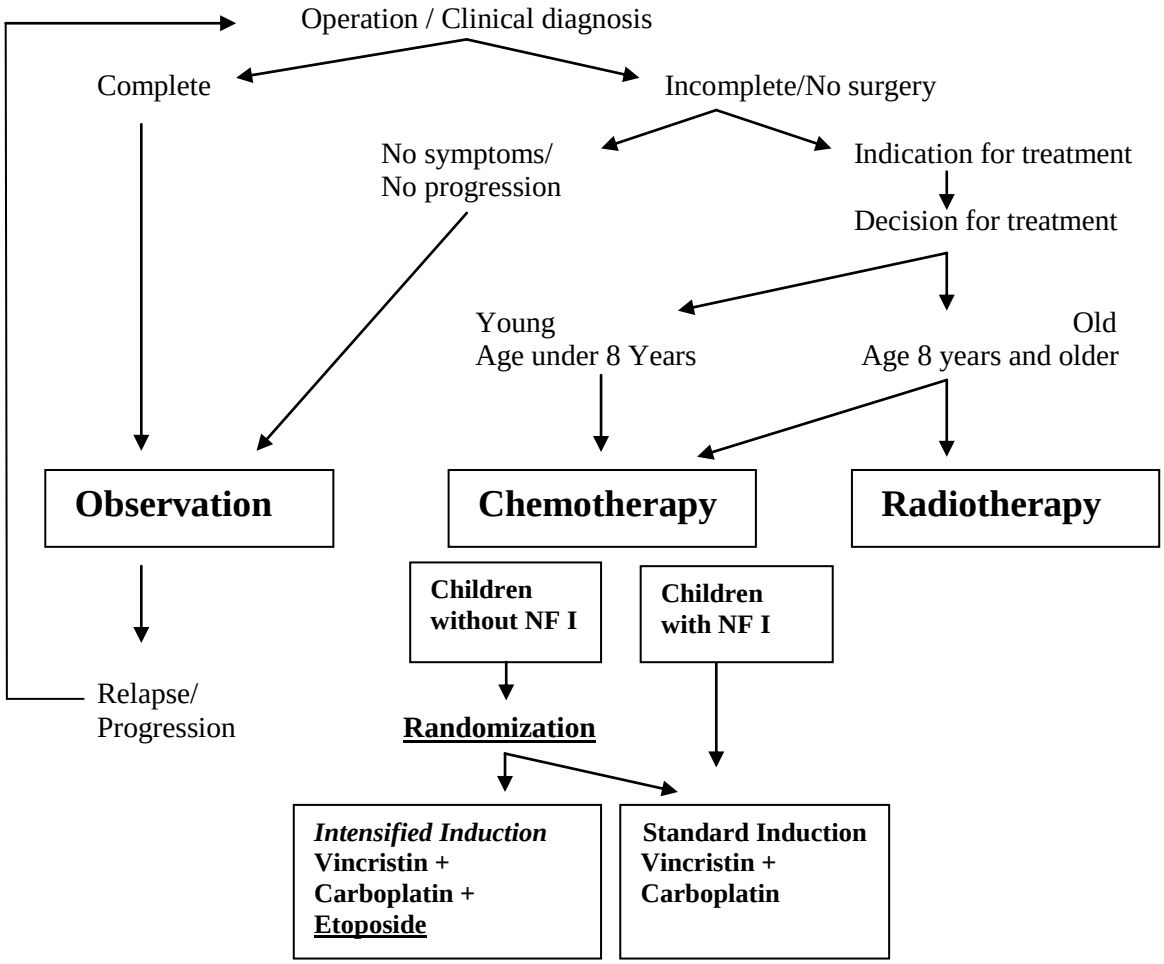
The study committee of the International Consortium of low grade glioma Research has recognized and accepted this complexity within the protocol, which allows a largely individualized therapy within a structured framework and offers the most up-to-date diagnostic and therapeutic approaches for the participating countries. By this, the committee hopes to meet the expectations of the study groups, pediatric cancer treatment centers and the patients and their families.

Scientific questions can only be posed and, hopefully, answered for the largest subgroups of patients, although recruitment rates for these patient groups can only be estimated at the time of writing. Thus a randomized therapy optimizing study is proposed for children not affected by NF I with supratentorial midline tumors. Study arms for all the other groups will undergo descriptive evaluation.

Most subgroups of patients with low grade glial tumors already have an excellent prognosis. The study is designed to improve the level of progression free survival for those children with the poorer long term prognosis. Yet the nature of low grade glial tumors makes it pertinent to not only evaluate short term survival, but to focus on ophthalmologic, neuroendocrine, and quality of life outcome as well. This study aims to investigate more closely into these outcome measures, in order to develop detailed recommendations for such follow-up, which in our view is indispensable for optimal patient rehabilitation.

2. Summary SIOP LGG 2004

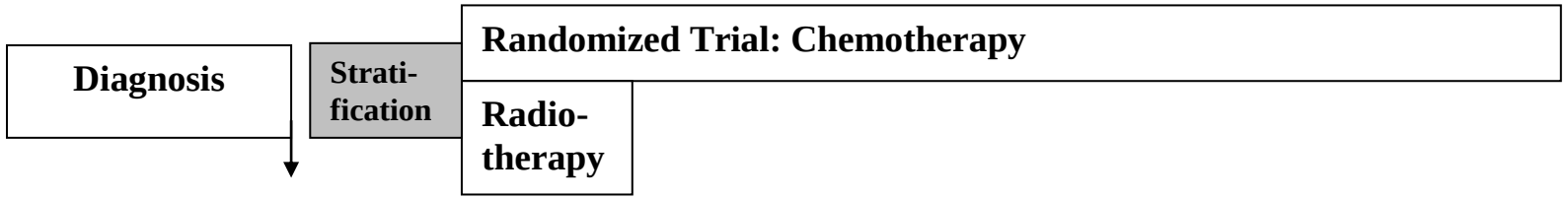
2.1. Flow diagram of the study



The study SIOP-LGG 2004 offers a common therapy strategy for all children and adolescents with a histologically (WHO criteria) or radiologically confirmed low grade glioma. Following complete resection patients will only be observed, as will be patients without symptoms or progression after incomplete resection or clinical diagnosis. Non-surgical therapy will be instituted at the presence of defined indications following incomplete resection, non-resectable relapse or progression of an unresectable tumor.

Older children (≥ 8 years) receive primary radiotherapy. Modern planning and treatment techniques shall reduce long term side effects upon surrounding tissues and organs at risk. At the presence of specific conditions these children may receive chemotherapy as well. The indication for interstitial radiotherapy is not age restricted. Younger children (< 8 years) receive primary chemotherapy. Children affected by Neurofibromatosis NF I shall be treated with chemotherapy at all ages. The duration of chemotherapy is 18 months. Children without NF I (stratified for age and tumor localization) will be randomized to receive standard induction with Vincristin and Carboplatin or intensified induction with Vincristin, Carboplatin and Etoposide, to test, if there is a difference in progression free survival. Additionally the distribution of tumor response at week 24 shall be investigated. Consolidation consists of ten 6-week cycles of Vincristin/Carboplatin therapy. For all children overall survival, progression free and event free survival will be calculated. The influence of clinical and histologic findings upon these parameters will be investigated. The extent of late effects of primary tumor and therapy shall be documented prospectively.

2.2. Flow diagram for investigation and treatment – Chemotherapy arm



Investigations:
Neuroimaging: Chemo- and Radiotherapy group

Time point	**1**	**2**		**3**		**4**		**5**	**6**
Histology (if obtained)	**X**	**(X)**							
Ophthalmology	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Endocrinology	**X**	**X**		**X**		**(X)**		**X**	**X**
Patient status	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Months after start of treatment		0	3	6	9	12	15	18	follow-up

Documentation:

Basic patient data
Central pathologic review and/or
Central neuroradiologic review
Ophthalmology
Neurology
Endocrinology
Education

Randomisation

Basic treatment data

Chemotherapy trial: Central Response assessment week 24

Chemotherapy documentation

Radiotherapy documentation

Documentation during treatment: neuroimaging, ophthalmology, neurology, endocrinology, status
At month: (3) **6** (9) **12** (15) **18**

Patient status report

If applicable:
Event report form

Post treatment:
Ophthalmology
Neurology
Endocrinology
Education
Late effects

2.3. Key information on the SIOP - LGG 2004 Study

Start of the main phase: 01.04.2004
Prospective end of patient recruitment: 31.03.2010
Prospective end of the study: 31.03.2012

EudraCt - NR: 2005-005377-29

1. Organisation

1.1. Title of the study: SIOP - LGG 2004 - Cooperative multicenter Study for Children and Adolescents with low grade glioma

1.2. Trial Management Committee

Chemotherapy protocol:

Dr. Astrid K. Gnekow
I. Klinik fuer Kinder und Jugendliche, Klinikum Augsburg
Stenglinstrasse.4
D-86156 Augsburg, Germany

Dr. Giorgio Perilongo
Clinica di Oncoematologia Pediatrica e Centro Leucemie Infantili
Via Giustiniani 3
I-35128 Padova, Italy

Prof. David A. Walker
Children's Brain Tumor Research Centre - Queen's Medical Centre
University of Nottingham
Nottingham, NG7 2UH, United Kingdom

Dr Jacques Grill
Département de Cancérologie de l'Enfant et de l'Adolescent
Institut Gustave Roussy
39 rue Camille Desmoulins,
F-94805 Villejuif, France

Radiotherapy protocol:

Dr. Roger E. Taylor
South West Wales Cancer Centre
Singleton Hospital Swansea, SA2 8QA, UK

Dr. Rolf - D. Kortmann.
Department of Radiotherapy - University of Leipzig
Härtelstr. 16
D - 04107 Leipzig, Germany

Dr. Giovanni Scarzello
Department of Radiotherapy - Padua General Hospital
Via Giustiniani 2
I-35100 Padua, Italy

Biostaticics:

Lead Data Analysis:
Dr. Andreas Faldum
Institut für Medizinische Biometrie,
Epidemiologie und Informatik
University of Mainz
Germany

Lead Data Management:
Dr. Gian Luca De Salvo
Clinical Trials & Biostatistic Unit
Istituto Oncologico Veneto
Busonera HospitalD-55101 Mainz,
Via Gattemelata 64
I-35128 Padova, Italy

National trial coordinators representating participating national oncology groups:

Austria: Irene Slavc, Vienna
France: Jacques Grill, Villejuif
Germany: Astrid K. Gnekow, Augsburg
Italy: Giorgio Perilongo, Padova
Norway: Tore Stokland, Tromsø
Spain: Ofelia Cruz, Bilbao
Sweden: Per Eric Sandstrom,
United Kingdom: Sue Picton, Leeds

International Data Center:

Clinical Trials & Biostatistic Unit
Istituto Oncologico Veneto
Busonera Hospital
Via Gattemelata 64
I-35128 Padova, Italy
Tel: 0039-049-8215704
Fax: 0039-049-8215706
email: siop-lgg2004@istitutoncologicoveneto.it

1.3. Primary study objectives (section 6 and 7)

1.3.1. Offer of a uniform, standardized concept for the treatment of children and adolescents affected by a low grade glioma.

1.3.2. Improvement of progression free survival following non-surgical therapy for children without NF I with low grade glioma by investigation of standardized treatment recommendations: Group 1: with tumors located in the supratentorial midline
Group 2: with tumors of the cerebral hemispheres, the cerebellum and caudal brain stem and the spinal cord

- Therapy arm: Radiotherapy
  Use of modern techniques for planning and treatment
- Therapy arm: Chemotherapy
  Prolongation of therapy for all children
  Randomized trial of intensification of induction therapy
  Common consolidation for all children with alternative in case of early progression or allergy

1.3.3. Investigation of standardized treatment recommendations for non-surgical therapy for the study group of children with NF I and low grade glioma of all locations (Group 3).

1.3.4. Reduction of the rate and intensity of possible late effects of therapy:

- by sparing organs of risk through optimized planning and treatment of radiotherapy.
- by deferring the start of or avoiding radiotherapy for young children and children with Neurofibromatosis by choosing a chemotherapy strategy.

2. Eligibility criteria (Section 9.1.)

2.1. Age: children and adolescents up to age 16 years.
2.2. Histology: Glioma of low grade malignancy (ICD O-Code)

Pilocytic Astrocytoma I°	9421/1
Subependymal Giant Cell Astrocytoma I°	9384/1
Dysembryoplastic Neuroepithelial Tumor I°	9413/0
Desmoplastic Infantile Ganglioglioma I°	9412/1
Ganglioglioma I° and II°	9505/1
Pleomorphic Xanthoastrocytoma II°	9424/3
Oligodendroglioma II°	9450/3
Oligoastrocytoma II°	9382/3
Astrocytoma II°	9400/3
Fibrillary Astrocytoma II°	9420/3
Protoplasmatic Astrocytoma II°	9410/3
Gemistocytic Astrocytoma II°	9411/3

Within the randomized part of the study all histologies will be randomized, since up to now there are no data to exclude any of the subgroups, e.g. children with oligodendroglioma, from this study.
Specific neuroradiological criteria may allow to diagnose a low grade chiasmatic-hypothalamic tumor without biopsy (section 8.5.).
2.3. Primary tumor localization: intracranial and spinal cord.
2.4. Dissemination: Children presenting with disseminated low grade glioma will be eligible for the study.
2.5. Associated conditions: Children are eligible for the trial regardless of the presence of associated genetic disease
2.6. Primary tumor diagnosis: The tumor should not be pretreated with chemotherapy or radiotherapy.
2.7. Informed consent: The patient and/or his legal guardian (parents) have to have declared their written informed consent to the study.

Randomization: All eligible patients without Neurofibromatosis NF I receiving chemotherapy as their first non-surgical therapy are eligible for randomization.

3. Exclusion Criteria (section 9.2.)

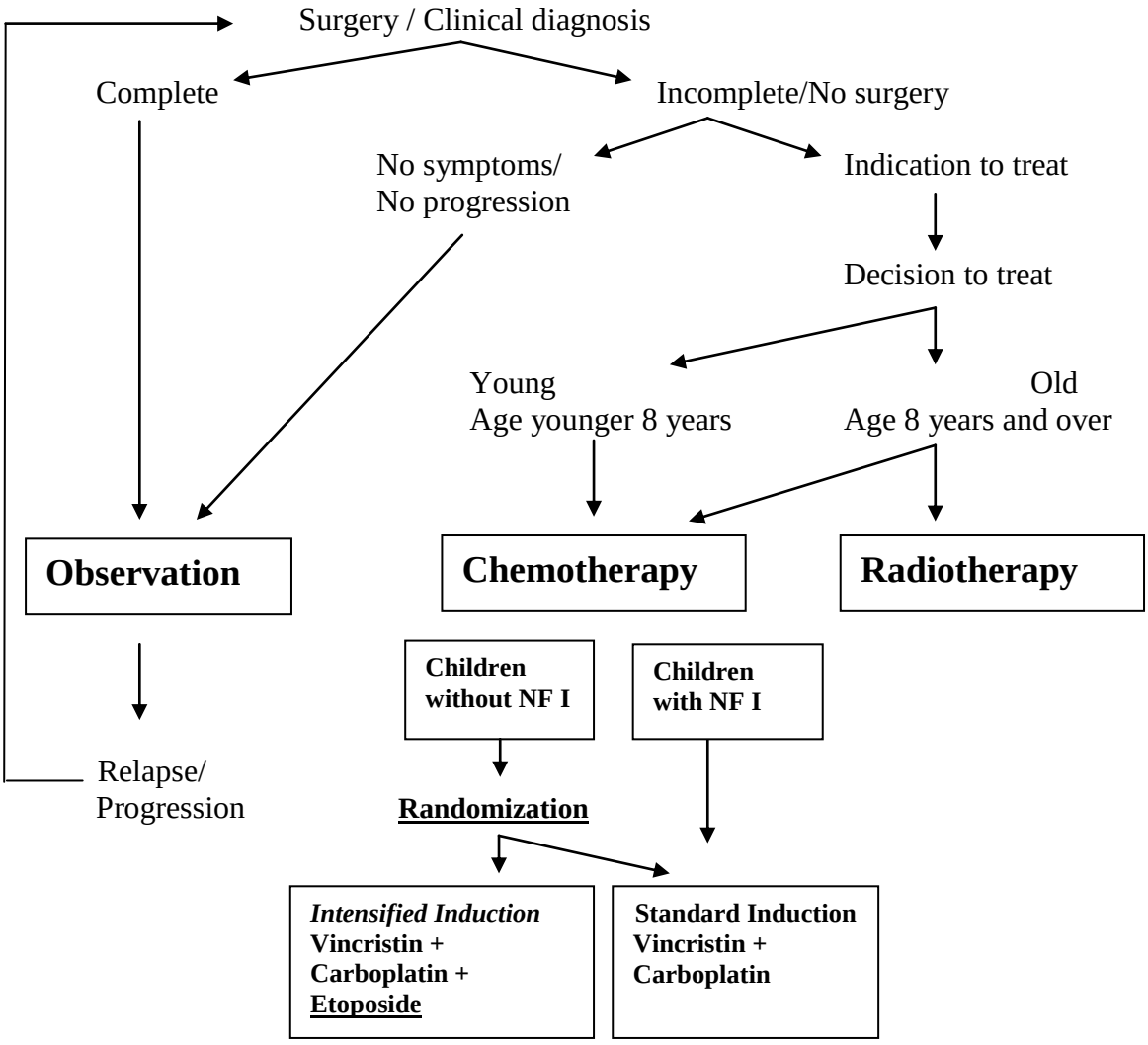
3.1. Primary tumor localization: diffuse intrinsic tumors of the pons, even if histologically an Astrocytoma II° is diagnosed.
Exception: pontine glioma II° in NF I patients may be entered into the study.
3.2. Special diagnosis: Patients presenting with rare intracranial neoplasms of low grade malignancy, but non-glial origin. Their data may be registered however, to learn about those therapeutic interventions which may prove useful to these patients and to develop

separate strategies in the future. Choroid plexus papilloma should be entered on the SIOP-CPT-study.
3.3. Pretreatment: Children treated with chemo- or radiotherapy prior to entering the study will be evaluated separately. Previous treatment with steroids is not considered a chemotherapeutic treatment.
3.4. Preexisting impairments of health status, making the conduct of the study impossible or ethically unwise.
3.5. Evidence of pregnancy or lactation period.

In case the patient participates in another clinical study simultaneously to being enrolled in the study SIOP-LGG 2004, but not interfering with the present treatment strategy (e.g. endocrinologic study), this should be known to the national study chairmen.

Concommittant medication for associated or other conditions (e.g. hormone replacement, anticonvulsants) should be recorded, but is no exclusion criteria.

4. Overview of protocol treatment (section 12.).



4.1. Basic Protocol Scheme

All patients with low grade glioma, eligible according to the criteria from section 9., should be entered into the current study and follow the same general strategy concerning non-surgical therapy. Dependent upon primary tumor localization and the presence or absence of Neurofibromatosis NF I patients are devided into three study groups:
Group 1: Non-NF I, supratentorial midline (section 12.1.)
Group 2: Non-NF I, cerebral hemispheres, cerebellum, caudal brainstem, spinal cord, optic nerve (section 12.2.)
Group 3: NF I, all locations (section 12.3.)

4.2. Treatment Subgroups

The indication for non-surgical therapy in a patient with low grade glioma following diagnosis is based upon the extent of surgical resection, the presence or absence of severe neurologic symptoms and the presence or absence of clinical and/or neuroradiological progression during a period of observation. Within all study groups there are thus three "treatment" subgroups:

4.2.1. Observation group:	Tumor completely resected
	Tumor not or incompletely resected, no severe symptoms
	Tumor not or incompletely resected, no progression
4.2.2. Treatment group at diagnosis:	Severe neurologic symptoms
	Severe ophthalmologic symptoms
4.2.3. Treatment group after observation:	Progressive neurologic symptoms
	Progressive ophthalmologic symptoms
	Neuroradiologic progression, including dissemination

4.3. Stratification of non-surgical therapy

For each study group details for an age-related stratification of non-surgical treatment are provided:

Primary chemotherapy:	"young" children, age < 8 years
	All children with NF I
Primary Radiotherapy:	"old" children, age ≥ 8 years
	Children of all ages whose tumor is amenable to interstitial radiotherapy (brachytherapy)

4.4. Indication to start non-surgical therapy (section 10.)

Clinical and ophthalmological symptoms will be recorded and regular neuroradiologic assessment be made to decide following initial diagnosis whether there is an indication for non-surgical therapy.

4.4.1. Indication to start non-surgical therapy at diagnosis following subtotal or partial resection (S2 – S3)

Severe preexisting visual disturbance (section 8.6.)
- Borderline vision in both eyes ("threat to vision")
- Definite history of visual deterioration
- Nystagmus due to poor vision (especially in infants up to two years indicative of visual disturbance)

Clinical indication
- Diencephalic Syndrome
- Symptomatic metastases

Note: The presence of a postoperative residual tumor is not an indication to therapy on its own.

4.4.2. Indication to start non-surgical therapy at diagnosis without prior tumor resection (following biopsy or radiological diagnosis)

Severe visual symptoms (section 8.6.)
- Borderline vision in both eyes ("threat to vision")
- Definite history of visual deterioration
- Nystagmus due to poor vision (especially in infants up to two years indicative of visual disturbance)

Severe neurologic symptoms
- Diencephalic syndrome
- Focal neurologic deficits secondary to tumor growth
- Symptoms of increased intracranial pressure secondary to tumor growth
- (Focal) Seizures secondary to tumor growth
- Symptomatic metastases

Note: The presence of a tumor is no indication to therapy on its own.

4.4.3. Indication to start non-surgical therapy following observation, if surgery is not feasible

Progressive neurologic symptoms
- Manifestation of new neurologic symptoms
- Manifestation of Diencephalic Syndrome

Progressive visual disturbances
- Reduction / loss of vision or of visual fields
- Any reduction / loss of vision in the second eye, if the other eye is blind

Neuroradiologic progression
- Definite increase of tumor size (Increase of the diameter of the optic nerve)
- Involvement of previously uninvolved areas of the brain
- Manifestation of tumor dissemination (including symptomatic or progressive metastases, symptomatic leptomeningeal dissemination)

4.5.Chemotherapy (section 14.)

4.5.1. Induction therapy

Induction treatment will be randomised between standard and intensified induction for study group 1 and 2 (No NF I, 1: supratentorial midline tumors, 2: LGG of all other locations).
Treatment group 3 (NF I, low grade glioma of any location) will receive standard induction.

<u>Standard Induction:</u>

1	2	3	4	5	6	7	8	9	10		13	17	21		24	week
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**			
C			**C**			**C**			**C**		**C**	**C**	**C**			
															MRI	

<u>Intensified Induction</u>

1	2	3	4	5	6	7	8	9	10		13	17	21		24	week
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**			
C			**C**			**C**			**C**		**C**	**C**	**C**			
Ex3			**Ex3**			**Ex3**			**Ex3**							
															MRI	

V	Vincristin	1,5 mg/m²	iv-bolus - d 1 of treatment week
C	Carboplatin	550 mg/m²	1h iv - d 1 of treatment week
E	Etoposide	100 mg/m²	1h iv - d 1 – 3 of treatment week

The evaluation at 24 weeks is decisional for entry into the consolidation therapy

4.5.2. Consolidation therapy
All patients will receive a common consolidation therapy:

25	31	37	43	49	week
55	61	67	73	79	
VVV	**VVV**	**VVV**	**VVV**	**VVV**	
C	**C**	**C**	**C**	**C**	

V	Vincristine	1,5 mg/m²	iv-bolus – d 1, 8, 15 of treatment cycle
C	Carboplatin	550 mg/m²	1h iv - d 1 of treatment week

4.5.3. Randomisation
Study group 1 and 2: Patients without NF I and LGG of the supratentorial midline, the cerebral hemispheres, the cerebellum, the caudal brain stem and the spinal cord will be randomised centrally between standard and intensified induction treatment.
Randomisation will be stratified according to age (< 1 year, 1-8 years, ≥ 8 years) and primary tumor site (pure chiasmatic tumors (Dodge II), all other supratentorial midline tumors, tumors of all other sites outside the supratentorial midline).

Study group 3: Patients with NF I and tumors of any location will not be randomised, they receive standard induction therapy and consolidation according to Option A.

4.6. Radiotherapy (section 15.)

Children receiving radiotherapy shall be treated according to modern treatment planning and application recommendations concerning fields and doses (total and per fraction). Stratification of age groups is identical to that for chemotherapy.

	Total dose	Dose per fraction	Treatment time
"Older" children: Brain	54 Gy	1,8 Gy	6 weeks
Spine	50,4 Gy	1,8 Gy	5 ½ weeks
"Young" children: Brain	Contact national radiotherapy chairman		
Spine			

5. Study end points

All study patients:	Feasibility of treatment
	Overall survival, progression free survival following diagnosis
Observation group:	Long term sequelae, health status, quality of life
Treatment group:	Progression free survival, event free survival, overall survival
	Response to non-surgical therapy
	Long term sequelae, health status, quality of life

6. Statistical considerations

6.1. Children with LGG of all sites not affected by Neurofibromatosis NF I.

The aim of the trial is to compare **standard induction therapy** with Vincristine and Carboplatin with the **intensified induction therapy** with Vincristine, Carboplatin and Etoposide with reference to progression free survival in children, who are not affected by Neurofibromatosis (type NF I), with low grade glioma of all sites necessitating chemotherapy as non-surgical therapy (according to patient eligibility criteria (section 9) and indication for non-surgical therapy (section 10)).

This therapy optimization trial is multi-national, multi-center, non-blinded, randomized and prospective.
The accrual period of the trial is 6 years followed by an observation period of 2 years.

The main question (PFS) will be analyzed on a significance level of α=0,05. The p-values corresponding to the secondary questions are regarded as explorative.
Defined variables will be checked with reference to their influence upon the survival variables by Cox regression.

6.2. Children affected by Neurofibromatosis NF I with LGG of all sites.

Chemotherapy according to this protocol is applied to delay or obviate the start of radiotherapy compared with a historical control group.
Statistical analysis will be only descriptive.

3.1. Introduction SIOP LGG 2004

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 I° or II° according to the revised system of the WHO of 2000 (Kleihues 2000). For clinical purpose some of the mixed glioneuronal tumors are included as well, if their glial component appears most relevant for biologic behavior.

About 30 to 40 % of all pediatric primary brain tumors are low grade gliomas. Their annual incidence is calculated as 10-12 per 1 000 000 children under the age of 15 years in western countries (France, Germany, USA (white population), Scandinavian countries) (Stiller 1994, Kaatsch 2001, Schütz 2002). Childhood cancer registries assume a systematic underreporting of these neoplasms, which in part is due to the limited patient referral to centers of tertiary care (Michaelis 2000, Stiller 1994).

These tumors occur at all ages. Mean age of diagnosis or operation varies according to the selection of the pediatric cohort, but is mostly between 6 and 11 years. There is no general consensus concerning the impact of age on the risk of disease progression.

The male to female ratio can generally be viewed as 1,1-1,2:1 (Stiller 1994, Kaatsch 2001), although some diagnoses like the DIGG/DIA show a more marked male preponderance.

Associated Predisposing Conditions and Genetics

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 development.

Neurofibromatosis type I (NF I) in its familial as well as in its sporadic form is caused by mutations within the Neurofibromin-gene, located on the long arm of chromosome 17 (17q 11.2). The NF I gene can primarily be regarded as a histogenesis control gene, which also functions as a tumor suppressor gene (Riccardi 2000). Yet, the occurrence of two independent mutations may not suffice to explain the development of low grade astrocytic lesions in NF I.
In as many as 5 to 15 % of cases (Riccardi 1992, Riccardi 1991, Lewis 1984, Listernick 1997) NF I is associated with low grade gliomas of the optic tract and the hypothalamus, but other regions of the brain as well (Vinchon 2000). The proportion of patients with NF I varies within neurooncological studies from 10 to 20 %, but may rise up to 60 %, if only visual pathway gliomas are considered (Capelli 1998, Castello 1998, Dutton 1994, Packer 1997). Since the presence of an optic pathway glioma puts NF I patients at risk for later development of other, even more malignant brain tumors, a subset of NF I patients may have an increased vulnerability for glial tumors. This may be caused by specific genetic mutations (Vinchon 2000, Friedman 1997) or by the effect of modifying genes, or from other modifying factors.

Tuberous Sclerosis complex is an autosomal-dominantly inherited multisystem disorder characterized by widespread hamartomas in almost every organ, but predominantly in brain, kidneys, liver, heart, skin and eyes. Molecular studies have shown mutations on chromosomes 16p13 and on 9q34. The presence of subependymal giant cell astrocytoma is one of the major

diagnostic criteria (Roach 1998). The tumors appear with increasing frequency throughout childhood reaching an incidence of 15 % in adolescence (Józwiak 2000).

Low grade astrocytoma is a trait of the Li-Fraumeni-syndrome as well, a genetic condition characterized by an excessive aggregation of tumors in more than two generations or in siblings, by the occurrence of tumors at an unusual age for the tumor type or in an atypical gender, as well as the sequential appearance of other cancers in the same individual, associated with genetic disorders and birth defects (Li 1982, Lynch 1985, Malkin 1990). A germline mutation in the p53 locus on chromosome 17p13 triggers the susceptibility to develop multiple tumors throughout life (Ohgaki 2000).

No prospective analysis of the prognostic significance of cytogenetic alterations has been performed. Despite repeated attempts of conventional karyotyping or of comparative genomic hybridisation, specific gene loci with frequent alterations could not be characterized in childhood low grade glioma as opposed to adult glioma, where progressive DNA-alterations within one given tumor representing progressive degrees of malignancy could be found (Miettinen 1999, Orr 2002, Smith 2000).
The association of NF I and juvenile pilocytic astrocytoma (JPA) WHO I° suggests a role for the (altered) NF I gene or its signal transduction pathway in the development of sporadic JPA as well, although this has not been proven yet by specific gene deletions or changes of gene expression. The occasional loss of chromosome 17q, including the region of the NF I gene, in sporadic pilocytic astrocytoma did not go along with specific mutations (von Deimling 1993, Ohgaki 1995). And even the differential expression of some NF I transcripts did not separate reactive and neoplastic astrocytes.

All types of low grade glioma are characterized by a biologically indolent growth pattern, not well explained by histological features. Only the newly characterized subtype of a pilomyxoid JPA seems to go along with an increased progression rate (Tihan 1999). Even after incomplete surgical resections some tumors do not exhibit a growth rate for extended periods of time. Alterations in blood supply, decelerating growth kinetics within the tumor over time due to a change in the ability of the tumor to maintain an adequate level of autocrine growth factors (like EGF-receptor, c-erbB-2 oncoprotein, TGF-alpha) or an increase in the spontaneous rate of apoptosis could contribute to the stable situation (Bodey 1999, von Bossany 1998, Rhodes 1998).
Conversely there are just speculations about factors responsible for tumor growth due to the lack of unequivocal findings concerning the role of the proliferation rate (Ki-67/MIB-1-staining), elevated levels of VEGF or a down-regulation of N-CAM, which may correlate with a higher rate of tumor progression (Abdulrauf 1998, Hoshi 1997, Sasaki 1998).

Natural History

Most children with low grade glioma will survive for long years, so analyzing overall survival (OS) as outcome parameter for the success of a given treatment strategy may not be the best way of discriminating treatment approaches. However, since long phases (10 to 15 years) of patient survival are common and the survivors will experience late effects of all treatments applied, it is pertinent to evaluate the additional damage produced by any therapeutic measure.

A substantial number of children will have recurrences following resection or experience progression following incomplete tumor removal or biopsy. Knowledge about the natural course of low grade gliomas is based on small series collected throughout long periods of

time. Since no clear-cut risk-profiles of either clinical, biologic or histopathologic features have been determined up to now, it cannot be predicted, which low grade tumors will show an indolent clinical behavior, and which will run an aggressive course. It is not known, whether all low grade tumors do possess a proliferative potential - therefore it is undetermined whether all low grade gliomas ultimately may need treatment. On the other hand, spontaneous involution has only rarely been documented unequivocally (Perilongo 1999, Kernan 1998). All of these tumors had been located in the chiasmatic-hypothalamic region. If reported, vision did not improve despite tumor shrinkage. Only for lesions in NF I patients tumor regrowth within the extended follow-up period has been reported (Schmandt 2000, Perilongo 1999).

Following numerous national and institutional trials with various treatment strategies for different subgroups of children with low grade glioma, this protocol aims to present an integrative approach for the treatment of all low grade gliomas irrespective of their location and histological subtype.

3.2. Background SIOP LGG 2004
Treatment strategies for low grade glioma

3.2.1. Surgery

There is general consensus that surgical excision should be considered first at diagnosis or at relapse. A variety of techniques can be used to optimise tumor location and complete resection (Berger 1994, Soo 2000, Pollack 1999).

Recent pediatric reports indicate that total removal is possible in up to 90 % of cerebral hemispheric glioma (Hirsch 1989), and in two thirds to 90 % of cerebellar astrocytoma (Smoots 1998, Due-Tonnessen 2002). Long term follow-up shows survival rates after complete resection above 90 % (Pollack 1995, Hirsch 1989, West 1995, Wallner 1988, Gjerris 1978 , Campbell 1996, Pencalet 1999).
But even in these cohorts a small percentage of progression occurs over time, necessitating further therapy.
Many tumors, however, are not amenable to complete resection either because of anatomical location or metastatic disease, and sometimes they only can be biopsied.
Stable disease for extended periods of time has been described following subtotal resection or less, yet historical data also demonstrate the impaired long term prognosis of 15 - 50 % survival after subtotal resection or less at various locations of the CNS, with a high rate of progression within the first years (Campbell 1996, Smoots 1998, Pencalet 1999, Garvey 1996, Hoffman 1993, Sutton 1995).
For cerebral hemispheric and cerebellar astrocytoma the volume of residual tumor proved to be the best predictor of the hazard of disease progression (Smoots 1998, Berger 1994). But irrespective of the tumor volume the probability of freedom from surgery or cytotoxic therapy after presentation is low for children with hypothalamic or visual pathway gliomas and dropped to 23 % at 2 and 19 % at 5 years for a series of 46 children (Janss 1995). The controversy concerning tumor management with radical or conservative surgery even for children with midline supratentorial glioma in order to reduce the rate of progression has to take postoperative functional status into consideration, as well (Wisoff 1990, Sutton 1995, Hoffman 1993).

Table 1 compiles the results of various neurosurgical reports. They demonstrate that following complete tumor resection relapse or progression are exceptional events, but that the extent of resection depends largely upon tumor location.

3.2.2. Radiotherapy

Introduction and the background concerning the role of radiotherapy in the treatment concept of low grade glioma are presented together with the rationale for the present study design and aims in Section 15.

Table 1: Results of the first neurosurgical intervention for children with low grade glioma

Author	Number of patients. Age	Localisation	Degree of resection	Results
Hirsch et al. 1989	42 median age: 4,25 y	Cerebral Hemispheres	Complete 40 incomplete 2 (2 irradiated)	1/40 Relapse 2/2 Progression Probability of "Non-Recurrence" 95% at 5 years 78,5% at 12 years
Pollack et al. 1995	71	Cerebral Hemispheres	Complete 21 subtotal 12 partial 26 (>50% resected) partial 12 (<50% resected) (irradiated: 2/21 post CR 33/50 post <CR)	0/21 Relapse 2/12 Progression 11/38 Progression additionally: 1/38 SMN PFS for all Patients: 88% at 5 years 79% at 10 years 76% ar 20 years
Sutton et al. 1995	33 mean age 4,3/4,5 y	Chiasma/ Hypothalamus	Biopsy 27 (<20% resected) subtotal 5 (20-50% resected) No OP 1 (irradiated 29/33 Chemoth. 18/33 14/18 Chemo- and Radiotherapy)	Survival 28/33 (after a mean of 10,9 y)
Vandertop et al. 1992	12	Mesence-phalon	partial 9 no OP 3 (Radiation at Progression 3/12)	4/12 Progression Survival: 100% at the time of the publication
Pollack et al. 1994	16	Mesence-phalon	No OP 13/16 Biopsy 3/16 at Progression: Radiation 3/16	4/16 Progression Survival: 100%
Reardon et al. 1998	24 median age 10 y.	Thalamus	"gross total" 4 "near total" 2 subtotal 2 Biopsy 16	All children monothal. bithal. tumor Survival 52% 85% 0% PFS 36% 58% 0% at 4 years
Abdollazadeh et al. 1994	66 mean age 7,3 y	Cerebellum	Complete 61 Incomplete 5 (irradiated 1/5)	0/61 Relapse 5/5 Progression
Campbell et al. 1996	72 mean age: 6,5 y.	Cerebellum	total 57 subtotal 15	6/57 Relapse 57/57 Survival 7/15 Progression 14/15 Survival
Pencalet et al. 1999	168 mean age: 6,9 y.	Cerebellum	Complete 149 (88,7%) Incomplete 19 (11,3%) (irradiated 5/168 - 3%)	8/149 Relapse (5,4%) 8/19 Progression (42,1%) Survival 95,8% at 7,7 y PFS 95% after complete resection 45% after incomplete resection

Abbreviations: Degree of resection: CR – complete resection, OP: operation, SMN: second malignant neoplasm, PFS: progression free survival, Localisation: monothal.: monothalamic, bithal.: bithalamic

3.2.3. Chemotherapy

Investigation of chemotherapy treatment (CT) strategies initially focussed on young children under 5 years of age to avoid early radiotherapy (RT), especially for those with visual pathway gliomas. Early reports produced evidence that cytotoxic drugs are active against low grade astrocytic tumors and that they may delay or obviate the need for radiation therapy. Although short term efficacy with transient tumor control has been the primary target for these approaches, no data exist clarifying the role of chemotherapy for long-term outcome, yet. Preliminary reports suggest improvement or stabilisation of vision in children with optic pathway tumors even in the absence of objective tumor shrinkage (Mitchell 2001).
Measuring response by conventional criteria like complete or partial response does not seem appropriate for low grade astrocytoma, a phase of prolonged stable disease is an adequate success of therapy (Packer 1997). Reports upon the effectiveness of chemotherapy in low grade glioma have comprised newly diagnosed as well as relapsed patients, treated with single agents or drug combinations for variable length of time.
The studies suggest that chemotherapy may have little or no significant adverse effects on cognitive or endocrine function, but their inherent long term risks concerning organ toxicity, carcinogenic and mutagenic risks have to be closely observed.

Following the termination of several larger, national studies, the role of chemotherapy, within a multidisciplinary approach, for the treatment of young children affected by a surgically unresectable, or progressive or symptomatic low grade glioma can now be considered firmly established in terms of achieving tumor responses including tumor volume reduction and a prolonged progression-free and radiation-free survival. The effects of chemotherapy on improving the actual clinical and neurological function, for example the visual and endocrinological function for supratentorial midline tumors, and ultimately on health status (HS) and quality of life (QoL), however, deserve further investigation.
It is difficult to compare the tumor response rates and ultimately long term results reported by the various trials run on childhood low grade glioma. Characteristics of the patient population, the indication to start therapy, the criteria defining response as well as the timing of tumor response assessment varied between the studies.

Table 2: Indication to therapy in various clinical trials:

Packer et al. 1997	• Within 4 weeks following documentation of clinical or radiographic tumor progression (> 25 % tumor volume) • Within 4 weeks following initial resection of less than 50 % of tumor volume
Prados et al. 1997	• Progressive symptoms like visual loss, intracranial hypertension, obstructive hydrocephalus, endocrinopathy • Radiographic tumor enlargement
Castello et al. 1998	• Incomplete tumor resection/biopsy (no biopsy required for large glioma of visual pathways and NF I) • Severe and/or progressive neurologic symptoms
Laithier et al. 2000	• Newly diagnosed, progressive optic pathway gliomas
Perilongo et al. 2000	• Patients with severe neurologic symptoms at the time of diagnosis (e.g. diencephalic syndrome) • Patients with progressive clinical symptoms and/or neuroradiologic progression following observation

3.2.3.1. The role of chemotherapy in terms of tumor response for low grade glioma

202 of the 204 eligible patients from the SIOP - LGG 1 study are presently evaluable for tumor response. The overall response rate, complete, partial and objective response and including stable disease, is 83.7%, with a complete (CR) and partial response (PR) rate of 50%. No central review of the actual MRI-scans to substantiate the data reported in the forms was carried out. The median time to tumor response evaluation was 3.6 months (range 1-21.5 months). It has not been investigated, if a more consistent timing of tumor response (TR) evaluation results in a different distribution of responses. The analysis of tumor response by clinical patients' characteristics such as age, sex, NF status, histology (astrocytoma nos., fibrillary astrocytoma, pilocytic astrocytoma and histology versus clinical diagnosis), site and the presence of disseminated disease did not reveal a significant influence.

The tumor responses reported by other major clinical trials such as the historical VCR/Actinomycin (Janss 1995) series from Philadelphia, the CCSG regimen, based on Vincristin/Carboplatin as well (Packer 1997), the San Francisco study using 6-Thioguanine, Procarbazine, Dibromodulcitol, Lomustine and Vincristin (Prados 1997) and the French "BB-SFOP"-trial, based on Carboplatin / Procarbazine; Cisplatin / VP 16; Vincristine / Cyclophosphamide (Laithier 2000, and personal communication), are reported below.

Table 3: – Tumor response in children with LGG as reported by the various chemotherapy trials

	Vincristin/ Carboplatin SIOP - LGG 1	TPDCV S. Francisco – regimen	Vincristin/ Carboplatin CCSG	VCR-ACT/D	BB – SFOP series
n	204	42	78	29	85
Complete response (CR)	4.0%	-	5%	-	-
Partial response (PR)	46.0%	-	28%	2*/29 (7%)	56%
Minor response (MR)	-	-	23%	17/29 (59%)	-
Stable disease (SD)	33.7%	-	37%	9/29 (31%)	31%
Progressive disease (PD)	16.3%	-	6%	1/29 (3%)	13%
CR+PR	50% ± 3.5%.	-	33%	7%	-
CR+PR+MR	-	35.7%	56%	66%	56%
CR+PR+MR+SD	83.7% ±2.6%	95.2%	93%	97%	87%

*50% tumor volume reduction
Legend: CCSG - Children's Cancer Study Group; SFOP - French Society of Pediatric Oncology; VCR - Vincristin; ACT-D - Actinomycin D; CR - complete remission; PR - partial remission; MR - minor response; SD - stable disease

The relevance of tumor volume reduction for long term patient outcome and functional status of children with LGG has to be discussed in conjunction with achieving the main primary goal of deferring radiotherapy. Translation of tumor response into progression free survival rates will be discussed below.

However, it should be added that tumor volume reduction may have a beneficial effect on severe neurologic symptoms at presentation, especially diencephalic syndrome (DS). Gropman et al reported the outcome of 7 children presenting with hypothalamic-chiasmatic glioma and DS (aged 9-20 months, median 11 months) treated with chemotherapy. At a median follow of 29 months (range 6-54 months) the patients' weights had increased by 66-95% (median 80%). On MRI four patients had a > 50% reduction of the tumor mass, one a

25-50% reduction and two stable disease. In those patients who showed a tumor volume reduction to CT, weight gain was accomplished by oral feeding in 4 of the 5 patients, whereas those with SD required nasogastric or gastrostomy tube supplementation to maintain weight. Only 2 of those children were censored progression-free at the end of the follow-up time (Gropman 1998).
Laithier investigated the clinical outcome of 14 children (age range 3-25 months) affected by a hypothalamic-chiasmatic glioma (HCG) and diencephalic syndrome. In this series weight gain was observed in those patients who responded to treatment. Tumor progression occurred in 11 of these children. Six of them were irradiated, at a median interval of 30 months from starting chemotherapy. Interestingly the 3-year progression free survival of children with HCG with and without diencephalic syndrome was 17% and 57% respectively (p=0.001) with however an overall survival of 89% in both groups (Laithier 2002).

3.2.3.2. The role of chemotherapy in terms of progression free survival for low grade glioma

Progression free survival would be the easiest parameter to judge the effect of chemotherapy on childhood low grade glioma. When comparing results from different studies, study population characteristics vary and influence the interpretation of results. The BB-SFOP data refer only to children with HCG and OPG, whereas the cohorts of the reports from Packer (1997) and Prados (1997), as well as the SIOP-LGG 1 study, include children with tumors of all sites. The timing and criteria of expressing treatment results are quite different. Most studies calculate 3-year progression free survival, which in terms of delaying radiotherapy is a relevant interval in the sense that: deferring progression for at least three years will allow the young children to reach an age of around 5 years before being irradiated. But it is not possible to compare 5-year PFS rates.

The 5-years progression free survival (PFS) of children affected by a low grade glioma and treated according to the SIOP-LGG 1 study is 48% (95%CI 31,6%-64,2%). As expected, the overall survival of this cohort of children is favorable with a 5-year OS 89,1% (95% CI 84,1-94,0%).
The PFS produced by other concurrent trials on LGG are reported in the table below (table 4). In the San Francisco experience the median time to tumor progression was 132 weeks (95% CI 106-186 weeks).

Table 4: Progression Free Survival in children affected by LGG and treated with chemotherapy

	SIOP-LGG 1	**CCGS**	**VCR-ACT/D**	**BB-SFOP**
Survival data	5 years PFS	3 years PFS	PFS at 6 years median F-U	3 years PFS
n	204	78	29	85
All patients	48% (95%CI 31.6%-64.2%)	68% ± 7%	~ 30%	48 % (37-60 %)

Legend: CCSG - Children's Cancer Study Group; SFOP - French Society of Pediatric Oncology; VCR - Vincristin; ACT-D - Actinomycin D; PFS - Progression Free Survival.

It can be concluded, that the PFS-data, particularly after a prolonged follow-up time, are not satisfactory, yet.

3.2.3.3. The role of chemotherapy in terms of radiotherapy-free interval for low grade glioma

One of the main motives to investigate chemotherapy in children with a low grade glioma is to defer the use of radiotherapy (RT) as long as possible (and hopefully forever), and thereby to avoid the deleterious effects of radiotherapy on a developing brain. Thus, the radiotherapy-free interval has been proposed as a criteria for judging the effect of chemotherapy. However, many young patients after having failed first line chemotherapy receive alternative chemotherapy-regimens instead of being irradiated. Thus, especially in very young children, the RT-free interval is the result of multiple interventions and can not be used as an indicator of the effect of one specific chemotherapy regimen, unless the other interventions are recorded and included in the analysis.

In the SIOP - LGG 1 study 41 children ended-up being irradiated. The median time interval between date of beginning chemotherapy and of radiotherapy was 22,2 months (range 1,3-67,6m). The median age of these children at the time of diagnosis was 54,3 months (range 3,5-164,8m) and at the time of beginning RT was 84,0 months (range 7,2-167,3m). In the VCR/ACT-D experience reported by Janss et al (Janss 1995) the RT delay in those children who were ultimately irradiated was of 4 years and 3 months (range 1 months and 10 years). As said, it is very difficult to compare these data, considering the many factors, which can influence the decision of irradiating a child.

Despite these limitations, the intent to delay radiotherapy in children with low grade glioma, specifically visual pathway gliomas, remains the primary goal for any therapeutic intervention.

3.2.3.4. The role of chemotherapy for progression free survival of hypothalamic-chiasmatic and optic pathway glioma

Hypothalamic-chiasmatic glioma (HCG) and optic-pathways glioma (OPG) represent a relatively homogeneous group of childhood low grade glioma, if for nothing else as for the clinical challenge they present. By themselves, the HCG and OPG do not represent a significant prognostic group, but since resection only plays a subordinate role, it is worth analyzing the data for this group of children separately. The PFS rates according to the different series are reported on table 5.
Table 5: Five years Progression Free Survival of children with Hypothalamic-Chiasmatic glioma treated with chemotherapy.

	SIOP - LGG 1	CCGS	VCR-ACT/D	BB-SFOP	St.Jude
n	204	78	29	85	??
Hypothalamic-chiasmatic LGG	39.2% ± 7.2%	77.6% *	~30%	~37%	12.11%

Legend: CCSG - Children Cancer Study Group; SFOP - French Society of Pediatric Oncology; VCR - Vincristin; ACT/D - Actinomycin D.
*3 years PFS

The 77.6% 3-year PFS survival produced by the CCSG cooperative study clearly stands quite significantly over the other treatment results. But the PFS-curve produced in the paper reporting the CCSG experience, does not have any plateau and at 5 years the curves seem to drop in the range achieved by the other study groups. It should also be noted that only three

children with a multicentric/disseminated LGG have been included in the CCSG series, while in the SIOP 14 children (11.3%) with such unusual variety of LGG have been registered and included in the survival curves.

In the VCR/ACT-D experience, 22 out of the 32 evaluable children experienced tumor progression after stabilisation or shrinkage. Median time to progression was 27 months (range 1-92 months). 72% of patients ultimately had tumor progression; CT delayed the use of RT beyond 5 years of age in more than 70% of the patients. Radiation therapy was delayed a median of 4 years and 3 months (range 1 month to longer than 10 years).

In the French experience with the 'BB - SFOP protocol' (including Cisplatin/Etoposide–Carboplatin/Procarbazin - Cyclophosphamide/ Vincristin) in a cohort of 85 hypothalamic-chiasmatic glioma the 3 years PFS was in the range of 37 to 60 %.

Sposto describing the survival data of a series of 18 children treated for a progressive or symptomatic HCG/OPG with a nitrosourea-based regimen, reported that no median time to tumor progression was reached at a median follow-up time of 78 weeks.

In summary the long term PFS of this cohort of LGG patients are not satisfactory results in any of the series. And they are identical to those published for other diencephalic tumors (Gururangan 2002). They justify searching for methods to improve outcomes.

3.2.3.5. Allergy to Carboplatin

Urticaria, eczema, abdominal or thoracic pain, cough, fever and dyspnea are symptoms of Carboplatin hypersensitivity (Chang 1995, Weidmann 1994).

As a whole 43 (21,1%) of the 204 patients entered into the SIOP - LGG study 1 had allergic reaction to Carboplatin at a time interval between the beginning of CT and "allergy" ranging from 1 to 52 weeks (median 33 weeks). However, this could be an underestimation of the real incidence of the problem; in fact, among the Italian patients, 17 out of 47 children (36,2%) actually manifested allergic reaction to Carboplatin. In the CCSG experience only 5 out of the 78 (6%) eligible patients had allergic reactions to Carboplatin, and only 6 out of the 60 (10%) of those treated in the pilot protocol (Packer 1993 and 1997). However, during the on-going randomised trial the number of Carboplatin-allergies exceeds 30 % (J. Ater, personal communication). The schedules within the Carboplatin / Vincristin regimen used by the CCSG group and the one used by SIOP are quite different, but the total doses are in the same range.

Table 6: Comparison of Carboplatin dosage between regimens.

	SIOP regimen	**CCSG regimen**
CARBOPLATIN (dose per cycle)	550 mg/m^2/d1	175 mg/m^2/d1 x 4 weeks
No. of doses/cycles	15	12
Duration of therapy, weeks	53	79
Cumulative dose of CARBOPLATIN	8250 mg/m²	8400 mg/m²
Allergic reactions	36,2% Italian population 21 % study population	5/78 (6%) institutional trial > 30 % randomised trial

In the literature the occurrence of hypersensitivity to Cisplatin is described in 5 to 20 % (Morgan 1994, Ciesielski-Carlucci 1997), while allergy to Carboplatin is mentioned with less than 5-6 % (Morgan 1994, Charlene 1996, Packer 1997). It is speculated that the number of exposures is responsible for the development of hypersensitivity reactions, since the risk of allergy to Cisplatin rose from 6 % in the 6^{th} cycle to over 67 % in the 10^{th} cycle in a series of adult women with ovarian cancer (Morgan 1994). Repetitive, weekly dosing has been reported to enhance the probability of allergic reaction in brain tumor patients (Yu 2001).

There are no known risk factors (Weidmann 1994, Chang 1995). Reports concerning hypersensitivity have been published following treatment with a variety of schedules and cumulative doses in different tumor types. Concomittant medication was variable. It is interesting to note that some reactions have occurred more than a year following first treatment with Carboplatin in the setting of a new therapy (Weidmann 1994).

The mechanism of the underlying immune reaction could not be elucidated yet. An IgE-mediated immune reaction with Platinum-compounds acting as haptens is possible, as well as an non-specific Histamine-release by platinum-salts (Weidmann 1997). Perhaps there is a reactive metabolite, activated by leucocytes, with infection or inflammation as risk factors for its release (Utrecht).

Some authors have reported successful desensitization in children, who had developed severe hypersensitivity reactions necessitating the interruption of Carboplatin-treatment (Charlene 1996). Desensitization with concurrent steroid and antiallergic medication has to start the morning of the planned treatment with extremely low starting doses. This procedure is only justified in case of unavailability of any alternative treatment. Cases have been described, where alternative therapy with Cisplatin has been successful despite previous allergy to Carboplatin (Weidmann 1994).

There are no data concerning the effectiveness of continuing therapy with Carboplatin once allergic reactions have developed.

Despite the risk for allergy, the use of Carboplatin can be considered one of the backbones of successful therapy for childhood LGG. Monitoring incidence, clinical symptoms and the course of disease after manifestation of allergy are necessary to define its impact for the overall treatment strategy.

3.2.3.6. Analysis of prognostic factors

Results given for the various trials, SIOP - LGG 1 included, are data derived from quite heterogeneous groups of children affected by a low grade glioma.

NF status

Among children affected by a progressive or symptomatic LGG and treated with chemotherapy according to the SIOP - LGG 1 study, the only patient / tumoral characteristic that predicted for tumor behavior was NF I status.

In the SIOP - LGG 1 study the NF I status predicted a prolonged PFS. In fact, the 5 years PFS for children without NF I were 50,9% (95%CI 40%-60%) and with NF I 66,5% (95% CI 53,7% -79,4%; $p > 0,016$) respectively. These data may reflect either a more favorable response to CT or a more indolent and benign course of the LGG associated with NF I than of those occurring in children without NF I. In a recent series of HCG/OPG treated with CT at the St.Jude Research Hospital the NF I status and the initial treatment with RT were the two most significant predictors of a longer PFS, while NF I status, tumor size < 10 cm^3, the lack

of ventriculomegaly and more than 50% tumor enhancement were the clinical findings positively influencing the outcome (Fouladi 2002).
There are certainly inconsistencies between studies with regard to NF status and eligibility criteria for enrollment. In this study NF I status is the major stratification factor. Case ascertainment will be critical, if the results are to be interpretable.

Tumor location
Most published series focus on the chemotherapy of tumors of the supratentorial midline, in particular hypothalamic-chiasmatic glioma. Although many studies have been open for tumors of other locations as well, their numbers have been small, not allowing a systematic analysis.
However, the response rate of Non-OPG tumors is relatively high compared to OPG in the French experience: The best objective response was 7/8 in intramedullary glioma (Doireau 1998), 10/11 in brainstem glioma (Pagnier 2002), while it was 45 % only in the OPG (Laithier, submitted). Few patients have been irradiated. In the CCSG series (Packer 1997) no difference of 3 year PFS was seen between diencephalic tumors, brainstem tumors and other cranial tumors, whereas all 3 tumors with leptomeningeal dissemination were progressive following an initial response in 2. In the SIOP-LGG 1 study, the number of tumors located outside the supratentorial midline is quite large. Responses (CR+PR+SD) were obtained in 9/11 tumors of the cerebral hemispheres, 26/34 of the posterior fossa and 6/7 of the spinal cord. No separate analysis of PFS for tumor location has been performed. Thus it is not clear whether primary tumor location plays a role for tumor response to chemotherapy or for PFS.

Tumor staging
Surprisingly, in the SIOP - LGG study 1, the presence of multicentric/disseminated disease did not have an influence on the patients' outcome. The 3 years PFS of children presenting with disseminated disease and treated with CT was 49% (95% CI 29,6-70,1%) and for the ones without 59,1% (95% CI 50,8-67,3%).
Timing of treatment
The only other clinical parameter, which in SIOP - LGG 1 seems to predict a different progression free survival, was the interval between diagnosis and the start of treatment. Children, who were treated at diagnosis had a 5 years PFS of 29,4% (95%CI 11,9%-46,8%), which was significantly inferior to the PFS of the children treated after a period of observation, 63,3% (95%CI 45,3%-81,4%; p=0,0063). The interpretation of these data is difficult. It has been assumed that the children treated at diagnosis had worse symptoms and therefore more aggressive tumors. The challenge for future studies would be to precisely identify those patients, by using some other criteria, since the present analysis does not define any clear-cut clinical or pathological risk-factors.
Furthermore, to explain this phenomenon some more imponderable reasons could be advocated such as the fact that after a prolonged period of observation, physicians and parents became "more nervous" in deferring treatment, and were more willing to submit their child to therapy, even in the absence of convincing clinical and neuroradiological evidence of tumor progression. It is hoped that greater standardisation of indications to commence therapy will emerge from the experience of the present study proposal.

Age at diagnosis
The data on the relevance of age at diagnosis as prognostic factor are contradictory.
In the CCSG trial age was pointed out as a possible predictor of different outcome. Children who were younger than 5 years did better than those older than 5; their PFS was 63,3% (45,3-81,4%) versus 29,4% (11,9% -46,8%) (Packer 1997). The mean age of their study population was 3.08 years. In contrast to the CCSG experience, in the San Francisco series the younger children did worse than the older ones (p=0.004; risk ratio 0.81) (Prados 1997). The

mean age in their study population was 5 years. Similarly, in the SFOP study children younger than 5 did significantly poorer than the older ones (Laithier 2000). Actually in the 10 year review of the LGG treated at the St. Jude Research Children's Hospital age seems to influence the outcome, once again being the children less than 5 doing worse than the over 5 years (Fouladi 2002).

Response to therapy
In the SFOP experience, after the NF I, status the most significant prognostic factor for a better PFS was the response to CT. Patients who had an objective response (PR and/or CR) to CT had a longer PFS than those who had a minor or stable disease after CT (3 year PFS 60% versus 25%). In the SIOP - LGG study 1 the 3 year PFS was 69,7 % (95% CI 58,7-80,7%) for the patients who obtained "some response" and 66,8.% (95%CI 53,9-79,7%) for the ones who had stable disease. Similarly, in the CCSG experience no difference in terms of 3-year PFS was documented between patients who had a major response and the ones who had just a minor response or stable disease: 83% ± 8% and 73% ±9% respectively (Packer 1997).

Pathologic/biologic criteria
No solid data exist on the role of possible pathologic and biological characteristics of childhood LGG in predicting different outcome.
Recently Tihan et al in the pathology file of the Johns Hopkins Hospital identified 18 cases of JPA with a distinctive monomorphous pilomyxoid histological pattern (monomorphous spindle bipolar cells in a fibrillary myxoid background, angiocentric arrangement and no Rosenthal fibers with a low labelling index (LI -Mib-1) in the range of 2% - 5% (Tihan 1999). The majority of the tumors occurred in infants and young children (median age 10 months) and involved the hypothalamic/chiasmatic region. In this cohort of patient the PFS at 1-year was 38,7%. In comparison they identified a control group of 13 classical JPA in the same range and location as the study group with a one year PFS of 69,2%, which was significantly better than that for pilomyxoid tumors (p=0.04). However, the precise definition of monomoprhous pilomyxoid pattern is still a matter of discussion.
Data exist on a small cohort of children which seems to indicate that the LI may be prognostically significant as well as the loss of 17p (Prados 1992, Willert 1995). However these data are still awaiting confirmation.

3.2.3.7. Functional/neurological outcome of children with LGG treated with CT

The vast majority of children affected by LGG are expected to be long term survivors. Thus, health status (HS) and the quality of life (QoL) remain significant criteria to judge the effect of a therapeutic approach. More specifically, for children with HCG and OPG the goal of any therapeutic intervention must also include the preservation and hopefully the improvement of the visual function and of the endocrinological status, besides the neurological status as a whole. The contribution of each specific modality of treatment to this functional aspects of children affected by HCG and OPG have not yet been fully investigated.

The fact that these children may have a poor "functional outcome" is outlined by some recent data. Cappelli (Cappelli 1998) studying a cohort of 44 long term survivors of HCG treated with RT, reported that 18 had major academic failures and that 12 were actually institutionalised. Ten of these 44 attended schools for blind. In the series reported by Sutton et al 43% of them required a "special school" including resources room, learning-disabled classes or special education. Of the 27 surviving patients for whom follow-up information was available, six were described as having "few or no friends", three were receiving Methylphenidate for attention deficit disorders, four were described as " passive" and two as

"very emotional" (Sutton 1995). Severe behavioural and also psychological and psychiatric disorders were also observed by Janss et al in a cohort of 46 long term survivors with HCG and OPG (Janss 1995).

Regarding the functional outcome in three large series of patients treated with chemotherapy for a progressive hypothalamic-chiasmatic glioma, it is said respectively that 15 out of 18 (Petronio 1991), 23 out of 24 (Packer 1988) and 19 out of 27 (Janss 1995) had visual stabilisation or improvement, however no more details are provided in the papers. Sutton reported the visual outcome in a cohort of 33 children with hypothalamic-chiasmatic glioma and stated that 5 were functionally blind in both eyes at the end of follow-up. Interestingly all children who were functionally blind had been very young at presentation. One of these children had an initial good response to CT given at the age of 2 and he is reported free of tumor at the age of 13, but blind. The other four children were irradiated at the age of 3 to 6, but it is not clear if this affected their vision (Sutton 1995).

Other investigators reported that RT seems to be more effective than CT in preserving and improving the visual function. Cappelli et al reporting the functional status in a cohort if 44 long term survivors of children with an HC glioma reported that after RT 18 had a visual improvement, 29 a stable vision and 7 some deterioration (Cappelli 1998).

In summary no prospective studies have been so far conducted evaluating carefully the visual outcome of children with HCG and OPG despite the relevance of this treatment outcome criteria. Unquestionably, the functional outcome of these children must become a crucial end-points of any study aiming to evaluate treatment strategies on these children. The data available so far seem to indicate that these children may suffer because of a variety of reasons of severe sequelae.

Endocrine sequelae
Almost all children with HCG need some hormone replacement following treatment, actually 28 out of 33 in the series reported by Sutton et al (Sutton 1995). Needless to say that children with supratentorial midline low grade glioma treated with chemotherapy are expected to have fewer endocrinological sequelae than the ones being treated with radiotherapy. Other than specific hormonal problems, children with HCG may seem to suffer from more complex growth disorders. In sutton's series of 33 children, it appears that these patients tend to cluster into obese (>90^{th} percentile for weight, 8 patients) and diencephalic (< 10^{th} percentile for weight, 8 patients), with the diencephalic one usually short in stature and the obese ones, tall.

3.2.3.8. Conclusions
Summarising the above data on the role of chemotherapy in low grade glioma, it can be said that:

- CT has a consolidating role in the treatment of children with LGG at least in terms of tumor response, PFS and radiotherapy-free interval;
- the progression free survival data are still unsatisfactory, especially for children with HCG and OPG;
- no reliable prognostic factors have been identified so far other than the NF1 status; the investigations into patient's clinical characteristics and into tumor histological and biological tumor profiles are becoming increasingly urgent;
- the functional outcome of the children treated should become a major end-point of any future studies directed to test specific therapies on children with LGG.

3.3. Rationale for a differentiated chemotherapy schedule for the study — SIOP LGG 2004

This protocol aims to present an integrative approach for the treatment of all low grade gliomas irrespective of their location and histological subtype.

Chemotherapy will be the primary non-surgical therapy for several subgroups of children. The chemotherapy strategy for childhood LGG shall be further developed within the context of a controlled prospective trial. The main reasons to launch the new strategy can be summarised as follows:

- ✓ to adopt the therapeutic concepts already proven to be potentially effective in treating these neoplasms (see section 3.2.)
- ✓ to stratify treatment for subgroups according to currently available prognostic criteria (see section 3.2. and 12.)
- ✓ to use as the standard treatment arm the "historical" regimen with Vincristin and Carboplatin from the SIOP - LGG 1 study (see section 4.)
- ✓ to introduce into the induction regimen a new drug which may improve the results for progression free survival and to test it by a randomisation procedure (see section 3.3)
- ✓ to extend the duration of therapy which may increase the number of major responses, as they seem to develop over prolonged periods of time
- ✓ to limit, as much as possible, the risks of long term side effects of chemotherapies employed
- ✓ to define more accurate and relevant end-points for treatment outcome evaluation (see section 17.)

Although no phase III prospective randomised clinical trial comparing different regimens has been completed so far, the combination of Vincristine/Carboplatin, as used in the previous SIOP - LGG 1 trial, represents the standard treatment for childhood low grade glioma in Europe at this time. This combination seems to respect appropriately the risk/benefit ratio for these children with minimal risks for late effects. Due to unsatisfactory progression free survival data in LGG this combination needs to be strengthened to improve outcome. The experience of delayed development of Carboplatin allergy may prevent a more extended schedule of this drug combination and justifies the consideration of adopting alternative regimens being proposed, where there is existing data.

3.3.1. Effective drugs in the treatment of low grade glioma

Except for the trials conducted by the POG on Carboplatin and Iproplatin (Friedman 1992) and by Gururangan on Carboplatin (Gururangan 2002) in progressive or recurrent low grade glioma, no other conventional phase II studies on childhood LGG have been run. For most drugs, used alone or in combination for treating LGG, only results on small series of patients form the basis to evaluate efficacy by response assessment as given in the reports.

Table 7: Chemotherapy trials in low grade glioma: Response assessment

ND: newly diagnosed; R: relapsed; diss: disseminated tumors; w: week(s); CT-scan: computed tomography; MRI: magnetic resonance imaging.
Response: CR: complete response, PR: partial response (tumor volume reduction of > 50 %), MR: minor response (tumor volume reduction of < 50 %, but > 25 % of initial volume), SD: stable disease, PD: progressive disease (tumor volume increase of > 25 %), Response Rate (for single drugs): CR+PR+MR+SD.
MI: missing information; *: Data included in subsequent reports.

DRUG/COMBINATION	NUMBER OF PATIENTS	DOSE / m²	TREATMENT INTERVAL	ASSESSMENT OF RESPONSE BY	TIME OF ASSESSMENT	CR	PR	MR	SD	PD	MI	Response Rate
CARBOPLATIN												90/105 – 85 %
Friedman (JCO 1992)	R 7	560 mg	4w	CT-scan/MRI	8w				5	2		
Moghrabi (J Neurosurg 1993)	ND 4, R 2	560 mg	4w	MRI	8w				6			
Aquino (J Neurooncol 1999)	ND 12	560 mg	4w				4		6	2		
Gururangan (JCO 2002)	ND 58, R 23	560 mg	4w	CT-scan/MRI	8w	2	17	4	46	11		
IPROPLATIN												11/15 – 73 %
Friedman (JCO 1992)	R 15	270 mg	3w	CT-scanMRI	6w		1		10	4		
CYCLOPHOSPHAMIDE												19/25 – 76 %
McCowage (MPO 1996)*	Diss 4	4-5 g	4w	MRI	no information		2	1	1			
Longee (J Neurosurg 1998)	R6, diss 4	4-5 g	4w				5	1	3	1		
Kadota (JPHO 1999)	ND 15	1,2 g	3w	CT-scan/MRI	12w	1			9	5		
IFOSFAMIDE												4/6 – 66 %
Heideman (J Neurooncol 1995)	R6	3 x 3g	3w	CT-scan/MRI	6w		1		3	2		
TEMOZOLOMIDE												9/20 – 45 %
CCG (unpublished)	R 20	5x200 mg	4w	CT-scan/MRI	8w		1		8		12	
MTX												7/10 – 70 %
Mulne (JPHO 2000)	R 10	7,5 mg x8 (q6h)	w	CT-scan/MRI	2 months		2		5	3		
TOPOTECAN												7/13 – 54 %
Blaney (Cancer 1996)	R 2	5,5-7,5 mg	3w	CT-scan/MRI	6w		1		1			
Kadota (J Neurooncol 1999)	R 11	3-3,75mg (CI)	3w	CT-scan/MRI	6w				5	6		
ETOPOSIDE												14/26 – 54 %
Chamberlain (JCO 1995)	R 14 chiasm-hypot.	50mg x 21 d	5w	CT-scan/MRI	8w	1	4		3	6		
Chamberlain (J Child Neurol 1997)	R 12 cerebellar	50mg x 21 d	5 w	CT-scan/MRI	8w		2		4	6		

DRUG/COMBINATION	NUMBER OF PATIENTS	DOSE / m²	TREATMENT INTERVAL	ASSESSMENT OF RESPONSE BY	TIME OF ASSESSMENT	CR	PR	MR	SD	PD	MI	Response Rate
VCR + ACTINOMYCIN D												
Packer (Ann Neurol 1988)	ND 24	1,5mg - 15 mcg	12 weekly		12w		3	6	14	1		
VCR + Carboplatin												
Packer (JCO 1993)	ND 37	1,5mg - 175mg	weekly	CT-scan/MRI	10w	1	15	7	13	1		
Packer (JCO 1993)	R 23	1,5mg - 175mg	weekly	CT-scan/MRI	10w		7	5	5	6		
Packer (J Neurosurg 1997)	ND 78	1,5mg - 175mg	weekly	MRI	10w	4	22	18	29	5		
Perilongo (MPO 2000)	ND 132	1,5mg - 550mg	3-4w	CT-scan/MRI	10w	5		56	49	22		
Carboplatin + VP 16												
Castello (MPO 1995 / CNS 1998)	ND 17, R2	300-1000mg - 600mg	3-4w	CT-scan/MRI	12-16w	1		6	8	4		
VP 16 + VCR												
Pons (J Neurooncol 1992)	R14, ND 6	1,5mg - 5x100mg	6w	CT-scan/MRI			1	3	11	5		
TDBCV												
Petronio (J Neuros 1994)*	ND 15	see paper	6w	CT-scan/MRI	no information			11	2	2		
Prados (J Neurooncol 1997)	ND 42	see paper	6w	CT-scan/MRI	6w			15	25	2		
BB SFOP												
Laithier (MPO 2000)	ND 84	see paper		CT-scan/MRI			47		26	11		

The compilation in Table 7 focuses upon response only, since survival and progression free or event free survival data are not available for the smaller series and can hardly be compared due to the variable settings.

It is not possible to judge from this data the superiority of a single drug or drug combination of drugs over another. It should be noted that responses have been reported for all drugs tested. It is tempting to say that “these tumors respond to everything”. VP 16 was selected by the SIOP - LGG study 2 committee to be added to the historical regimen during the early induction phase in order to evaluate its impact on improving “the effectiveness” of Vincristin/ Carboplatin, mainly for its possible synergism with the platinum derived agents.

3.3.2. Rationale for the intensification of induction treatment

In the SIOP - LGG 1 study, 84 children (41,2%) of the 204 evaluable patients suffered from a tumor-related event. 34,5% of these failures (29/84) occurred in the first 4 months of therapy. Although one of the possible explanations is that, at the time period the study was conducted, clinicians were still not used to treat the low grade glioma with chemotherapy and tended to interpret any tumor enlargement as progression and therefore overstate chemotherapy failure. It has been a common experience to observe some tumor volume increase during the very first weeks of therapy, followed by a stabilisation or by decrease of the tumor dimensions. Since, as in comparable trials as well, there was no central radiologic assessment, a definite conclusion as to the relative importance of this assumption is impossible.

In the CCSG experience only 6% of the patients failed during the first 10 weeks of therapy while the vast majority of the tumor failures were documented after stopping therapy. The median time to tumor progression in the cohort of 42 children they treated with TPDCV was 132 weeks (95% CI 106-186 weeks), thus half of the progressions occurred within the first 24 months of therapy

Table 8: Occurrence of tumor progression; comparison between SIOP low grade glioma Study 1, the CCSG trial and the BB-SFOP study

	SIOP study	**CCSG trial**	**BB-SFOP**
n	204	78	85
Median time of follow-up	35,4months	30 months	52 months
Patients with PD	84/204 (41,2%)	27/78 (35%)	46/85 (54 %)
Patients lost in induction	29 (14,2%)	5 (6%)	11 (13 %)
During maintenance	14 (6,9 %)	6 (7%)	7 (8 %)
After stopping therapy	41 (20,1%)	16 (21%)	28 (33 %)

No previous study has investigated the impact of the intensity of induction treatment upon long term tumor control in low grade glioma. As discussed in section 3.2. neither response rate nor progression free survival rates can be compared between studies and no significant differences have been detected between regimens. But as suggested by trials like the rather intensive regimen BB-SFOP a higher rate of objective responses may be expected to prolong progression free survival.

To reduce the high number of early tumor progressions, in the SIOP - LGG 2004 trial the initial phase of chemotherapy (Induction) shall be intensified by adding Etoposide in a prospective, randomised trial. It is expected that a reduction of the early progression rate will result in an improved long term progression free survival. As suggested by some studies, especially the SFOP experience, a more favorable response distribution may also improve the long term PFS.

3.3.3. Rationale for the differentiation of consolidation therapy

1. Overall therapy duration
The problem of the "optimal" time duration of chemotherapeutic treatment for LGG has never been addressed properly. The duration of the various regimens so far published varies quite significantly. In several published series, authors stress that the number of patients with a "major" therapy response is increasing as treatment continues.

Table 9: Duration of therapy in chemotherapy trials for the treatment of low grade glioma.

Drug combination	**Duration**
Cisplatin/Vincristin	from 16 to 32 weeks
6-Thioguanine, Procarbazine, Dibromodulcitol, Lomustine, Vincristine	24 weeks
Vincristin / Actinomycin D	48 weeks
Cisplatin/VP 16 –	12 months
Carboplatin/Procarbazin; Cisplatin/VP 16; Vincristin/Cyclophosphamide	12 months
Vincristin/VP 16	18 months
Carboplatin/Vincristin	Up to 79 weeks

Considering the difficulties in asking in a prospective randomised fashion, on top of the Etoposide question (randomisation of induction), also the "duration of therapy" one, it was elected to treat all children for 18 months in the subsequent trial, assuming the working hypothesis that these children are in fact affected by a sort of chronic, slow growing disease which deserves prolonged therapy. The time duration chosen was the one adopted by the CCSG trial, which is 18 months.
Ideally, this change should also be introduced in a prospective, randomized manner. However, due to the fact that recruitment rates even within a large European trial do not allow multiple randomisations, this has been considered unfeasible.
By adopting standardized cycle length and total treatment time to the American CCG trial an international comparability of trial results will be feasible in the future.

2. Prolonged time intervals between courses during the continuation therapy
To avoid increasing substantially the cumulative doses of the drugs chosen for the study when prolonging therapy to 18 months, the time interval between courses during the continuation-therapy phase shall be extended to six weeks, analogous to other so-called maintenance treatments. Yet, to avoid prolonged treatment free intervals (6 weeks) additional Vincristin will be given in weeks 2 and 3 of each cycle.

3. Alternative drug combinations for children developing allergy to Carboplatin
For those children who at some time during their chemotherapy schedule develop allergy to Carboplatin, this has been a major problem to maintain total treatment time. Depending upon

the time of manifestation of allergy a variety of measures have been adopted. Besides premature termination of therapy in individual cases, the majority of children has received "alternative" drugs, with mostly individually chosen schedules and cumulative doses. So no coherent analysis of these various measures can be taken.
Within the SIOP-LGG 2004 trial a uniform approach following Carboplatin allergy is recommended, which has the goal to maintain total treatment time of 18 months.
To ensure this goal the study recommends a standardized approach. Two alternating couples of drugs shall be administered sequentially on a 6-week schedule, as for Carboplatin/Vincristin, with additional Vincristin given in weeks 2 and 3 of each cycle: Cisplatin/VCR and Cyclophosphamide/VCR. Combinations of Cisplatin and Cyclophosphamide have shown efficacy when alternated with Carboplatin in the French "BABY-SFOP" LGG study. They will be combined with Vincristin instead of applying Procarbazin and additional VP 16 to avoid long term toxicity. To limit cumulative doses of Cisplatin and Cyclophosphamide no more than 5 cycles of both combinations shall be given.

4. Alternative drug combinations for children with progression following chemotherapy
Although the primary aim of using chemotherapy in case of a symptomatic and/or progressive low grade glioma has been to defer radiotherapy, and thus it would only appear consequent to start radiotherapy upon tumor progression during or after chemotherapy, various circumstances will make such a choice unwanted.
Many of those children who were very young at diagnosis, will still be young, if they suffer from tumor progression during chemotherapy or within the first years after its terminations. Thus the arguments to defer radiotherapy still hold, especially if the tumor had been responsive to primary chemotherapy.
Especially for children with Neurofibromatosis NF I the rationale to avoid radiotherapy is valid thoughout childhood and thus sequences of alternative chemotherapies are preferred to early institution of radiotherapy.
Despite these basic considerations, a systematic strategy of sequential chemotherapies has not been investigated up to now. Within this study the recommended treatment for unequivocally progressive tumors, in which radiotherapy shall be further delayed, is to alternate the two combinations of Cisplatin/Vincristin and Cyclophosphamide/Vincristin. Dependant upon the time at which progression is diagnosed the duration of therapy has to be determined.

- For children with primary progressive tumors individual strategies have to be designed.
- For those with early progression, following initial response (as measured at week 24) the same strategy can be used as for the children with allergy (see above).
- For children, where progression gradually develops at any time following the end of primary therapy, resuming chemotherapy at a time schedule as presented for the initial Carboplatin/Vincristin therapy in SIOP-LGG 2004, but substituting Carboplatin/Vincristin by alternating Cisplatin/Vincristin and Cyclophosphamide/Vincristin should be considered.

3.3.4. Safety considerations for the choice of drugs

The cumulative dose (expressed in term of mg/m^2) of the drugs used in the regimens of the studies SIOP-LGG 1 and SIOP-LGG 2004 (2) are reported in the table below:

Table 10: Cumulative doses within the chemotherapy regimens of SIOP-LGG 1 and 2004.

	Vincristin	Carboplatin	Etoposide (randomised)	Cisplatin	Cyclophos-phamide
SIOP-LGG 1	**31,5 21 doses**	**8,250 15 doses**	**-**	**-**	**-**
SIOP-LGG 2004 – TRIAL ARM	**64,5 43 doses**	**9350 17 doses**	**1200 4 cycles à 3 doses**	**-**	**-**
SIOP-LGG 2004 - ALLERGY ARM	**64,5 43 doses**	**variable**	**1,200 4 cycles à 3 doses**	**maximum 300 5 cycles à 2 doses**	**maximum 7500 5 doses**

1. VP 16

The risk of VP 16 related secondary leukemia or myelodysplastic syndrome can be considered to be low counting the facts that:

- the cumulative dose is much less than the one potentially associated with the risk of developing secondary leukaemia;
- the schedule is different from the one thought to be related to secondary AML development (weekly or twice-weekly administration) (Smith 1999).

The Cancer Therapy Evaluation Program of the National Cancer Institute developed a monitoring plan to obtain reliable estimates concerning the risk of secondary leukaemia after epipodophyllotoxin treatment. The main conclusions reported are the following:

"..for cumulative doses of Etoposide of 5 grams/m² or less (given primarily on a daily times five schedule), the risk of secondary leukaemia is not inordinately increased above that contributed by other agents used in the regimens (studied)...";

"..within the context of multiagent regimens that include alkylating agents,…., factors other than epipodophyllotoxin cumulative dose are important in determining the risk of secondary leukaemia..";

"..the Etoposide administration schedule associated with the highest cumulative incidence of secondary leukaemia is weekly to twice weekly administration.."

2. Cisplatin

The risk of Cisplatin (CDDP) related organ toxicity should be low considering:

- That in most circumstances the cumulative dose of Cisplatin will be below the maximum possible dose.
- The fact that the cumulative dose of Cisplatin is administered on a low dose daily schedule, a modality ofadministration, which seems to minimise the risk of organ toxicity. Nevertheless, regular surveillance of organ functions is mandatory for all children receiving the alternative arm.

3. Cyclophosphamide

The risk of developing sterility and secondary tumors associated with the use of 3 gr/m2 cumulative dose of Cyclophosphamide seems to be almost negligible. In fact, only doses of Cyclophosphamide in excess of 5 g/m² have been associated with a risk of sterility, estimated in the 10% range. Several reports have shown that the risk of AML and MDS among patients

with early breast cancer who received standard dose of Cyclophosphamide-containing adjuvant chemotherapy is not much higher than in the general population (Valagussa 1994; Tallman 1995; Holdener 1994). In children treated for rhabdomyosarcoma 3 cases of secondary leukaemia were reported among 68 children treated with a cumulative dose of Cyclophosphamide higher than 16,8 g/m2 and none in the group who received a lesser cumulative dose of the drug (Scaradovou 1995.) Only very high doses of Cyclophosphamide seem to be associated with an increased risk of secondary leukaemia (Kushner 1998).

3.3.5. Rationale for a "chemotherapy-only" schedule in patients with Neurofibromatosis NF I.

The occurrence of brain tumors is a trait of Neurofibromatosis NF I, yet the true incidence of symptomatic CNS-tumors is not known (Huson 1994, Listernick 1997), but estimates range from 0,9 to 15 % (Listernick 1989, 1997).
Data support the concept that low grade glioma arising in children with NF1 have a different biological behavior, but within the NF1 population the clinical and biological behavior of LGG can vary quite significantly, although the majority has a particularly indolent clinical course. Within this group of children cases of spontaneous partial regression of hypothalamic and OPG have been clearly described (and none in non-NF1 children). It has been assumed that only a minority of these children will ever have progressive disease, that this will not occur beyond 6 years of age and that only few children thus need therapy (Listernick 1994). Recent studies have shown however, that delayed tumor progression in these patients is not uncommon (Grill 2000) and within the SIOP-LGG 1 study age of NF I patients needing non-surgical intervention ranged from 1-12 years (median 3,5 years) for those receiving chemotherapy and from 4-11,7 years (median 9 years) for those receiving radiotherapy (Garré 2002).
NF I patients have been included in all recent series upon the treatment of low grade glioma and constituted from 14,3 % (Prados 1997) to 19,2 % (Packer 1997) and 27 % (Kalifa, unpublished) in the larger (chemotherapy) series, and 21,1 % in the SIOP-LGG 1 trial. Most often they were treated according to the age related strategies with radiotherapy for the older and chemotherapy for the younger children.

Although the clinical course of children with NF I, even if unaffected by a CNS-tumor, is extremely variable, a third of these patients experience additional learning difficulties and minor to moderate mental retardation (Huson 1994). Children with NF I and optic pathway tumors treated with chemotherapy had a worse neuropsychological outcome due to the preexisting brain dysfunction even in the absence of radiotherapy, whereas children without NF I receiving chemotherapy as first line treatment have preserved intellectual capacities (Lacaze, in press). The use of radiotherapy for the treatment of visual pathway gliomas in NF I-patients, especially if they are extensive and need large radiation portals, increases the risk of intellectual deterioration. Additionally patients with NF I suffer from an enhanced incidence of radiation induced vasculopathy (Grill, 1999).
A certain percentage of children with NF I having a symptomatic visual pathway glioma will develop other tumors of the central nervous system subsequently, some of them malignant, with reports indicating an incidence of 13 to 52 % (Friedman 1997, Riffaud 2002). Since these tumors may need radiation therapy on their own, it is prudent to avoid primary radiation for the OPG.

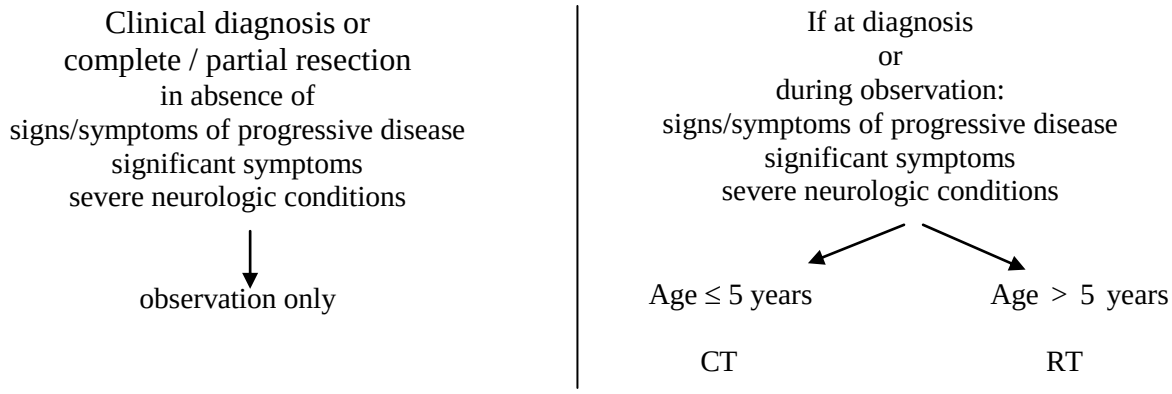
When treated with chemotherapy for progressive visual pathway gliomas, children with NF I demonstrate comparable high response rates, but significantly longer progression free survival

as compared to children without NF I (Packer 1997, Laithier 2000). This was confirmed in the SIOP-LGG 1 study as well with the application of Vincristin and Carboplatin (Garré 2002). Only few children had progression following therapy, thus NF I patients may benefit from prolonging treatment, but intensification of induction treatment does not seem necessary. Additionally, the risk of inducing secondary malignancy by the use of epipodophyllotoxins or alkylating agents in children with an inherent high risk for secondary cancer shall be avoided.

Therefore this protocol proposes a strategy of first line chemotherapy for children affected by NF I with tumors of low grade malignancy of all CNS-sites.

4. Results of SIOP-LGG 1 SIOP LGG 2004

4.1. Study design of SIOP-LGG 1:



SIOP - LGG 1 (1993) was the first European study to offer a standardised scheme of therapy for children and adolescents with low grade glioma.

Primary objectives were to evaluate results of these treatment criteria and to determine the effectiveness of chemotherapy (Carboplatin and Vincristine) in treating children aged less than 5 years, with severe or progressive symptoms or unequivocal imaging evidence of tumor growth.

> Consistent with the lack of schedule dependency for platinating agents, the entire dose was given in 1 day instead of distributing it over 4 weeks. Intensified Vincristine was given during induction to augment CNS-concentration.

Secondary Objectives were to provide a standardised clinical treatment scheme within which clinical and biological criteria, including NF1 status, may be studied in order to identify prognostic factors for tumor progression, chemosensitivity, radiosensitivity and overall survival;
....to collect clinical, treatment and outcome data centrally within Europe, so that the natural history of a large number of these tumors can be described within a short time period using modern imaging and therapeutic techniques.
It was hoped to provide an international organisational framework for the initiation of studies on biological material from children with “low grade glioma”.

Only the data derived from patients treated with chemotherapy and / or radiotherapy have been combined in the central file; the study report will be focused only on the information derived from these children. The data of study opening varied among nations. It was 1992 for Italy, 1993 for the first German patients and 1995 for the United Kingdom. Recruitment to the international study was closed as of December 31st, 1999, and eventually continued on a national base.

4.2. Chemotherapy part of the study

4.2.1. Patients accrual, time of treatment, clinical characteristics

Patient accrual: 244 patients have been intended to be treated with chemotherapy; 40 were not eligible for the study (Table 11). The recruitment rate by nation is the following: Germany 90, Italy 47, United Kingdom 59, Others 8.

Table 11: Eligibility

	N.	%
Eligible	**204**	**83.6**
Not Eligible	**40**	**16.4**
different CT	11	4.5
no LGG	3	1.2
second tumor	1	0.4
started CT without evidence of disease	3	1.2
malignant tumor	1	0.4
other site **	3	1.2
Protocol closed	8	3.3
Too many missing data	10	4.2

** Pons

Time of treatment - 130 patients (63.7%) have been treated at diagnosis, while 74 (36.3%) started after a period of observation. The time interval between diagnosis and the date of starting chemotherapy ranged from 0.1 to 30.9 months (median: 23 days) while for the patients who were “intended to be observed”, it varied between 2.1 – 164.3 months (median 12.7 months). Patients have been also subdivided, if the treatment started before or after the first three months from diagnosis, regardless of how patients were intended to be treated (Table 12).

Table 12: Time of treatment.

	N.	%
≤ 3 months	117	57.4
> 3 months	87	42.6
Total	204	100

Clinical characteristics – (Table 13) As expected the vast majority of the children treated with chemotherapy were young (median age 35.6 months; range 2.4 – 170.3m), without a clear sex prevalence. Almost a quarter of all patients were affected by Neurofibromatosis type I (NF1). Very few children with a fibrillary astrocytoma have been registered into the study. The reasons could be that:

i) these children are older than the ones affected by a juvenile pilocytic astrocytoma (JPA) and
ii) being these patients older, they are preferentially treated with radiotherapy.

This fact also explains, why few hemispheric LGG are treated with chemotherapy.
25 children (12.3%) aged between 4.5-140 m (median 31 m) presented with a multicentric/ disseminated LGG. The spelling out of their main clinical characteristics (sex, age, primary site and NF status) is reported in Table 14. 16 of them had a histological diagnosis of JPA, 3 of Astrocytoma, 1 of Fibrillary Astrocytoma, 1 Desmoplastic Astrocytoma, 1 Ganglioglioma and the other one Xantoastrocytoma. 2 Children had a clinical diagnosis only.

Table 13+14: Distribution of clinical characteristics:

	all patients			patients with disseminated tumors	
	N.	%		N.	%
Age:					
≤ 1 year	41	20.1		9	36
> 1 year and ≤ 3 years	62	30.4		5	20
> 3 years and ≤ 5 years	42	20.6		3	12
> 5 years and ≤ 10 years	39	19.1		5	20
> 10 years	20	9.8		3	12
Sex:					
Male	99	48.5		16	64
Female	105	51.5		9	36
NF1 status:					
Yes	43	21.1		-	-
No	161	78.9		25	100
Histology:					
Astrocytoma n.o.s.	23	11.3		3	12
Fibrillary A.	7	3.4		1	4
Pilocytic A.	104	51.0		16	64
Only clinical diagnosis	61	29.9		2	8
Other diagnosis	*9	4.4		**3	12
Primary site:					
Cerebral Hemisphere	11	5.5		2	8
Midline, Supratentorial	152	74.2		15	60
Posterior Fossa	34	16.8		7	28
Spine	7	3.5		1	4
Primary site:					
Cerbral Hemisphere	11	5.5		2	8
Hypothalamus	19	9.3		1	4
Thalamus	7	3.4		-	-
Chiasma	56	27.5		4	16
Hypothalamus-Chiasma	49	24		10	40
Optic Nerve	12	5.9		-	-
Basal ganglia	2	1		-	-
III Ventricle	6	2.6		-	-
Pineal Gland	1	0.5		-	-
Cerebellum	13	6.4		3	12
Mesencephalon	2	1		1	4
Brain stem	19	9.4		3	12
Medulla	10			1	
Pons	2			1	
Midbrain	5			1	
Nos	2			-	
Spine	7	3.5		1	4
Total	204	100		25	100

* 3 Oligodendroglioma, 1 Desmoplastic A., 4 Ganglioglioma, 1 Xantoastrocytoma

**1 Desmoplastic Astrocytoma, 1 Ganglioglioma, 1 Xantoastrocytoma.

4.2.2. Results

"Best Tumor response" (at any time)

202 of the 204 eligible patients are presently evaluable for tumor response, 1 is not evaluable because of interruption of chemotherapy after 8 days and 1 for parental refusal. The overall positive response rate (including Stable Disease) is 83.7 % ± 2.6, while the Complete and Partial response rate is 50% (Table 15). No central review of the MRI films was requested; thus, more than "complete" or "partial" response, one should talk of "some tumor volume

reduction". The time of response evaluation varied between 1-21.5 m (median 3.6m). The tumor response by age, sex, NF status, histology, site and disseminated (multicentric/metastatic) disease is collectively reported in Table 16. No significant findings emerged.

Table 15: Distribution of primary response.

	N.	%
Complete Response	8	4.0
Tumor Volume Reduction	93	46.0
Stable Disease	68	33.7
Progressive Disease	33	16.3

Table 16: Tumor response as related to age, sex, NF I-status, histology and tumor site.

	Complete Response	T. volume decreased	Stable disease	Progressive disease	Total
Age:					
≤ 1 year	1	18	10	11	40
> 1 year and ≤ 3 years	3	33	21	5	62
> 3 years and ≤ 5 years	1	23	15	3	42
> 5 years and ≤ 10 years	2	12	15	9	38
> 10 years	1	7	7	5	20
Sex:					
Male	6	43	33	15	97
Female	2	50	35	18	105
NF1 status:					
Yes	1	23	14	6	44
No	7	70	54	27	158
Histology:					
Astrocytoma n.o.s.	1	7	9	6	23
Fibrillary	2	-	3	2	7
Pilocytic A.	4	53	32	14	103
Only clinical diagnosis	1	31	19	10	61
Other	-	2	5	1	8
Primary site:					
Cerebral Hemisphere	2	4	3	2	11
Midline, Supratentorial	5	70	53	22	150
Posterior Fossa	1	15	10	8	34
Spine	-	4	2	1	7

Progression free and overall survival

PFS: For calculating progression free survival the following definitions were applied: Children in complete remission following chemotherapy had an event at the occurrence of relapse or death and the time from start of chemotherapy up to relapse or death was calculated. Children with a residual tumor had an event at the occurrence of progression or death following chemotherapy and time from start of chemotherapy to progression or death was calculated.

OS: Overall survival is calculated from the time of start of chemotherapy to the time of death.

Fig. 1: Low grade glioma Study: Progression free survival in patients treated with chemotherapy.
The 3-year PFS of the entire population is 57.5%(95% CI 49.7-65.3).

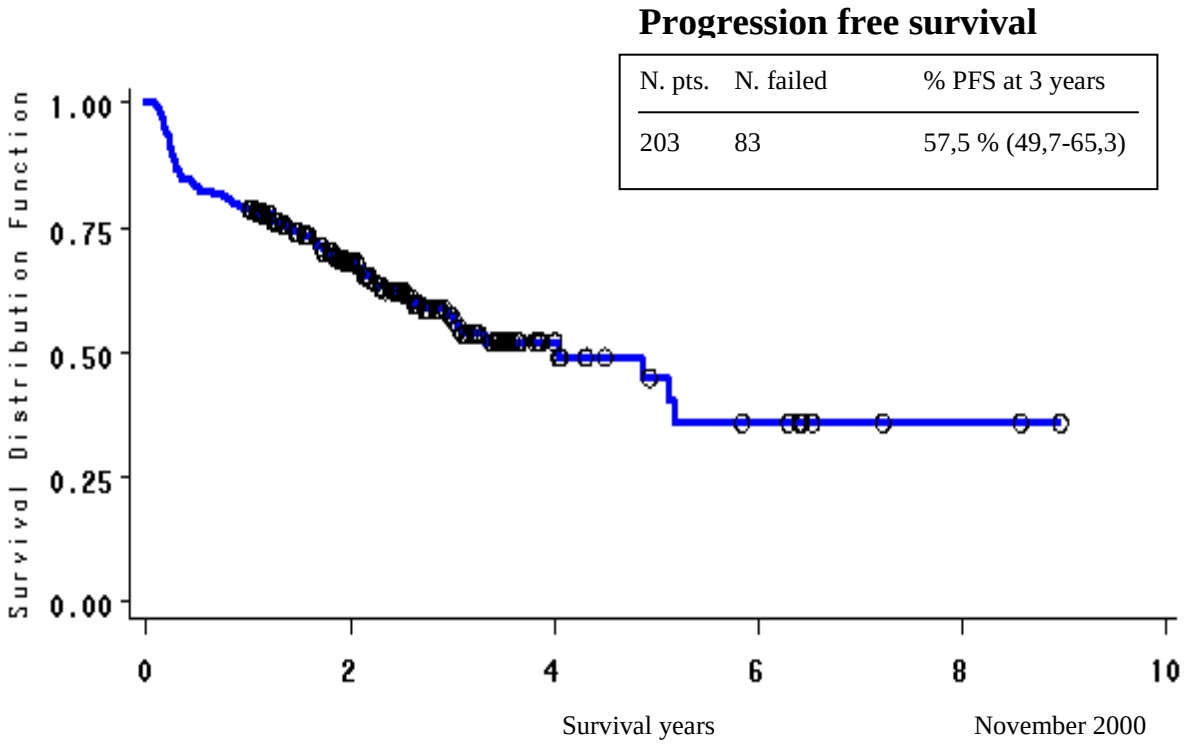
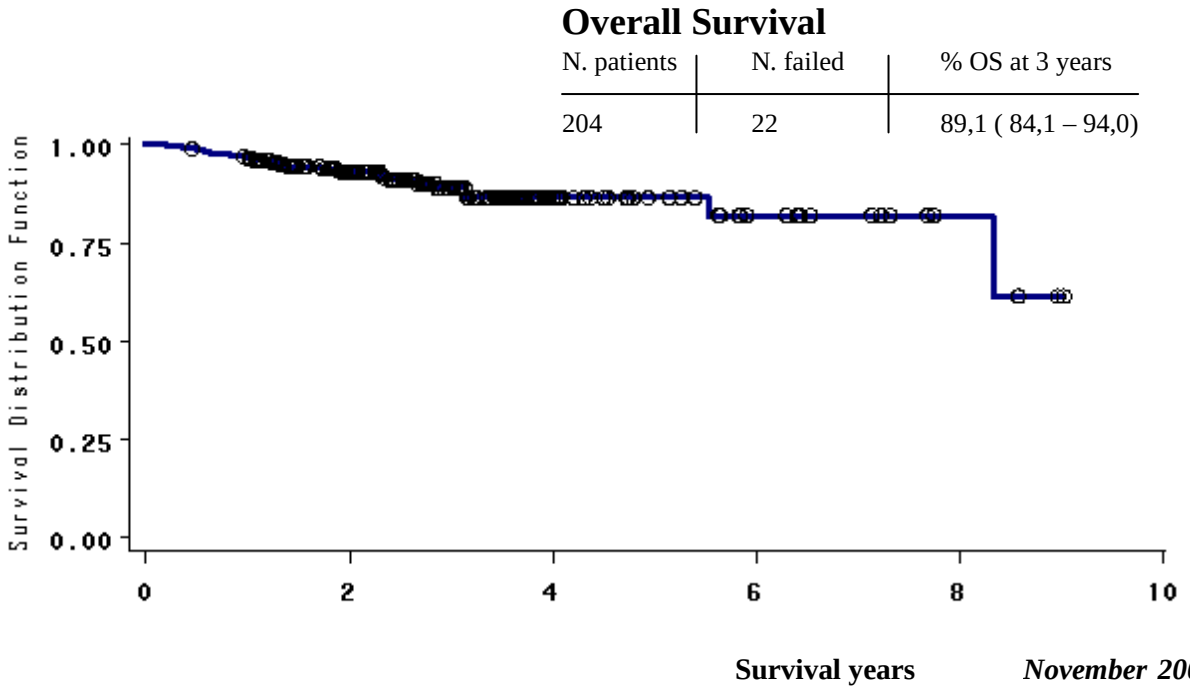


Table 17: PFSs by some patients' clinical characteristics

	No. pts.	No. Failed	% of PFS at 3 years	p-value
Time of treatment:				
At diagnosis	130	63	53.0 (43.5-62.5)	0.002
Post event	73	20	66.5 (53.7-79.3)	
Sex:				
Male	99	39	59.3 (48.3-70.3)	0.5
Female	104	44	55.9 (45.0-66.9)	
Neurofibromatosis:				
Yes	44	12	67.5 (51.9-83.2)	0.02
No	159	71	54.9 (45.9-63.8)	
Age at diagnosis:				
≤ 5 years	144	58	56.2 (46.7-65.7)	0.4
> 5 years	59	25	62.4 (49.9-74.8)	
Metastases at diagnosis:				
Yes	25	12	49.9 (29.6-70.1)	0.1
No	178	71	59.1 (50.8-67.3)	
Histology:				
Pilocytic A.	103	45	56.1 (45.1-67.2)	0.1
Only clininical diagnosis	61	19	66.2 (52.8-79.5)	
Initial surgery:				
Only clinical diagnosis	63	19	67.1 (54.0-80.1)	0.004
Biopsy	72	40	41.0 (27.7-54.2)	
Response to chemotherapy:				
Stable disease	68	20	66.8 (53.9-79.7)	0.5
Good Response	100	30	69.7 (58.7-80.7)	

Although time of treatment seems to be a highly significant factor for the risk of progression following therapy, this variable is insufficiently precise, since in the SIOP-LGG 1 study the indications for starting therapy were not clearly defined.
The improved outcome for children without initial surgery reflects the high number of children with NF I who entered the study upon clinico-radiological criteria in the majority of cases.

Fig. 2: Low grade glioma Study: Overall free survival in patients treated with chemotherapy. **The 3-year OS of the entire population is very good: 89.1% (95% CI 84.1-94.0).**



Events and delay of radiotherapy

84 patients (41.2%) of the 204 evaluable patients suffered of a „tumor-related event“ (TRE) which was a progressive local disease in 80 (95.2%), a local relapse in 2 (2.4%) and a combined local and distant relapse in the others (2.4%). The median time interval between date of beginning CT and date of event was 11.3 months (range: 1-62.3 m). 12 (14.3 %) of these 84 patients with a TRE had a diagnosis of multicentric/disseminated disease. It is disturbing that the time to failure from beginning of chemotherapy to progressive disease was less than 4 months in a third of the patients, thus immediately following induction (Table 18). In Table 19 the time interval between stopping therapy and date of tumor progression (where known) is reported.

Table 18: Time to failure from the start of chemotherapy

Time to failure from beginning CT to PD	Patients initially “observed”	Patients intended to be treated at diagnosis	Total
≤ 4 months	6	23	**29 (34.5%)**
>4 – ≤ 6 months	2	3	5
>6 – 12	-	9	9
>12 months	13	28	**41 (48.8%)**
TOTAL	21	63	84

Table 19: Intervall between the termination of the 12 month chemotherapy and tumor progression (n=23)

	No.	**Time interval between stopping therapy and tumor progression** (months)	MEDIAN (range)
Patients initially "observed"	10	+0, +2, +3, + 7, + 8, +14, +17, +19, +19, +23	**+ 11m** (0 – 23 m)
Patients intended to be treated at diagnosis	13	+0,+1,+2,+7,+8,+8,+9,+11,+14,+16+26,+47, +50	**+ 9m** (0 – 50 m)
TOTAL	23	+0,+0,+1,+2,+2,+3,+7,+7,+8,+8,+8,+9,+11, +14,+14,+16,+17,+19,+19,+23,+26,+47,+50	**+ 9m** (0 – 50 m)

The detailed outcome of the patients who suffered of an event in relationship to the time to progression is spelled out in table 20. An early tumor failure to chemotherapy seems to predict an unfavourable outcome: 12 of the 29 patients (41,4 %) suffering from an early event (within 4 months from the start of chemotherapy) later on died and another 3 continue to be progressive. Another 4 of 14 (28,6 %) with progression during chemotherapy but following induction died and 3 of these 14 are progressive, but only 5 of 41 patients (12,2 %), who completed therapy, succumbed to progression and 10 of 41 are continuously progressive. Since observation time even is longest for the children having completed chemotherapy, this differentiation is not biased by different lengths of time since entering the study.

Table 20: Further course of patients after relapse or progression:

- **Less than 4 months from starting chemotherapy (29 patients):**

Status	**n**	**Follow-up (months)**
Alive with SD	**12**	**Median follow-up = 46.1 months**
After RT	6	+ 17,9, +40,7, + 44,9, +47,3, +70,5, +118
After surgery followed by RT	1	+ 59,1
After CT followed by RT (for further PD)	3	+ 13,6, + 68,3, + 87,2
After RT followed by CT	1	+ 19,8
After 2 surgeries	1	+ 12,3
Alive with PD	**3**	**Median follow-up = 19,2 months**
After RT	3	+ 17,7, + 19,2, + 32,2
Dead of disease	**12**	
After RT	4	9, 10,4, 23,3, 32,6
After surgery only	1	40
No further therapy	5	3,3, 4.6, 18, 21,4, 118
After surgery followed by CT	1	16,2
After CT	1	28,9
Lost to follow-up	**2**	+ 33,1, + 32,6

- **Between 4 and 6 months from starting chemotherapy (5 patients):**

Status	**n**	**Follow-up (months)**
Alive with no evidence of disease	**1**	
After CT followed by 2 surgeries	1	+ 46,8
Alive with stable disease	**1**	
After partial resection	1	+ 50.1
Alive with PD	**1**	
Not known how presently treated	1	+ 16.4
Dead of disease	**2**	
After RT followed by CT	1	15,3
No further therapy	1	6,6

- **Between 6 and 12 months from starting chemotherapy (9 patients):**

Status	**n**	**Follow-up (months)**
Alive with SD	**5**	**Median follow-up = 30.8 months**
After RT	3	+ 22,0, + 30,8, + 33,7
After further CT	2	+ 24,1, + 40,8
Alivewith PD	**2**	
After CT followed by RT	1	+ 27,9
After only a biopsy	1	+ 33,7
Dead of disease	**2**	
After surgery followed by CT	1	15,2
No further therapy	1	7,9

- **More than 12 months from starting chemotherapy (41 patients):**

Status	**n**	**Follow-up (months)**
Alive with no evidence of disease	**2**	
After surgery	1	+ 23,3
After RT	1	+ 57,4
Alive with responding disease on therapy	**1**	
During other CT	1	+34.6m
Alive with SD	**22**	**Median follow-up = 55 months**
After RT	12	+ 31,3, + 35,6, + 45,2, + 47,8, + 48,3, + 54,5, + 55,4, + 62, + 67,8, + 73,5, + 88,4, + 107,8
After further CT	2	+ 37,8, + 69,2
After further CT followed by RT	1	+ 52,3
After surgery	4	+ 35,7, + 37,4, + 64, + 93,1
After surgery followed by CT	1	+ 79,7
No further therapy	2	+ 27,9, + 63,5
Alive with PD	**10**	**Median follow-up = 49.1 months**
After surgery	2	+ 49,4, +64
After 2 surgeries	1	+ 44,8
After surgery followed by RT	1	+ 32,4
No further therapy	3	+ 24,6, + 48,7, + 75,4
After RT	1	+ 43,9
After RT followed by CT and RT	1	+ 112,5
After CT	1	+ 71,2
Alive n.o.s.	**1**	
After CT	1	+ 38,3
Dead of disease	**5**	
After surgery	3	29,0, 37,7, 66,8
After CT followed by RT	1	38,4
No further therapy	1	28,5

Although 39,3 % of all children suffering from progression had been primarily refractory to chemotherapy, there were as many (36,9 %) who had had a complete response or tumor volume reduction.

Table 21: Distribution of events by type of response to primary chemotherapy:

	No.
Complete Response Tumor Volume Reduction Stable disease	1 30 20
Progressive Disease Not evaluable, interrupted CT after 8 days of therapy Not evaluable, refusal to continue treatment	31 1 1
Total	84

Radiotherapy as treatment post-event

32 children (38%) after having suffered of an event ended-up receiving RT immediately; 8 were treated with secondary chemotherapy (+ surgery in one case and + RT in six cases after further PD), 14 were treated with surgery alone (+ RT in two cases after further PD and + CT in two cases).1 child had received a new biopsy only, 14 were merely observed (+RT in one case after further PD), 2 are lost to follow-up and for one child it is too early for evaluation. As a whole 41 children were irradiated, for 23 of whom detailed information of the treatment were reported.
The time interval between date of beginning of CT and of RT for 37 patiens was 22,2 months median time with a range of 1.3 to 67.6 m. Age at start of chemotherapy for the irradiated children (41 children) had been 54,3 months (range 3,5 – 164,8 m) and their age at the start of radiotherapy (37 patients) was 84,0 months (7,2 – 167,3 months).

Current status following progression/relapse

Obviously, an event after chemotherapy does not necessarily predict a fatal outcome as 43/84 children are alive without evidence of disease or with stable disease on or off therapy. For those alive the time interval between event and last follow-up (62 pts.) ranges from 12.3 to 118.0 months with a median of 45.1 months

Table 22: Current status of 84 children following relapse or progression

		No.	%
Alive	without evidence of disease off therapy	3	3.6
	with stable disease on therapy	1	1.2
	with stable disease off therapy	39	46.4
	with progressive disease	16	19.0
	not otherwise specified	1	1.2
Dead		22	26.2
Lost to follow-up		2	2.4
Total		84	100

4.2.3. Toxicity

Detailed information on the haematological and organ toxicity of the combination Carboplatin and Vincristine was not centrally recorded. The allergy to Carboplatin seems to be a major limiting factor for full compliance to the protocol. As a whole 43 (21.1%) of the 204 patients had allergic reactions to Carboplatin, at a time interval between the beginning of chemotherapy and "allergy" ranging from 1 to 52 week (median 33 weeks). However, this could be an underestimation of the real incidence of the problem; since among the Italian patients 17 out of 47 children (36.2%) actually manifested allergic reactions to Carboplatin at approximately the same time interval between starting CT and "allergy". The further treatment for the 43 patients who had allergic reactions to Carboplatin was: 24 with different CT, 2 with VCR/Carboplatin but with reduced dose of Carboplatin, 4 with only VCR, and 13 no further therapy. The outcome of these patients is listed in table 23.

Table 23 Current status of 43 children following Carboplatin allergy:

		No.	%
Alive	without evidence of disease off therapy	1	2.3
	with stable disease on therapy	1	2.3
	with stable disease off therapy	39	90.8
	with progressive disease	1	2.3
Dead		1	2.3
Total		43	100

4.3. Main conclusions

The SIOP-LGG 1 study must be considered a feasibility study aiming:

a) to demonstrate the actual recruitment rate of children affected by LGG eligible to chemotherapy by the pediatric (neuro-) oncology groups in Europe,
b) to get pediatric oncology used to treat these patients with chemotherapy,
c) to demonstrate advantages and limit of the chemotherapy treatment, trying to duplicate the results produced by the concurrent studies run by the CCSG in U.S.A.,
d) to learn more about the “natural history “of LGG treated with chemotherapy,
e) to pilot a data collection process whith each participating nation collecting own data and then transferring them into a common database.

With respect to these aims it can be stated that:

a) the recruitment rate was representative, but not complete: it is expected to grow,
b) treatment centers gained expertise on how to treat these children,
c) the effect of single dose Carboplatin combined with Vincristin chemotherapy in terms of response and survival is comparable to the results shown by the CCSG experience,
d) the excess of early events (34.5% of the events occurred less than 4 months from diagnosis) calls for modification of therapy,
e) the allergy to Carboplatin seems to be a major problem for proceeding with the same regimen,
f) the data collection process seem to be working effectively.

Inadequate data was collected concerning the quality of care or on the health status of these patients in relationship to the treatment received.

5. Changes within SIOP-LGG 2004 as compared to SIOP-LGG 1996

As in the previous SIOP study, the protocol offers a comprehensive strategy for all children up to an age of 16 years with glial tumors of low grade malignancy. But treatment recommendations differ according to tumor localization and the presence or absence of Neurofibromatosis NF I.

In the previous study the age of 5 years was empirically chosen as the cut-off age for recommending chemotherapy or radiotherapy as non-surgical therapy for symptomatic or progressive tumors. In the light of more data, which have been accumulated on the effect of chemotherapy on low grade glioma, it is possible to extend this cut-off to the age of 8 years. According to individual decisions even older children may receive primary chemotherapy.

Disseminated disease is recorded, but children are treated according to their main therapy subgroup determined by NF I-status and tumor site. Primary chemotherapy is suggested.

A randomized study question is asked for children without NF I stratified for primary tumor location at either the supratentorial midline or the cerebral hemispheres, the cerebellum, the caudal brainstem and the spinal canal, if they are to receive chemotherapy.

Thus changes for the newly defined patient subgroups are the following:

1. Supratentorial midline tumors	No NF I	Age 0 to 16 years

1. Non surgical therapy is stratified for age: young = under 8 years, older = 8 years and older.
2. Chemotherapy group
   Duration of chemotherapy is extended to 18 months for all children.
   Induction therapy is randomized:
   - Standard induction: Vincristin and Carboplatin
   - Intensified induction: Vincristin, Carboplatin and Etoposide
3. Radiotherapy group
   Apply highly focussed radiation at standard dose and fractionation.
   Record and monitor the integral dose to tumor and normal tissue.
   Assess impact of craniospinal irradiation in disseminated disease.
   Assess response of tumor and clinical symptoms.

2. Tumors of all other locations	No NF I	Age 0 to 16 years

1. Non surgical therapy is stratified for age: young = under 8 years, older = 8 years and older.
2. Strategies are adopted to consider the specific conditions for tumor location in the spinal canal, cerebral hemispheres, cerebellum or caudal brain stem.
3. Chemotherapy group
   Duration of chemotherapy is extended to 18 months for all children.

Induction therapy is randomized:
- Standard induction: Vincristin and Carboplatin
- Intensified induction: Vincristin, Carboplatin and Etoposide

4. Radiotherapy group
   Apply highly focussed radiation at standard dose and fractionation.
   Record and monitor the integral dose to tumor and normal tissue.
   Assess impact of craniospinal irradiation in disseminated disease.
   Assess response of tumor and clinical symptoms.

3. Tumors of all locations	NF I present	Age 0 to 16 years

1. All children shall receive primary chemotherapy as non-surgical therapy
2. Chemotherapy group
   Duration of chemotherapy is extended to 18 months for all children.
   All children receive Standard induction and Consolidation with Vincristin and Carboplatin
   Upon progression successive chemotherapy treatments should be investigated.
3. Radiotherapy
   Primary radiotherapy is <u>not</u> indicated for children with NF I, except in individual patients with optic nerve gliomas restricted to the intraorbital portion of the optic nerve or in the case of progression following (multiple) chemotherapy interventions.

6. Aims of the study SIOP-LGG 2004

6.1. Improve response and progression / event free and overall survival

It is envisaged to arrive at high treatment response rates and improved event free and progression free survival rates for children and adolescents with a central nervous system low grade glioma by:

- applying stringent criteria for diagnostic work-up, guidelines for surgical procedures and clear indications to start non-surgical therapy
- offering an individualized sequence of treatment modalities according to established guidelines for subgroups defined by tumor location and the presence or absence of Neurofibromatosis NF I
- prolonging chemotherapy for all children stratified to receive chemotherapy

Comparison will be made to preceding national and international studies.

6.2. Reduced late effects and improvement of the quality of life at short and long term

It is envisaged that late effects of the central nervous system following radiotherapy will be reduced and the health status and quality of life of long term survivors be improved by:

- avoiding radiotherapy for a larger proportion of young children by raising the cut-off age for primary chemotherapy in non-NF I patients and
- offering primary chemotherapy to all children affected by NF I irrespective of age
- using modern equipment for treatment planning and stereotactic or conformal radiotherapy arriving at reduced doses to organs at risk for children stratified to receive radiotherapy

No prospective or comparative studies evaluating this aspect exist. Short and long term side effects of chemotherapy will be monitored and their impact upon the development of the children be evaluated.
Improvement of progression free survival following initial therapy is only a surrogate parameter of an improvement of the quality of life. The study will try to evaluate whether improvements of PFS translate into quality of life.

6.3. Improvement of individualized patient management

Histopathologic diagnosis, neuroradiologic diagnosis and neuroradiologic indication for therapy shall be centrally reviewed to assure correct assignment of patients to treatment arms.

It is envisaged that the prognosis will be improved by quality control of radiotherapy and chemotherapy as well as by individualized counseling for surgical and non-surgical procedures.
Careful follow-up investigations of the impact of treatment on the development of the children will be carried through.

6.4. Evaluation of prognostic factors

Prognostic factors other than the extent of resection for progression free survival have not been firmly established for low grade glioma. Therefore, factors that might be important for prognosis shall be evaluated prospectively. If their impact can be established reliably, they will serve for a more risk adapted stratification within the framework of a successive trial.

Pathology	Tumour type and WHO grade Markers of proliferation (e.g. Ki 67 / MIB-1) Molecular-pathologic markers (e.g. p 53 mutation)
Tumor	Tumor size preoperatively (Product of the two largest diameters in cm) Tumor size postoperatively (Product of the two largest diameters in cm) Extent of surgery Localization and extent within the supratentorial midline for visual pathway gliomas (Dodge classification II, III)
Dissemination	primary/secondary Type and extent of dissemination
Symptoms	Severe, visual or neurologic symptoms relevant for the decision to start non-surgical therapy will be described according to their presence or absence: Visual symptoms Neurologic symptoms Increased intracranial pressure Diencephalic syndrome
Age	< 8 and ≥ 8 years (To investigate the „young“ and „older“ age groups) < 1 year, 1 to 4, 5 to 10, > 10 years (Comparison to previous trial) Continuous variable
Sex	male / female

Observation time following diagnosis before starting therapy

Therapy related factors:	Type of Induction therapy (I or II) Response at week 24 Therapy modifications due to allergy

7. Study questions SIOP LGG 2004

7.1. Children not affected by NF I with tumors of all sites (1. the supratentorial midline, 2. all other sites)

Main study question:
To investigate, if adding Etoposide (VP 16) to the standard induction treatment of Carboplatin and Vincristin will lead to a different progression free survival than the induction treatment with Carboplatin and Vincristin only.

Secondary study questions:
To investigate, if the radiological tumor response at week 24 depends upon the type of induction therapy with either standard induction with Vincristin and Carboplatin or intensified induction with Vincristin, Carboplatin and Etoposide.

To investigate, if adding Etoposide (VP 16) to the standard induction treatment of Carboplatin and Vincristin will lead to a different event free survival than the induction treatment with Carboplatin and Vincristin only.

To investigate, if adding Etoposide (VP 16) to the standard induction treatment of Carboplatin and Vincristin will lead to a different overall survival than the induction treatment with Carboplatin and Vincristin only.

The study questions will be analysed for group 1 and 2 together. For explorative reasons these questions will also be analysed separately for the two groups.

7.2. Children affected by NF I with tumors of all sites

For this group of children the study is a documentation study, yet the data shall be compared to the historical series of SIOP - LGG 1.

To investigate, if the prolonged (18 months) chemotherapy with Carboplatin and Vincristin leads to a different progression free survival than the historical treatment with a shorter (12 months) chemotherapy or radiotherapy.

To investigate, if the prolonged chemotherapy with Carboplatin and Vincristin leads to a different event free survival than the historical treatment with a shorter chemotherapy or radiotherapy.

To investigate, if the prolonged chemotherapy with Carboplatin and Vincristin leads to a different overall survival than the historical treatment with a shorter chemotherapy or radiotherapy.

8. Investigations at diagnosis and during follow-up SIOP LGG 2004

8.1. Primary tumor diagnosis – preoperatively

- **Essential investigations:**

1. Neurologic examination

2. Ophthalmologic examination: fundoscopy, if possible visual acuity and visual fields in supratentorial midline tumors (see section 8.6.).

3. Cranial MRI without and with Gadolinium enhancement (see section 8.5.)
   (MRI must be done in order to enter patients into the trial, CT-scan only cannot be accepted. CT-scan should only be done, if MRI is not available)

4. Spinal MRI without and with Gadolinium enhancement – if indicated (see section 8.5.)
   Indications for a spinal MRI in low grade glioma are:
   1. Multiple lesions demonstrated on cranial MRI
   2. Spinal (cervical) lesions seen on cranial MRI
   3. Clinical symptoms that might relate to spinal lesions

5. General preoperative diagnostic procedures:
   - complete physical examination including anthropometric measurements, assessment of NF I status by thorough skin examination, symptoms of diencephalic syndrome or other symptoms
   - preoperative laboratory investigations: full blood cell count and differential, urea, serum-creatinine, electrolytes, Magnesium, ALT/AST, Bilirubin
   - chest X-ray, ECG/UCG

- **Recommended investigations:**

(pre- or postoperatively, depending on the condition of the child at diagnosis and if relevant)

1. Neurophysiologic investigations
- EEG
- Extended Ophthalmologic investigation (see section 8.6.)
- Visual evoked potential (if available)
- Audiogram – pure tone where possible (age 3 years or over), otherwise free field testing or otoacustic emissions

2. Neuropsychologic investigations (see section 8.7.)

3. Neuroendocrine investigations
- Base line endocrinologic investigation (see section 8.4.).
- Tumor-induced primary hypothalamo-pituitary dysfunction is rare in low grade glioma even in case of chiasmatic-hypothalomic localisation. It should be investigated however in all children with diencephalic syndrome, short stature or relevant clinical findings at diagnosis.
- Pregnancy has to be excluded by HCG-determination in fertile adolescent girls.

4. Health status, quality of life (see section 8.7.).

8.2. Postoperative diagnostic procedures

1. Neurologic examination

2. Cranial MRI without and with Gadolinium enhancement within 24 to 48 (maximum 72) hours postoperatively (see: section 8.5.)
   (CT-scan only, if MRI is not available)

3. Spinal MRI without and with Gadolinium enhancement – only if not done preoperatively, yet indicated (see section 8.5.)

4. Lumbar CSF cytology – if indicated (see section 8.5 and 12.4).
   Lumbar CSF sampling will be performed only, if imaging procedures demonstrate disseminated disease.
   The purpose of CSF sampling is to investigate the presence of CSF neoplastic cells following a process of centrifugation. Intracranial hypertension should be excluded, so that the patient is not put at risk through the performance of a spinal tap.
   The presence of neoplastic cells in the CSF is regarded as stage M 1 (see 16.1. for tumor staging).

   Protein level in the CSF should be recorded in a parallel fashion to follow the patients during treatment.

8.3. Histopathologic diagnosis

The acquisition of histological samples for tissue diagnosis is strongly recommended in all cases. Children with NF1 and hypothalamic/visual pathway glioma and children without NF I, whose tumor shows unequivocal contiguous involvement of the visual pathways (see section 8.5.), may enter the study without biopsy.

NEUROPATHOLOGIC GUIDELINES

The purpose of histological assessment in these tumors is to:

- confirm the presence of tumors corresponding to grade 1 or 2 (WHO) and to exclude anaplastic gliomas and glioblastomas.
- provide a standardised classification, which will facilitate detailed clinicopathological studies, with particular reference to neuroradiological findings.
- investigate the clinical significance of proliferation indices (as determined by immunocytochemistry) in the low grade gliomas of childhood.

It is recognised that the exact classification and histogenetical typing as well as the grading of low grade gliomas in childhood may present difficulties. Therefore it is undispensible that tumor material of all children, registered within the SIOP - LGG trial be classified centrally. A panel of neuropathologists will assess these tumors. Facilities for “fast- track” pathology review will be provided for cases of particular diagnostic difficulty or uncertainty.

Children entering the randomised chemotherapy trial must have had central review of their biopsy specimens, if obtained.

From each patient representative, paraffin embedded tissue and the documentation form should be sent to the national brain tumor reference center. All material will be returned to the sender following handling and final statement, except for proof-slides that will be kept. Central pathologic assessment includes conventional histologic and immunohistochemical staining. In case of unusual and diagnostically difficult tumors, members of the pathology panel and other experts will be consulted. All findings will be documented on a report form designed for this study and sent back to the local pathologist or neuropathologist as well as to the national/international study data center. Standardised histopathological parameter of each patient will be stored in a data base (German Brain Tumor Reference Center: Data base: Filemaker Pro). Study material and the data base will be available for all participating colleagues.
The criteria for classification are based upon the WHO classification in its current, revised version including the grading system (Kleihues 2000).

National brain tumor reference centers:

Germany:
Hirntumorreferenzzentrum
Prof. Dr. T. Pietsch
Institut fuer Neuropathologie
Sigmund-Freud-Strasse 25
D 53105 Bonn

Italy
Prof. Felice Giangaspero
Institute of Anatomical Pathology
Bufalini Hospital
Via Ghirotti 286
I 47023 Cesena

United Kingdom:
James Ironside, Edinburgh

France:
Marie-Madeleine Ruchoux, Lille
Anne Jouvet, Lyon
Dominique Figarella Branger, Marseille
Arielle Lelouch-Tubiana, Paris

NEUROPATHOLOGY – LABORATORY GUIDELINES

Besides warranting a uniform neuropathologic diagnosis, a series of cytologic, histologic and immunophenotypic parameters shall be raised and documented from the materials sent in. A goal of these investigations is to identify parameters of prognostic significance.

Conventional histology
All biopsy specimens for histological evaluation should be fixed in formalin (preferably 10% neutral buffered formalin) and embedded into paraffin wax. Since it is anticipated that many of the histological specimens for this study will be derived from stereotactic biopsy specimens, the material for review will sometimes be limited. The material requested for histological review consists of:

- 4 unstained paraffin embedded sections 5-6 μm in thickness and cut onto poly-l-lysine coated slides (or equivalent) to facilitate immunocytochemistry.
- The original paraffin block (if possible)
- The pathology report from the originating hospital, along with patient details including the age of the patient and site of biopsy.

Investigations to be performed:

1. Staining with haematoxylin and eosin for standard morphological assessment.

2. Immunocytochemistry: glial fibrillary acidic protein, others as needed.

3. Immunocytochemistery of the cellular proliferation rate of the tumor. (e.g. by means of an antibody directed against an epitope of the Ki67/MIB-1-antigen. This will be performed following microwave antigen retrieval.)

4. Immunohistochemical investigation of differentiation antigens.

5. Evaluation of characteristic histological parameters (certain growth patterns, patters of vascularisation, infiltration with inflammatory cells)

Results of this histological review and other investigations will be sent to the submitting pathologist in all cases. Proof-slides submitted into study will be retained for purposes of central review at least until the study is completed.

Scientific investigations
Knowledge concerning molecular pathogenesis of pediatric malignant glioma is scant as compared to the more frequent adult glioma. However, a large proportion of molecular investigations is only possible with unfixed, shock-frozen material.
Therefore additional investigations will be done for limited numbers of patients only, although an increasing number of investigations may be performed on paraffin embedded tissue. It is an aim of the study to obtain fresh frozen material for molecularpathologic studies from as many patients as possible.

In Germany, throughout the recent years the competence network "pediatric oncology" has established a structure facilitating the asservation, the mailing and the storage of tumor probes. Manuals for handling, tumor boxes for shipment and tumor banks for storage are available. The brain tumor bank works under the supervision of an independant scientific council. Material can be made available for scientific investigations following a formalized proposal. The aim of these investigations is to identify prognostic factors and to define the molecular pathogenisis of gliomas.

Patients/parents have to consent to the use of tumor material for these investigations, an appropriate explanation is included into the forms for study participation. Tumor material should be prepared in a standardised manner together with the local pathologist/neuropathologist and sent to the tumor bank accompanied by the documentation forms, which are available at the pediatric oncology units:

Germany (for German patients only):
Hirntumorbank des Kompetenznetzes Paediatrische Onkologie
Prof. Dr. Torsten Pietsch
Institut fuer Neuropathologie
Universitätsklinikum Bonn
Sigmund-Freud-Strasse 25
D 53105 Bonn

8.4. Status assessment

8.4.1. Status evaluation during chemotherapy and early follow-up

1. History at every visit.

2. Complete physical and neurological examination, including anthropometric measurements.

3. Laboratory data: Full blood cell count and differential; urea, serum creatinine, electrolytes, Mg^{++} and Ca^{++}, ALT/AST; Bilirubin.

4. Cranial contrast enhanced MRI
   For children receiving chemotherapy the relevant time points for assessment of cranial MRI are :

Time 1	at diagnosis
Time 2	where applicable after observation to demonstrate progression or measure changes at the time of start of chemotherapy
Time 3	six months after commencement of chemotherapy
Time 4	twelve months after commencement of chemotherapy
Time 5	eighteen months after commencement / at the end of chemotherapy
Time 6	scan of those obtained at six-monthly intervals until progression

5. Spinal contrast enhanced MRI, if previously pathologic at the same time points as 4.

Central review: For assessing response to chemotherapy in the randomised arms of the chemotherapy study all relevant scans (as defined in section 8.5.) have to be sent in for review during the pre-treatment and treatment periods to the national radiodiagnostic reference center (see section 8.5.).

6. CSF sampling to be performed only in case of disseminated disease and if previously positive

7. Ophtalmological examination: every 3 months during chemotherapy (and at least every 6 months during follow-up) (see section 8.6.).

8. Glomerular filtration rate (GFR) as measured by Creatinin and/or 51 Cr-EDTA clearance
   - see guidelines for chemotherapy (14.2.4.)

9. Audiogram – pure tone where possible (age 3 years or over), otherwise free field testing or otoacustic emissions
   - see guidelines for chemotherapy (14.2.4.)

10. Endocrine investigation as detailed below

Minimum requirements for patient follow-up during the chemotherapy study are listed in Addendum 21.13.1.

8.4.2. Follow-up investigations without therapy or following chemo- or radiotherapy

1. Complete physical and neurological examination, including anthropometric measurements, and history.

2. Laboratory data: Full blood cell count and differential; urea, serum creatinine, electrolytes, Mg^{++} and Ca^{++}, ALT/AST; Bilirubin
   - For those having had chemotherapy: every 6 months during the 1st and 2nd year. Later only, if indicated.

3. Brain and / or Spine: Contrast enhanced MRI
   (Spine: in case of evidence of tumor dissemination at the Gd-enhanced cerebral MRI)

4. Ophtalmological examination (see section 8.6.)

5. Glomerular filtration rate (GFR) - for those having had chemotherapy

6. Audiogram – pure tone when possible (age 3 years and over), otherwise free field testing or otoacustic emissions - for those having had chemo- and/or radiotherapy, or where the tumor affects the auditory pathways.

7. Endocrine investigations - as detailed on next page.

Table 25: Follow-up investigations.

	First, second and third year	**Fourth and fifth year**	**Sixth to tenth year**
Physical examination and neurological examination, including anthropometric measurements;	Every 3 months	Every 6 months	Annually
Ophthalmological examination	Year 1: 3 monthly Year 2: 3-6 monthly Year 3: 6 monthly	Every 6-12 months	Annually, yet six-monthly in OPG
Contrast enhanced cerebral and spinal (if indicated) MRI	Every 6 months	Every 6 months	Annually
Audiogram – pure tone where possible age 3 years or over, otherwise free field testing or otoacustic emissions	Every 6 months	Not indicated if previously repetitively normal	---
Glomerular filtration rate (GFR)	6 months after CT, then yearly, if not indicated otherwise	Not indicated if previously repetitively normal	---
Endocrinologic investigation and, if indicated, bone age and hypothalamic-pituitary functioning test	Yearly, if not indicated otherwise	As indicated by stage of growth and puberty and previous chemo- or radiotherapy	As indicated by stage of growth and puberty and previous chemo- or radiotherapy

8.4.3. Extended endocrine investigations and monitoring of growth

Depending upon tumor location, the extent of surgery and the effects of non-surgical therapy children may suffer from complex endocrine sequelae. It is essential that an experienced pediatric endocrinologist is involved in the care of these patients. These guidelines are intended to help the oncologist, but the endocrinologist will be needed to advise appropriate tests and their interpretation, and decide upon treatment.

1. Anthropometric Data

At diagnosis:	Mother's height, father's height, gestation (weeks), birth weight (kg).
All assessment points:	Decimal age, standing height, sitting height, weight (These results should be plotted on standard growth charts.) occipitofrontal head circumference (in the young)

2. Pubertal/reproductive Data

All assessment points:	Tanner score for breast development, pubic and axillary hair and genital development (testes volume in ml right and left), record date of menarche and of last menstrual period.

3. Biochemical Data

All assessments: (until growth complete)	LH (IU/ml), FSH (IU/ml), Oestradiol (pmol/l), Testosterone (nmol/l), free T4 and T3 (nmol/l), TSH (mU/l). IGF I and IGF-BP 3 (esp., if body measurements are at or below 3rd percentile)
At growth retardation:	Bone age (esp., if body measurements are at or below 3rd percentile) Growth hormone testing including GnRH, TRH, and measurements of cortisol 24 hour urinary Cortisol

If the patient has thirst polyuria (especially at night), persistent or recurrent hypernatraemia or other symptoms suggestive of diabetes insipidus: Water deprivation test with measurement of urine and plasma osmolality.

4. Timing of investigation

At diagnosis investigation should take place before or after surgery, but before radiotherapy and chemotherapy, and preferably the patient should not be receiving dexamethasone.

Table 26: Timing of investigations to monitor endocrine functions

	Time Points	**Timing of Investigation**
Diagnosis:	before or after surgery	
Follow-up:		
Observation group	until growth is completed	annually, but more often, if clinically indicated
	after growth is complete	3 (to 5) yearly assessments
Treatment: Chemotherapy	during CT	+6, +12, +18 months / end of CT
	after therapy until growth is complete	annually, but more often, if clinically indicated
	after growth is complete	3 (to 5) yearly assessments
Treatment: Radiotherapy	after completion of RT	at end of radiotherapy one year after end of RT (obligatory)
	until growth is complete	annually, but more often, if clinically indicated
	after growth is completed	annually

5. Documentation

For documentation use Endocrine status forms (Status after registration and post treatment/during follow-up) from Addendum 21.13.5.

8.5. Guidelines for Neuroradiologic assessment (Dr. Warmuth-Metz)

MRI has become the preferred modality for the evaluation of pediatric brain tumors because of its non-ionising nature and superior spatial and contrast resolution. In addition, the multiplanar imaging capabilities of MRI are very valuable in defining the extent and infiltration of complex tumors. The evaluation of primary spinal tumors and CSF-dissemination of CNS tumors by MRI has replaced CT-scan assisted myelography (CAM), although if MRI is not available or there are specific contraindications to MRI (such as metallic foreign bodies) CAM can be used as a substitute. If postoperative examination can only be done by CT-scan (because of local availability or access to MR scanning) preoperative CT scanning should be undertaken additionally to enable better evaluation of the results of surgery, as the two different modalities cannot be directly compared.

8.5.1. MRI

- **Minimum requirements for <u>cranial</u> MRI**

Since MRI imaging is performed at many institutions, the following minimum requirements are defined:

〉 The standard examination should consist of a T2-weighted SE dual echo sequence preferably in the axial plane. The short echo T2-sequence may be substituted by a FLAIR-sequence. The slice thickness should not exceed (5-) 7 mm and the slice factor should not exceed 20%.

〉 A T1-weighted sequence, preferably in the axial plane, should be obtained followed by the same scan sequence after intravenous contrast administration. Additional T1-weighted post-contrast sequences in the coronal and sagittal plane are very helpful. In small or irregular tumors slice thickness should be correspondingly small.
Conventional spin echo-techniques are preferred to all kinds of gradient echo sequences, because flow-related enhancement of cerebral vessels by gradient echo- sequences may cause problems in differentiation from meningeal enhancement and the extent and degree of enhancement may be of a lesser order than conventional T1-weighted imaging.

〉 On all images a ruler must be shown.

〉 Generally, follow-up scanning should be comparable with prior examinations as it can be very hard to make direct comparisons between studies using different imaging planes and machines.

- **Application of contrast media**

The administration of Gadolinium should follow the general rule of a slow intravenous injection of 0.1mmol/kg bodyweight Gadolinium. The post-contrast scan should not be started until after the full injection of the contrast medium.
Due to the availability of different Gd-containing contrast-media it should be observed to always apply equivalent amounts of Gadolinium.

- **Minimum requirements for <u>spinal</u> MRI (in case of CSF dissemination)**

Indications for a spinal MRI in low grade glioma are:

- Multiple lesions demonstrated on cranial MRI
- Spinal (cervical) lesions seen on cranial MRI
- Clinical symptoms that might relate to spinal lesions

〉 The minimum requirement is a post-contrast T1-weighted sagittal sequence of the entire spinal canal (down to at least S2 as the thecal sac usually ends there, but may be even longer). In many cases the normal enhancement of intradural veins covering the conus and distal cord can be mistaken as pathological leptomeningeal enhancement if only sagittal scans are available. T1-weighted post-contrast imaging of this region in axial direction is often necessary and helpful in evaluating this region.

〉 T2-weighted sequences are rarely required for the evaluation of CSF-dissemination. If necessary, they can be added after the T1-weighted post-contrast MRI has been acquired, without problems associated with artefacts. Generally fast spin echo sequences are preferred because they show less CSF-pulsation artefacts.

〉 Metastatic disease on imaging is defined as the presence of nodular leptomeningeal and/or sub-ependymal enhancing nodules or of a diffuse leptomeningeal enhancement.

- **Post-operative radiologic investigation of primary tumor**

Scanning should be undertaken within 48 hours following surgery to minimise the effects of reactive post-surgical enhancement. Every effort should be made to establish whether foreign material such as surgical or chemotherapeutic wafers was placed in the surgical bed. MRI is the imaging modality of choice. The same sequence parameters should be employed as in the pre-operative diagnostic study to facilitate comparison.
CT-scan is accepted in case MRI is not available and should be performed without and with contrast medium as indicated prior to surgery within a time frame of 48 hours (max. 72 hours post surgery).

- **Spinal MRI after surgery**

If preoperative imaging of the spinal canal in case of a possibly disseminating tumor was not performed, it can be done at any convenient time point after surgery. However, after surgery of the posterior fossa investigators have to be aware of unspecific subdural enhancement of various degrees within the spinal canal. This rarely impedes the exact definition of meningeal dissemination, but must not be misinterpreted for intradural enhancement as a consequence of dissemination. Unspecific enhancement is usually most extensive immediately after surgery and diminishes thereafter.

8.5.2. CT-Scan

- **Requirements for cranial CT-scan (in case MRI is not available or contraindicated)**

The gantry angulation should be adjusted to minimise direct irradiation of the lens of the eye. At least 4 to 5 mm thick contiguous sections should cover the posterior fossa and base of the skull. In the supratentorial compartment 8 to 10 mm thick section are adequate. A spiral scanning technique should only be used, if secondary reconstruction in the coronal or sagittal plane is planned, because irradiation doses are higher than with sequential imaging. The slice thickness should be approximately 1mm.
Ideally identical slices should be obtained after slow intravenous injection of iodinated contrast medium (up to 2 ml/kg bodyweight of 300mg/ml Iodine concentration).

- **Timing of CT-Scan-Investigations**

If MRI is not available and pre- and postoperative investigations have to be performed using CT-scans, their timing should correspond to the appropriate timing of MRI investigations and use of contrast media.

8.5.3. Imaging requirements for patients recruited, if no histological confirmation of a presumed low grade glioma is planned

If on MRI the tumor is clearly arising from the optic nerve, tract and chiasm and is not confined to only one part of this pathway no additional imaging to MRI is required, especially if the patient is affected by NF I.

If on MRI the tumor is arising from the chiasmal region without contiguous involvement of other structures of the optic pathways, various different processes such as germinoma or craniopharyngioma may mimic a hypothalamic glioma. Differentiation according to MRI signal intensities may not be possible.
As craniopharyngiomas are usually at least partly calcified, CT scanning can be helpful for differential diagnosis as calcifications are not reliably demonstrated by MRI.
In addition, since germinomas are usually iso- to hyperdense due to their intrinsic high cellularity, pre-contrast CT-scan imaging (only covering the tumor region) can be helpful in assessing a suprasellar mass. At present it is not yet clear, if diffusion weighted MRI is able to substitute CT-scan in the assessment of the cellular density of germinomas.

8.5.4. Central radiologic review

Central radiologic review will be organized within the participating national groups. The national radiologic reference centers will follow the guidelines as detailed within the protocol.

The images of any case of tumor not biopsied or resected for diagnosis **should** be seen by a dedicated neuroradiologist and sent in for central review.

The images **must** be sent in for central radiologic review in all children entering the randomised arm of the chemotherapy trial.

For assessing response to chemotherapy in the randomised arms of the chemotherapy study all relevant scans have to be sent in for review during the pre-treatment and treatment periods.

To answer the question of response distribution at week 24 following induction treatment for children entering the chemotherapy arm of the study, it is necessary to review the relevant scans centrally (national radiodiagnostic reference center). Additionally it shall be assessed, when the "best response" throughout treatment is reached, so scans shall be performed at 6-monthly intervals. Qualitative changes of contrast enhancement will be described and correlated with response.

Definitions of "relevant time points" for the central radiologic review of radiodiagnostic images for children participating in the chemotherapy trial:

Time 1	at diagnosis
Time 2	where applicable after observation to demonstrate progression or measure changes at the time of start of chemotherapy
Time 3	six months after commencement of chemotherapy
Time 4	twelve months after commencement of chemotherapy
Time 5	eighteen months after commencement / at the end of chemotherapy
Time 6	"progression scan": scan during or after therapy showing progression

Scans will need to be centrally reviewed from time-points 1 and 2 in order to validate radiological criteria for tumor progression and to confirm radiological or diagnostic imaging criteria.

At time point 3 scans have to be reviewed to validate the response and assess the distribution of response at week 24 following induction treatment.

At time points 3 to 5 central radiologic review needs to take place to validate the best response during treatment and for comparison against subsequent scans (time point 6), where progression was deemed to have occurred in order to validate the time of progression.

In all cases of neuroradiologic progression during observation/before starting treatment and during or following therapy review should confirm that the criteria for progressive disease have been met (see section 16.3.). Minimal or transient changes of tumor size should not be termed progressive disease. All comparisons of tumor size have to be made

- to the size at diagnosis for those being observed,
- to the size at start of therapy to assess treatment response at the defined time points,
- to the size at "best response" for subsequent assessment of tumor status for those having been treated.

Table 27: Minimum required sequences for central radiologic assessment:

	Cranial MRI preoperatively	Cranial MRI postoperatively 24-48 (-72) hrs and follow-up	Spinal MRI
PD or Flair	X	X	-
T 2 axial	X	X	-
T1 without Gd	X (axial)	X (axial)	(X) (sagittal)
T1 with Gd	X (axial)	X (axial)	X (sagittal)

T1 with Gd (additional planes)	X (coronal or sagittal)	X (coronal or sagittal)	X (axial in areas of suspicious enhancement)

8.6. Ophthalmological assessment

Introduction
Children who have been diagnosed as having optic pathway and hypothalamic gliomata, either with or without Neurofibromatosis Type I, require a regular and structured ophthalmic assessment. No prospective study has tested the various types of assessment of visual function. A decision of whether to commence chemotherapy or radiotherapy is often based on optic nerve function, although there has never been a consensus regarding a structured approach to this testing.

All ophthalmic centres linked to oncology centres participating in the low grade glioma Trial would be expected to perform a standard set of tests of visual function. It is hoped that by performing these tests in a structured prospective manner it will be possible to identify which tests are the most sensitive and consequently the most useful in terms of screening children with optic pathway gliomas.

Aims
The aim of this part of the low grade glioma Study is to introduce a standardised methodology of visual assessment in children of all ages with optic pathway glioma. The data will be collected in order to assess the feasibility of the tests of visual function in an international setting.

It is not possible at this stage to validate these tests as there is no known gold standard with which to compare. Therefore patients can also be entered into a pilot study of visual function testing including the use of visual evoked potential, and comparing formal tests with subjective assessment of visual function by the parent and patient, a vision behaviour check list and with radiology (See section 19).

Tests of visual function
Children should be assessed through a combination of direct and indirect testing pertinent to their ages. The modalities for testing come under the following headings:

1. Visual acuity
2. Visual fields
3. Colour vision
4. Contrast sensitivity
5. Ocular motility assessment
6. Pupil responses
7. Fundoscopy

1) Visual acuity
Visual acuity testing should be recorded using a Logmar chart which, with matching cards, can be used in children as young as 2 ½. The Logmar chart can be used either as a letter format or as LEA symbol format. For children under 2 ½ or in those where there are communication problems or other difficulties, acuity card preferential looking should be used. Visual acuity is graded from 8 (best) to 1 (worst):

Grade	LOGMAR/LEA	PL (c/d)
8	0-0.2	≥19.5
7	0.3-0.4	14.2-9.8
6	0.5-0.7	7.5-4.8
5	0.8-1.0	3.6-2.4
4	1.1-1.3	1.8-1.2
3	Hand/Toy movement	
2	Perception of light	
1	No perception of light	

2) Visual Fields

Formal perimetry should be carried out in children who are old enough to co-operate with the test. Certainly children over the age of 6 or 7 should be able and sometimes younger children can also comply. Goldmann visual fields using an experienced examiner are often both more accurate and more possible than static perimetry using an automated system. In young children confrontation testing using a toy or bright object and two examiners is a better technique. Visual field assessment is also graded on an 8-part scale:

Grade	Achievement
8	Monocular Full
7	Monocular Quadrantic
6	Binocular Quadrantic
5	Monocular Hemionopic
4	Binocular Hemionopic
3	Monocular Hemi and Quadrantic
2	Binocular Hemi and Quadrantic
1	Total Loss

3) Colour Vision

The PVC 16 colour vision testing system is likely to be the best option for testing children in this patient group. There is a reduced version of the Farnsworth 100 hue test, which involves a child matching colours. Depending how accurately these colours are matched colour vision can then be assessed and consequently graded. The Isschihara plate system is a historical test, which was devised primarily to identify patients with red/green colour-blindness. The axis of colour loss in children with optic nerve pathology is more likely to be in the blue-yellow spectrum and as a result the Ishihara test is not particularly useful. The grading system for colour vision using the PVC 16 test can be used:

PV 16	Colour Test
Grade	Chart Results
8	Colour Circle complete
7	Close caps confused
6	One crossing of circle 7 <--> 15
5	Up to 2 crossings (other than 7 <-> 15)
4	Up to 4 crossings (other than 7 <-> 15)
3	5 crossings (other than 7 <-> 15)
2	6 crossings (other than 7 <-> 15)
1	7 crossings (other than 7 <-> 15)

Defect Axis	Protan / Deutan / Tritan / Mixed (please indicate)

Additional Guidance for
Grading Colour Vision using Panel 16 Colour Vision Test

- Use appropriate method for age of child
- Test on a white background and use the same illumination at each test
- Use masking discs whenever possible, as this stimulates a smaller area of retina, and therefore picks up defects more easily
- Test monocularly
- Record on the colour circle chart provided with the test
- In children this test exposes confusion of colours in the Protan,Deutan, and Tritan axes
- Colour vision defects are shown on the chart as crossings of the colour circle
- Minor confusions around the circle are considered within normal limits.
- Crossing from 7 ↔ 15 is also considered normal
- More than 4 crossings on a definitive axis, is considered abnormal
- We should be looking for changes in results on retests (N.B. there may be an initial improvement on 1st retest, due to the "learning curve")

The examiner should also document the principal colours that are predominately missed (blue, red, green etc.).

4) Contrast Sensitivity

There is evidence that contrast sensitivity testing can be used to pick up subtle changes in optic pathway function and as such should be incorporated into a standard screening protocol for these children. Contrast sensitivity develops at a faster rate than visual acuity during the first 30 weeks of life. Contrast sensitivity testing has been shown to be more sensitive than acuity, field and colour vision testing in optic neuropathy. It has also proved helpful in-patients with visual pathway glioma. (Day 1997)

The VISTECH vision contrast system or the LEA contrast sensitivity test should be used on all children. With the LEA matching cards it should be possible to test children down to 2 ½ to 3 but the VISTECH system may be difficult in children under the age of 4. Using the VISTECH vision contrast test there is again a grading system on an 8-part scale:

Grade	Column "A" (1.5 c/d)
8	Grating 8
7	Grating 7
6	Grating 6
5	Grating 5
4	Grating 4
3	Grating 3
2	Grating 2
1	Grating 1

Gradings for Lea Contrast Sensitivity:

	VA -0.2 to 0.175 Log MAR test at 3M	VA 0.2 to 0.475 Log MAR test at 3M	VA 0.5 - 0.775 Log MAR test at 1M	VA 0.8 to 1.0 Log MAR test at 1M

Grade	No of Symbols seen	No of Symbols seen	No of Symbols seen	No of Symbols seen
8	25 - 22	25 - 18	25 -22	25 - 16
7	21 - 18	17 - 16	21 - 18	15 - 12
6	17 - 14	15 - 13	17 - 14	11 - 10
5	13 - 10	12 - 9	13 - 10	9 - 7
4	9 - 7	8 - 6	9 - 7	6 - 5
3	6 - 4	5 - 3	6 - 4	4 - 3
2	3 - 2	2	3 - 2	2
1	1	1	1	1

Additional Guidance for Contrast Sensitivity Testing

- Essentially we should measure CHANGES in Contrast Sensitivity as "normal" has a very wide range
- Contrast Sensitivity is related to visual acuity., therefore if VA falls, then the number of C S symbols read will be reduced, however, actual CS may still be normal
- The best measure of CS with the **Lea chart** is to measure the gradient of the slope (VA against No of symbols read at specific distance) as recorded on the chart ("normal" 65° / 75°)
- For the purpose of "grading" of **Lea Chart** results, it is proposed that the attached charts are used, which are dependant on Visual acuity
- The grading for **Vistech** testing uses the lowest special frequency on the chart, to allow for poor visual acuity.
- It is not possible to note changes by comparing Lea tests with Vistech tests, therefore the same test should be used continually in individual cases.

5) Ocular motility assessment

Children with poor vision can develop strabismus and consequently recording of the presence or absence of a squint is important. There is no grading system as such for this although it should be documented whether a squint is convergent or divergent or vertical and a measurement of either the prism cover test or the prism reflection test (this would be in degrees or prism diopters). The presence of nystagmus should be noted which will also include its orientation (horizontal, vertical or rotary) and nature (jerk, pendular etc).

6) Pupil responses

All children should be assessed for a relative afferent pupillary defect. This is achieved using the swinging flash light test. There is no grading for this but it should be noted if a relative afferent pupillary defect is present and if so can this defect be neutralised with neutral density filters. These filters come in an increasing density and consequently mimic a loss of luminance in the eye that is being tested. By putting these filters in front of the good eye an attempt can be made to classify the relative afferent defect in the bad one.

7) Fundoscopy

Whilst not assessing optic pathway function the appearance of the optic nerves is important to document. The appearance of optic atrophy should be noted.

Frequency of examinations

The consensus statement of the NF I optic pathway glioma task force (Listernick 1997) suggests ophthalmological examinations for children with optic pathway gliomas every 3 months during the first year following diagnosis and six-monthly until 36 months and yearly thereafter. But this however relates to surveillance and the frequency will need to be increased for children experiencing visual deterioration nor to children under treatment, who will need closer follow-up. During chemotherapy it has been suggested that 3-monthly investigations should take place (Lorenz 2002). Table 27 shows the recommended frequency of ophthalmological examination for children participating in this study.
If there is a change in a child's condition they should be returned to 3 monthly assessment for 12 months and then to 3-6 monthly and then to 6 monthly.

Table 28: Recommended frequency of ophthalmological examination during treatment and follow-up (Lorenz 2002):

At diagnosis				
Surgery	before	after	2 weeks after	each surgical intervention
Chemotherapy	before	3 monthly		during chemotherapy
Radiotherapy	before	3 monthly		after end of radiotherapy
Follow-up	1st year	3 monthly		
	2nd year:	3-6 monthly		More frequently, if indicated
	3rd year	6 monthly		More frequently, if indicated
	4th year and later:	6-12 monthly		More frequently, if indicated

Documentation

For documentation of all findings the Ophthalmology data form in Addendum 21.13.6. should be used and completed forms be sent to the national data collecting center.

8.7. Health status and quality of life assessment

Aim
To determine the quality of survival of children treated for low grade gliomata, and compare this between different trial arms.

The secondary aim is standardisation of morbidity assessments across European pediatric brain tumor clinical trials, in order to enhance compliance and completion of data sets consequent upon familiarity of clinical teams with the system. Comparison of morbidity data between tumor groups will be possible.

Methodology
The former UKCCSG and SIOP Brain Tumor Group have agreed upon a standardised framework for monitoring of morbidity burden consequent upon the diagnosis and treatment of brain tumors (Glaser et al, 1999). This will be adopted to national structures with appropriate modifications due to developments in methodologies since its publication. Four of the original questionnaires (Strengths and Difficulties Questionnaire[SDQ], Health Utilities Index[HUI], Medical Examination Form, Medical/Educational/Employment/Social Form) will be used. Additional health-related quality of life measures will be used.

The HUI and SDQ have been widely used and are available in 7 European languages (Goodman 1994, Feeny et al 1995). Their use is supported by the SIOP Brain Tumor Group. The medical examination form and medical/employment/education/social form for patients and parents need to be adapted for individual countries as educational qualifications and support will vary. This system is being adopted in SIOP PNET 4. The same forms will be used in this study as for PNET 4.

Health-related quality of life measures are important in providing information about patients, and their parents, perception of their health and well-being. Few measures are suitably translated, and validated, for inclusion in an international study across Europe. In keeping with SIOP PNET 4, three measures will be available for this study; the PedsQL (Varni et al,1999), PEDQOL (Ravens-Sieberer and Calaminus, 1998) and the Child Health Questionnaire[CHQ] (Landgraf et al, 2000). In the United Kingdom the PedsQL will be used, whilst in Germany the PEDQOL will be the measure of choice. The CHQ is available in multiple European languages and should be adopted by other participating countries (data is only by parental proxy response). Aged 18 + years, the EORTC QLQ-C30 with brain tumor specific add-on module (Aaronson et al, 1993) is recommended for use in all countries.

Schedule of assessments
Both, medical/education/employment/social assessment and Quality of Life, should be assessed at diagnosis, 1 year, 3 years, 5 years, 10 years from diagnosis and at age 20 years.

9. Patient Eligibility SIOP LGG 2004

9.1. Inclusion Criteria

1.1 **Age**: children and adolescents up to the completion of the 16th year of life.

1.2 **Histology**: low grade glioma according to ICD O Code

Pilocytic Astrocytoma I°	9421/1
Subependymal Giant Cell Astrocytoma I°	9384/1
Dysembryoplastic Neuroepithelial Tumor I°	9413/0
Desmoplastic Infantile Ganglioglioma I°	9412/1
Ganglioglioma I° and II°	9505/1
Pleomorphic Xanthoastrocytoma II°	9424/3
Oligodendroglioma II°	9450/3
Oligoastrocytoma II°	9382/3
Astrocytoma II°	9400/3
Fibrillary Astrocytoma II°	9420/3
Protoplasmatic Astrocytoma II°	9410/3
Gemistocytic Astrocytoma II°	9411/3

Children with chiasmatic-hypothalamic tumors may be eligible without histological diagnosis, if neuroradiologic findings meet unequivocal criteria for the presence of a low grade glioma.

1.3 **Primary tumor localization**: intracranial and/or spinal cord.

1.4 **Dissemination**: Children presenting with disseminated low grade glioma will be eligible for the study.

1.5 **Associated conditions**: Children are eligible for the trial regardless of the presence of associated genetic disease: Neurofibromatosis NF I will be the prominent one, all children with NF I are entered into the study arm III in case of an indication for non-surgical therapy. Other conditions like Tuberous Sclerosis etc. should be registered and their impact on the course of disease and/or therapy be followed.

1.6 **Primary tumor diagnosis**: The tumor should not be pretreated with chemotherapy or radiotherapy.

1.7 **Informed consent**: The patient and/or his legal guardian (parents) have to have declared their written informed consent to the study.

Randomization: All eligible patients without Neurofibromatosis NF I receiving chemotherapy as their fist non-surgical therapy are eligible for randomization.

9.2. Exclusion Criteria

2.1. **Primary tumor localization**: diffuse intrinsic tumors of the pons, even if histologically an Astrocytoma I° or II° is diagnosed.
Exception: pontine glioma II° in NF I patients may be entered into the study.

2.2. **Special diagnosis**: Patients presenting with rare intracranial neoplasms of low grade malignancy, but non-glial origin may be followed according to the low grade glioma strategy but they are not subject of this therapy trial. Their data may be registered however, to learn about those therapeutic interventions which may prove useful to these patients and to develop separate strategies in the future. Choroid plexus papilloma should be entered into the SIOP-CPT study (PD. Dr. J. Wolff, Children's Hospital, Regensburg, Germany).

2.3. **Pretreatment**: Children treated with chemo- or radiotherapy prior to entering the study will be evaluated separately. (Previous treatment with steroids is not considered a chemotherapeutic treatment).

2.4. **Preexisting impairments** of health status, making the conduct of the study impossible or ethically unwise.

2.5. **Evidence of pregnancy or lactation period**.

Participation in another clinical study.
In case the patient participates in another clinical study simultaneously to being enrolled in the study SIOP-LGG 2004, which is not interfering with the present treatment strategy (e.g. endocrinologic study), this should be known to the national study chairmen.

Medication.
Concommittant medication for associated or other conditions (e.g. hormone replacement, anticonvulsants), not containing cytostatic drugs, should be recorded, but is no exclusion criteria.

10. Indications to start non-surgical therapy SIOP LGG 2004

The indications to start non-surgical therapy are identical for all low grade glioma, with non-surgical therapy being either chemotherapy or radiotherapy. Since a first attempt of resection should be performed, if feasible, while some children will be diagnosed on neuroradiological grounds only, there are three major settings, where the decision to start non-surgical therapy has to be made.

The decision to start non-surgical therapy – differently to tumors of high malignancy – is a critical one. It is difficult to elaborate objective and reproducible criteria. Acknowledging this fact, all physicians entering patients into the trial are requested to verify carefully, if the criteria to start therapy are met, and to specify very clearly the possible reasons in case these criteria are not respected.

I. Indication to start non-surgical therapy at diagnosis following subtotal or partial resection (S2 – S3) (see section 16.2. for definition of extent of resection)

Severe preexisting visual disturbance (see section 8.6.)
- Borderline vision in both eyes (“threat to vision“)
- Definite history of visual deterioration
- Nystagmus due to impaired vision (especially in infants up to two years indicative of visual disturbance)

Clinical indication
- Diencephalic Syndrome
- Symptomatic metastases

Note: Neuroradiological indication
- The presence of a postoperative residual tumor is not an indication to therapy on its own.

II. Indication to start non-surgical therapy at diagnosis without prior tumor resection (following biopsy or radiological diagnosis)

Severe visual symptoms
- Borderline vision in both eyes (“threat to vision”)
- Definite history of visual deterioration
- Nystagmus due to impaired vision (especially in infants up to two years indicative of visual disturbance)

Severe neurologic symptoms
- Diencephalic syndrome
- Focal neurologic deficits secondary to tumor growth
- Symptoms of increased intracranial pressure secondary to tumor growth
- (decompensated hydrocephalus occlusus should be treated by a shunting procedure)
- (Focal) Seizures secondary to tumor growth
- Symptomatic metastases

Note: Neuroradiological indication
- The presence of a postoperative residual tumor is no indication to therapy on its own.

III. Indication to start non-surgical therapy following observation, if surgery is not feasible

Progressive neurologic symptoms
- Manifestation of new neurologic symptoms
- Increase of severety of existing neurologic symptoms
- Manifestation of Diencephalic Syndrome

Progressive visual disturbances
- Reduction / loss of vision or of visual fields
- Any reduction / loss of vision in the second eye, if the other eye is blind

Neuroradiologic progression
- Definite increase of tumor size * (Increase of the diameter of the optic nerve)
- Involvement of previously uninvolved areas of the brain
- Manifestation of disseminated disease (including symptomatic or progressive metastases)

* Assessment of tumor size (two- or three-dimensional) should always be performed in the same way in the same patient (see section 8.5.).

Tumor size (volume) progression – Unequivocal increase of tumor size (volume) is a criteria to start therapy. However, pilocytic astrocytoma may have solid and cystic components. If only the cystic component(s) enlarge, while the solid ones remain unchanged, this is no sufficient evidence of tumor progression, although neurosurgical intervention may be necessary to relieve symptoms of local or generalized pressure.

Decrease of the visual function - The evidence of an increasingly compromised visual function (marked decrease of the visual acuity and/ or the visual field) regardless of tumor volume changes, and in the absence of any other overt cause, should be considered a criteria for starting therapy. Clinicians have to be aware, that quite often in young children the results of the ophthalmological examinations may vary according to the child's compliance to the procedure and the tests. Thus, particularly in face of a radiologically stable disease, any visual function changes should be confirmed by two consecutive ophthalmological tests. This is especially important for children with NF1. Visual evoked potentials may help to confirm clinical findings, but by themselves are not considered a sufficient criteria to evaluate tumor progression.

Diencephalic syndrome –DS in itself is a clinical condition for starting therapy.
Main characteristics are a progressive emaciation and failure to thrive (regarding body weight and less growth !) in an apparently alert, cheerful infant. DS is usually due to a low grade glioma involving the hypothalamus. Treatment with aggressive surgery and / or radiotherapy is variably successful in controlling the disease, but may result in severe neurologic sequelae. Chemotherapy seems effective in controlling the clinical symptoms despite a rather long time period until changes are seen.

Disseminated low grade glioma at diagnosis – the presence of multicentric, disseminated disease by itself is not necessarily an indication to start therapy, if no other criteria to initiate non-surgical therapy are met. A very careful and accurate period of clinical observation may be appropriate.

NF I – Metachronous tumors – Patients with NF I are at risk to develop multiple (brain) tumors, especially if they presented with optic pathway glioma (Friedman 1997). Such metachronous tumors have to be distinguished from secondary dissemination of a LGG. Thus, these tumors have an indication to therapy on their own.

Please contact the study chairmen for any unconventional situation before the start of non-surgical therapy and / or randomisation.

11. Patient Registration and Randomisation SIOP LGG 2004

11.1. Patient registration

All patients diagnosed to have a low grade central nervous system glioma should be registered according to national policies at the national study office and the national children‘s cancer registry.
Forms for registration at the national children’s cancer registry are provided nationally. Where there is no pre-organized national information transfer, registration to the national study office can be done by the form provided in Addendum 21.6.1.

Patients receiving either chemo- or radiotherapy will be centrally registered at the international study office. Data transfer between the national study offices and the international trial office confers to regulations of data security (see section 18.)

The trial coordinating center (international trial office) is located at the:

SIOP-LGG 2004 International Data Centre
Clinical Trials & Biostatistic Unit
Istituto Oncologico Veneto
Busonera Hospital
Via Gattemelata 64
I-35128 Padova, Italy
Telefone: 0039-049-8215704
Fax: 0039-049-8215706
email: siop-lgg2004@istitutoncologicoveneto.it

11.2 Patient randomisation

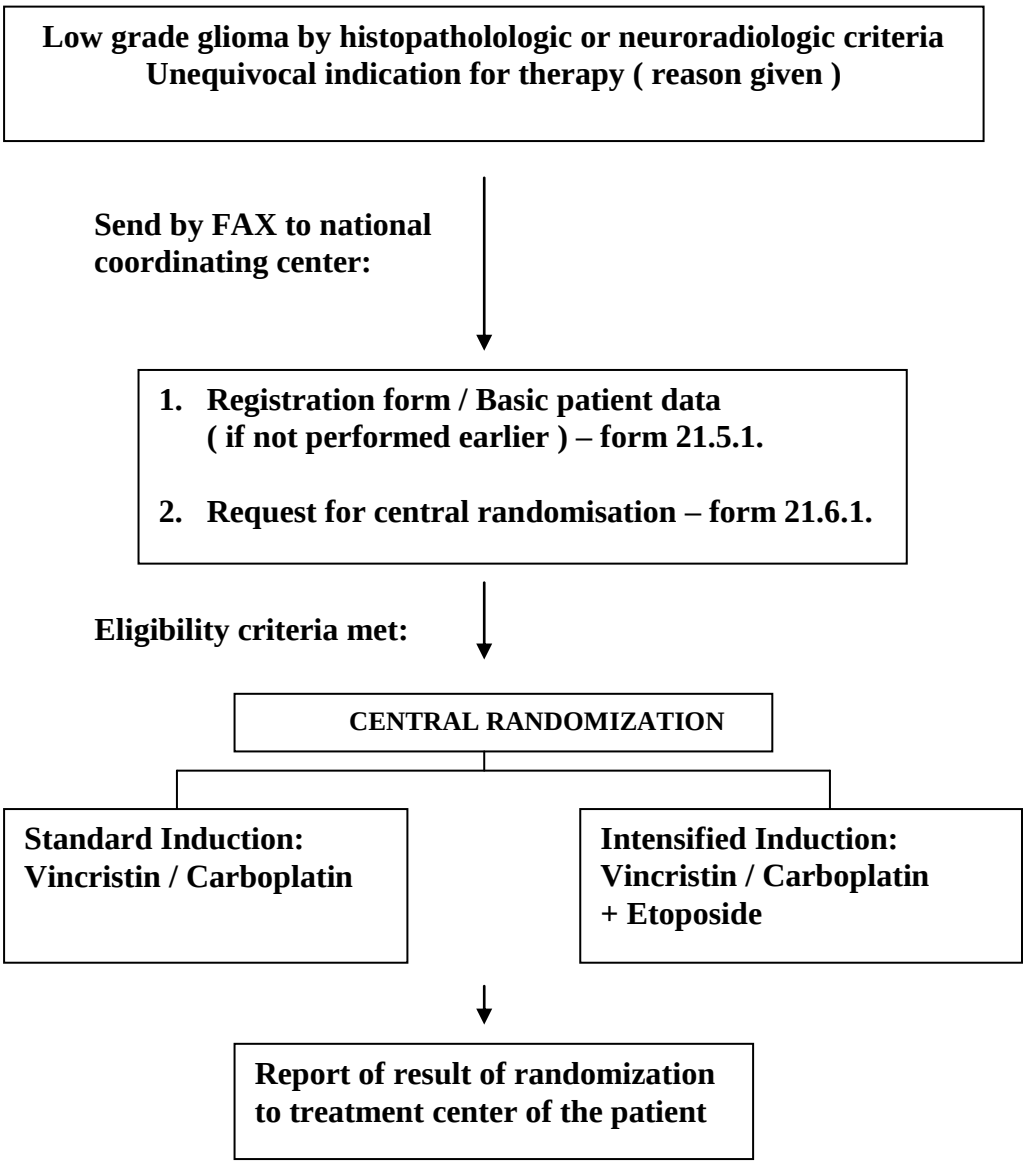
Randomization is provided centrally by a computer-based service (supplied by CINECA, Casalecchio ITALY) that is accessible via Internet, for all patients without NF I, for whom it is applicable. Access to the randomisation system is managed according to specific policies adopted by each country (both direct local site and mediated by national data centre access are possible). All eligibility criteria (section 9.) and requirements for randomization have to be fulfilled prior to the randomization process:
The presence of a low grade glioma should be confirmed either by central neuro-pathologic review, if a biopsy has been obtained, or by central neuro-radiologic review, if the diagnosis is made on the basis of MRI / CT investigation only.

Randomization will be stratified according to age (< 1 year, 1-8 years, ≥ 8 years) and primary tumor site (pure chiasmatic tumors (Dodge II, Dodge 1958), all other supratentorial midline tumors, tumors of all other sites outside the supratentorial midline). To reduce possible imbalances in the number of treatment assignments, a randomised blocked design will be used.

Patients for whom randomization is requested have to be registered at their national trial office. The national center will check the eligibility of the patient and then obtain central

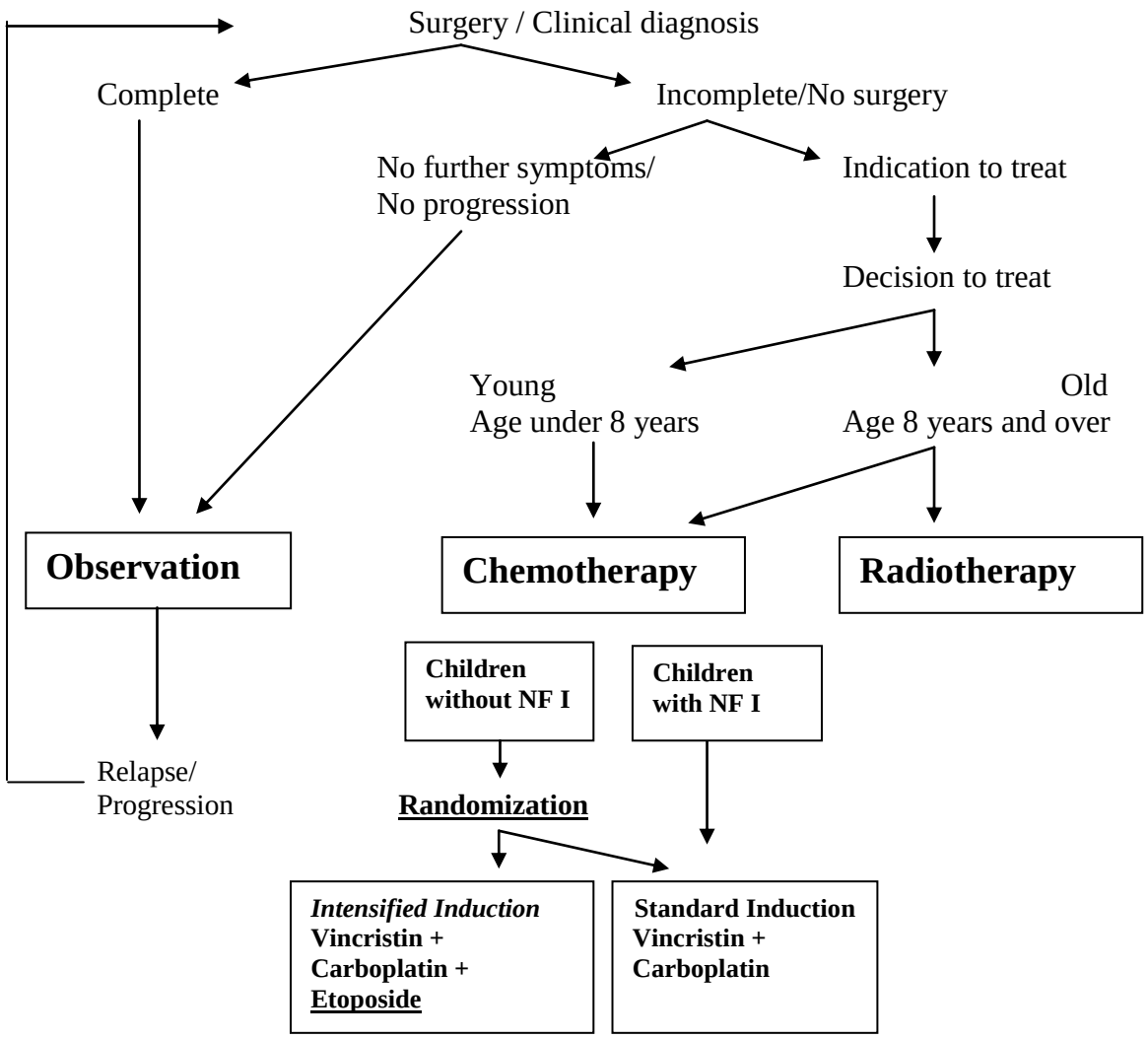
randomization. The result will be reported back to the patient's treatment center. This procedure will require two working days. This should be kept in mind when planning treatment.

Before randomization the patient and/or his/her legal guardian/parents have to be adequately informed about the study, the background of this strategy and the possible therapeutic alternatives. Their written informed consent has to be obtained prior to randomization.



12. Study Overview SIOP LGG 2004

Treatment Scheme:



All patients with low grade glioma, eligible according to the criteria from section 9., should be entered into the current study and follow the same general strategy concerning the non-surgical therapy. Dependent upon primary tumor localization and the presence or absence of Neurofibromatosis NF I patients are devided into three therapeutic groups:

12.1.
Group 1: Children not affected by NF I with low grade glioma of the supratentorial midline.
12.2.
Group 2: Children not affected by NF I with low grade gliomas of all other sites.
12.3.
Group 3: Children affected by NF I with low grade glioma of all sites.

Rationale to separate the treatment groups

Considering that childhood low grade glioma are a very heterogeneous group of neoplasms, it is difficult to elaborate detailed common therapeutic guidelines applicable to all children with tumors of all sites. On the other hand the basic strategy of low grade glioma treatment can be applied to all children, if the specific conditions of separate tumor locations, tumor size and age of the child are considered. For example, the present refinements in the radiotherapy techniques (conformal or stereotactic fractionated radiotherapy) allow to conceive that radiotherapy may be delivered safely in selected primary sites and for selected targets even in young children (e.g. small residual of cerebellar astrocytomas). In the previous study the age of 5 was empirically chosen as the cut-off age for recommending chemotherapy or radiotherapy. In the light of more data, which have been accumulated on the effect of chemotherapy on low grade glioma, it is possible to extend this cut-off to the age of 8.

1. Supratentorial midline tumors in children not affected by NF I.

HCG and OPG represent a relatively homogenous group of LGG. Additionally the small number of tumors of the basal ganglia, the thalamus and the upper midbrain pose the identical clinical dilemma of mostly unresectable tumors. Thus, it is conceivable to elaborate detailed common therapeutic guidelines for them. In particular, due to the obvious limitations of any potential surgical acts aiming to remove completely the tumor, the role of CT, as outlined above, is much less controversial and their long term outcome needs to be improved with high priority.
For this subgroup of children the impact of intensifying the induction period will be investigated in a randomized study.

2. Low grade glioma arising at all other sites in children not affected by NF I.

Separate therapeutic guidelines will be elaborated for children with LGG arising from other sites of the CNS. This is true also for children with pure optic nerve glioma.
For this group of patients surgery plays a major prognostic role. After incomplete surgery the progression rate is between 40 and 50 % without adjuvant treatment (Fisher 2001), but for the treatment of relapse, surgery alone can result in long-term progression free survival especially in hemispheric and cerebellar tumors (Bowers 2001). Consequently, adjuvant treatment should be avoided, if second surgery is a complete resection. Even in case of late progression, several years after a first partial resection, a second partial resection can be considered.
Residual pilocytic astrocytoma may regress spontaneously, especially when the residual is small.
Additional prognostic factors may depend upon tumor location:
The interval between first symptoms and diagnosis is inversely correlated with the outcome in children with spinal tumors (Bouffet 1998).
Brainstem involvement is a significant risk factor for incomplete surgery and bad outcome in children with benign cerebellar astrocytoma (Pencalet 1999); these tumors probably need a different treatment strategy than classical cerebellar astrocytoma.

In these locations many other histologic types of low grade glioma are encountered as well, whose natural history is hardly predictable, but may be less favourable. In some locations, e.g. brainstem, focal lesions with a histology of pilocytic astrocytoma can be clearly distinguished from more diffuse tumors of either pilocytic or fibrillary types in terms of biological behaviour and prognosis (Fisher 2001). Therefore diffuse intrinsic pontine glioma, even if astrocytoma WHO I° or II°, has been excluded from the study and should be entered into trials for high grade glioma.
For the small subgroup of children needing chemotherapy the impact of intensifying the induction period upon primary response shall be investigated in a randomized fashion.

3. Low grade glioma of all sites in children affected by NF I.

Diagnosis of NF I should use the criteria published from the consensus conference on glioma in NF1 patients (Listernick 1997). Minor criterias for NF1 can be listed as well according to Cnossen (1998). A special case should be made for UBOs (unidentified bright objects) that are both a new diagnostic criteria and a diagnostic dilemma in some cases.

Almost quite uniformly all the studies run on childhood LGG have documented that the NF1 status is a favorable prognostic factor (see section 3.2.). But children with NF1 have specific problems. They are affected by a cancer-predisposing syndrome and concern exists on treating those children with potentially oncogenic agents (e.g Etoposide, RT…). Radiotherapy can be particularly deleterious for these patients in face of the pre-existing brain dysfunction, in that these children may suffer more sequellae, because of the NF1 status. Furthermore, NF1 children treated with cerebral irradiation may be at a higher risk than the normal population of developing severe and potentially fatal vascular complications (Capelli 1998, Grill 1999).

Within this trial children affected by NF I and necessitating non-surgical therapy will be treated separately according to the historical, but extended regimen with Vincristin / Carboplatin, regardless of their age at presentation. They should not be irradiated unless the chemotherapy and surgery options have failed.

Endpoints for treatment outcome evaluation

As previously stated due to the very long life expectancy of children affected by a LGG it is clear that the health status (HS) and the quality of life (QoL) in general and at least the neurological, visual and endocrinological function must be among the primary end-point of any treatment strategy directed to childhood LGG. The fact that reliable tools for measuring HS and QoL in young children are not available, make it impossible to test those two criteria for therapy effect; however the assessment of the visual, endocrinological and neurological function will be included in the outcome measurement.

12.1. Study overview: Children not affected by NF I (NF I-ve) with low grade glioma of the supratentorial midline. SIOP LGG 2004

This subgroup comprises a relatively homogenous group of low grade glioma. Hypothalamic-chiasmatic glioma and optic pathway and the small number of tumors of the basal ganglia, the thalamus and the upper midbrain pose the identical clinical dilemma of mostly unresectable tumors. Thus, the role of non-surgical therapy, and in particular chemotherapy for the young, is much less controversial and the long term outcome for these children needs to be improved with high priority.
For this subgroup of children the impact of intensifying the induction period of chemotherapy shall be investigated.

Eligibility criteria to this treatment group:

Tumor location: optic pathways/chiasmatic-hypothalamic region, basal ganglia, thalamus, mesencephalon (lamina quadrigemina, tectum mesencephali)

Staging Chiasmatic-hypothalamic and optic pathways gliomas should be classified additionally according to the Dodge classification (Dodge 1958):
Dodge II: tumors of the optic chiasm with or without optic nerve involvement.
Dodge III: tumors of the optic chiasm with extension into the hypothalamus and other diencephalic structures.

Histology: Low grade glioma according to section 9.1.
Histologic diagnosis is primarily made by the local pathologist, yet for all children randomized central pathologic review has to be obtained prior to randomization.

Alternatively:
Clinical diagnosis: Neuroradiologic criteria fulfilled according to section 8.5.
Neuroradiologic criteria have to be fulfilled for all children not biopsied and central neuroradiologic review has to be obtained prior to randomization.

Surgery: Any extent of primary surgery

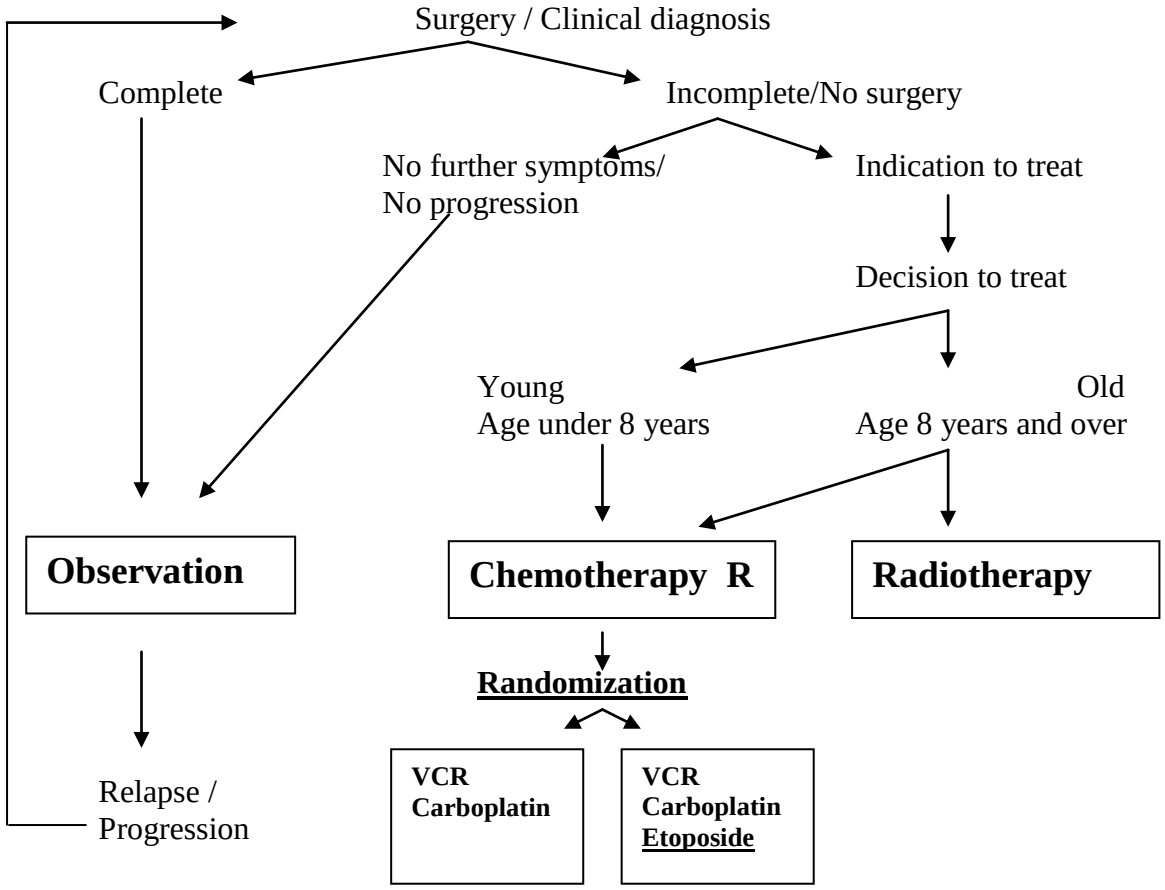
Neurofibromatosis I: absent.
It should be noted that in very young children the signs of NF I may not be apparent and it is necessary in patients with tumors compatible with Neurofibromatosis that the patient is repeatedly re-evaluated in the first five to seven years of life for signs of emerging criteria (careful examination of skin is recommended).
Standard reassessment will be requested during follow-up at the age of six years.

Age eligibility: If there is an indication for non-surgical treatment and parents and physicians have made the decision to treat, the choice of either radio- or

chemotherapy has to consider the age of the patient (and the size of the tumor):

- It is recommended that all children younger than 8 years will be entered into the chemotherapy study as „young age group".
- Those of eight years and older as the „old age group" could be entered into the chemotherapy study and randomized - or could be entered into the radiotherapy study at the patient / parent / physicians's preference.

Treatment strategy for children unaffected of NF I with low grade glioma of the supratentorial midline :



Registration:

Patients shall be registered nationally at diagnosis irrespective of the indication for or type of non-surgical therapy. National data centers will forward information of all treated and non-treated patients into the common international data-bank.
The national data center is responsible for quality assurance of data handling and management.

Randomization:

Request for randomization is forwarded to the national data center, where patient eligibility is checked. Central randomization will be performed only, if the preconditions are fulfilled completely, and the result of central randomization will be communicated to the treatment center as well as to the national study office.

Treatment modalities:

A. Surgery

I. Surgery at diagnosis/biopsy

The extent of surgical removal has to be discussed in the light of tumor location and local or distant tumor extension. In the case of hypothalamic chiasmatic tumors with either severe or progressive reduction of vision and loss of visual fields the aim of surgical debulking has to be carefully considered.

Irrespective of the extent of tumor removal relief of increased intracranial pressure by shunting procedures where indicated, should be performed.

II. Second surgery

If there is the chance for a more complete tumor resection following primary tumor resection, or during observation or during the course of non-surgical therapy, this possibility should be discussed within the local treatment team, with the national study chairman and/or with the reference surgeon. Although tumor resections are recommended, the child should never be endangered by surgical intervention or suffer from severe neurologic / visual impairment postoperatively.

B. Chemotherapy

Children, for whom there is an indication to be treated by chemotherapy and for whom the decision has been made to actually start treatment, shall be randomized and receive either standard induction treatment with Vincristin and Carboplatin or intensified induction with Vincristin and Carboplatin plus Etoposide (see section 14. for details).

> **Note:** Neuroimaging should be obtained prior to start of therapy at an interval less than 4 weeks !

I. Standard Induction:

Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

II. Intensified Induction:

Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).
Etoposide is given as an intravenous 1-hour infusion at a dose of 100 mg/m²/day on day 1 to 3 of week 1, 4, 7 and 10. (no dose adaptation for children < 10 kg body weight).

III. Consolidation

All children will receive consolidation therapy up to week 81 with ten 6-week cycles of Vincristin and Carboplatin. Cycles start in week 25, 31, 37, 43, 49, 55, 61, 67, 73 and 79.
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each cycle (maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of each cycle (dose for children < 10 kg body weight: 18,3 mg/kg/day).

IV. Allergy

In case a patient develops allergy to Carboplatin during consolidation, therapy shall be continued with alternative drug combinations (Cisplatin/Vincristin and Cyclophosphamide/Vincristin) maintaining treatment intervals and total treatment time. A maximum of 5 cycles with both drugs should not be exceded to limit cumulative doses.
Allergy during induction treatment is a rare event, further treatment should be individually planned following discussion with the national study center.
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each cycle (maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Cisplatin is administered at 30 mg/m² as a 3-h infusion on day 1 and 2 of each cycle (dose for children < 10 kg body weight: 1 mg/kg/day).
Cyclophosphamide is given at 1500 mg/m² as a 1-h infusion on day 1 of each cycle (dose for children < 10 kg body weight: 50 mg/kg/day).

V. Recommendation in case of early progression

In case progressive disease is diagnosed and the commencement of radiotherapy shall still be deferred, the recommended chemotherapy is the use of Cisplatin/Vincristin and Cyclophosphamide/Vincristin as in the case of allergy.

C. Radiotherapy

Older children, who upon indication for non-surgical therapy will receive external beam radiotherapy, will be irradiated with 54 Gy tumor dose conventionally fractionated at 1,8 Gy given on five days per week. The specific aims of the radiotherapy study are a maximal sparing of organs at risk by applying radiotherapy with modern planning and technical equipment (see section 15.).

In case, that it is necessary to give radiotherapy to younger children, it is recommended to contact the national study chairmen for radiotherapy (see section 15.).
Interstitial radiotherapy (brachytherapy) may be indicated in tumors amenable for this type of therapy.

D. Central neuroradiologic evaluation

Within the chemotherapy arm of the study central neuroradiologic assesment is mandatory and scans have to be sent in at definite time points (see section 8.5.):
- in order to validate radiological criteria for tumor progression and to confirm radiological or diagnostic imaging criteria (time point 1 and 2).

- to validate the response and assess the distribution of response at week 24 following induction treatment (time point 3),
- to define the point, when the “best response” throughout treatment is reached (time points 3 to 5)
- to compare subsequent scans (time point 6) where progression was deemed to have occurred in order to validate the time of progression.

Scans following radiotherapy will be assessed in a comparable pattern.

Qualitative changes of contrast enhancement will be described and correlated with response. See section 8.5. for radiodiagnostic guidelines and section 16. for tumor response and remission criteria.

E. Treatment recommendations following tumor progression

Despite all efforts to prevent tumor progression by primary therapy, a significant number of children will suffer from progression during or after first line therapy. Thus, the treatment strategy for low-grade gliomas has to incorporate recommendations for second (and third) line treatment approaches. In each case the possibilities for a meaningful surgical intervention should be checked, as well.

I. Progression during chemotherapy (early progression) in a young child (< 8 years)
Chemotherapy in these children is started to postpone radiotherapy. So, if PD occurs at the first evaluation at week 24 or later during consolidation and the child is still young, it is recommended that therapy be continued with the alternative chemotherapy regimen as in the case of Carboplatin allergy (section 14.1.3.). The two drug combinations of Cis-Platin/Vincristin and Cyclophosphmid/Vincristin are expected to offer an effective treatment.

II. Progression during chemotherapy (early progression) in an older child (≥ 8 years)
In case of progression at the first evaluation at week 24 or later during consolidation in a child older than 8 years, it should be assessed, if radiotherapy can be applied as second line therapy. If radiotherapy is no option, the alternative chemotherapy regimen (14.1.3.) should be used.

III. Progression following the end of chemotherapy
For children, who experience tumor progression following the end of therapy, several points have to be considered:
- age: Children still in the young age group, in whom radiotherapy should be further postponed, should receive second line chemotherapy.
  Children still in the young age group, in whom highly focussed radiotherapy appears possible, can go on to receive radiotherapy.
  Children in the older age group receive radiotherapy as second line therapy.
- time since the end of chemotherapy: If the first chemotherapy has been completed for more than a year, and the child has not had Carboplatin allergy, restart of standard Carboplatin/Vincristin chemotherapy may be taken into account. The alternative chemotherapy (14.1.3.) can be used as well.
  If the intervall between the end of first chemotherapy is shorter than a year and/or the child has had Carboplatin allergy, the use of the alternative regimen (14.1.3.) is recommended. The national chairman should be contacted to plan details for the "induction" phase.

- previous allergy: If first line chemotherapy has already been complicated by Carboplatin allergy and the alternative drug combinations thus have already been applied and second line chemotherapy is indicated, it is recommended to contact the national chairman for the investigation of Phase II-treatment protocols. A trial with Vinblastin will be offered by the Phase II coordinators of the study.

IV. Progression following radiotherapy

For all children, who have received radiotherapy as their first treatment, chemotherapy is the first option in case of tumor progression. They will not be randomized and receive standard induction and consolidation with Vincristin and Carboplatin.

12.2. Study overview: Children not affected by NF I (NF I-ve) with low grade gliomas of all other sites. SIOP LGG 2004

This section will provide guidelines for the treatment of tumors, which have been incompletely resected (primary or following relapse) or which are disseminated at sites other than the supratentorial midline in patients, who have not got the clinical signs of Neurofibromatosis NF I.
For the small subgroup of children receiving chemotherapy the impact of intensifying the induction period of chemotherapy shall be investigated.

Eligibility criteria to this treatment group:

Tumor location: For the purposes of this section five main anatomical groupings are considered:
1. Cortical tumors
2. Cerebellar tumor
3. Brain stem tumors
4. Spinal tumors
5. Optic nerve tumors (intraorbital, anterior N II; Dodge I)

Staging: Staging investigations for supratentorial tumors need only include spinal imaging, if there is evidence of intracranial dissemination or symptomatic spinal disease.
Infratentorial / spinal tumors should have spinal imaging as a routine.

Histology: Low grade glioma according to section 9.1.
All tumors should at least be biopsied, neuroradiological criteria do not allow the differentiation of the various histological subtypes at these locations.
Histologic diagnosis is primarily made by the local pathologist, yet for all children central pathologic review is recommended. It is mandatory for children entering the randomized trial.
Diffuse intrinsic astrocytoma of the brainstem are not elegible (see section 9.2.)

Surgery: Any extent of primary surgery

Neurofibromatosis I: absent.
It should be noted that in very young children the signs of NF I may not be apparent and it is necessary in patients with tumors compatible with Neurofibromatosis that the patient is repeatedly re-evaluated in the first five to seven years of life for signs of emerging criteria (careful examination of skin is recommended).
Standard reassessment will be requested during follow-up at the age of six years.

Registration:
Patients shall be registered nationally at diagnosis irrespective of the indication for or type of non-surgical therapy. National data centers will forward information of all treated and non-

treated patients into the common international data-bank.
The national data center is responsible for quality assurance of data handling and management.

Randomization:
Request for randomization is forwarded to the national data center, where patient eligibility is checked. Central randomization will be performed only, if the preconditions are fulfilled completely, and the result of central randomization will be communicated to the treatment center as well as to the national study office.

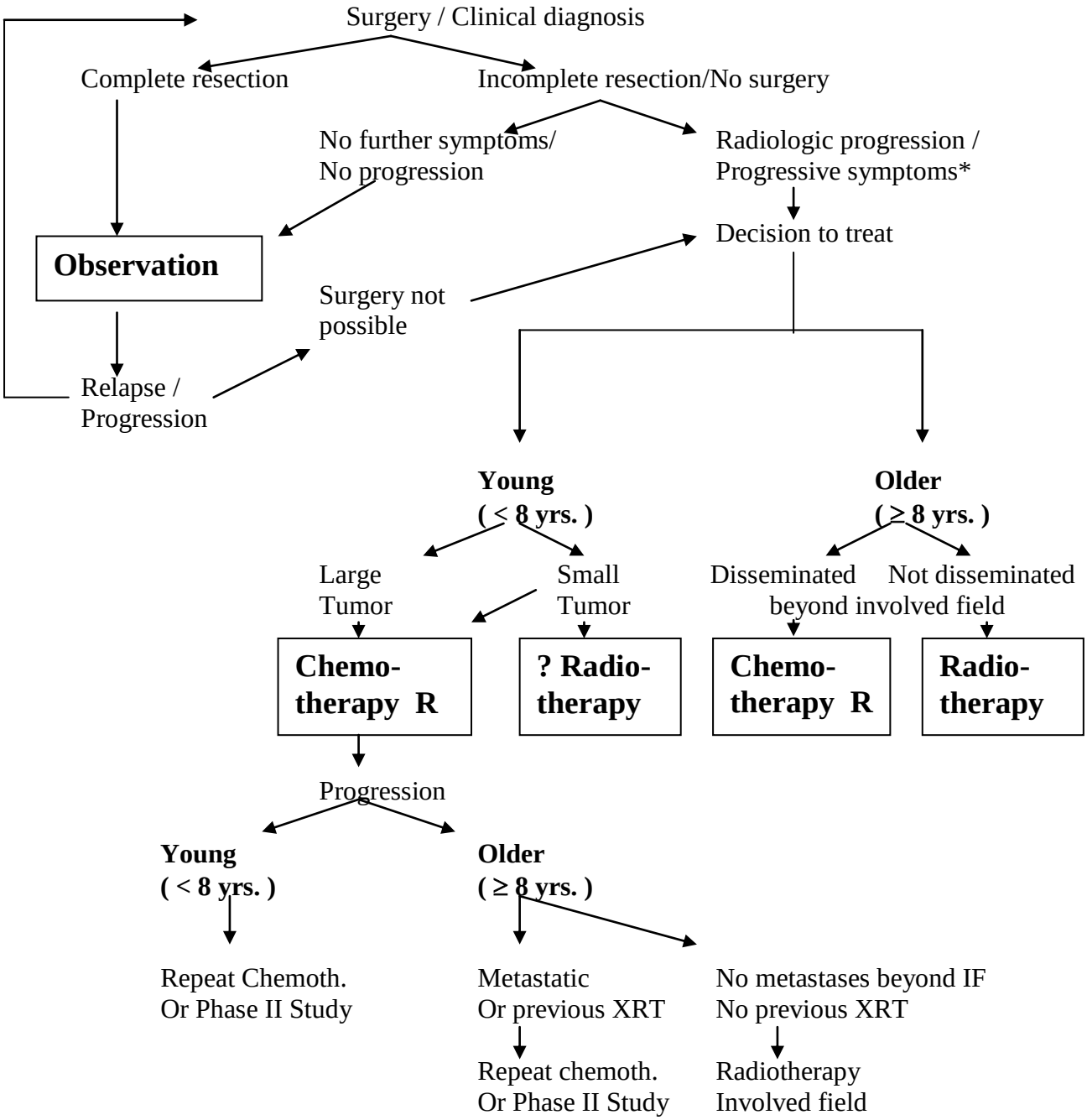
Age eligibility: Guidelines for non-surgical therapy

If there is an indication for non-surgical treatment according to section 10. and parents and physicians have made the decision to treat, the choice of either radio- or chemotherapy has to consider the age of the patient (and the size and state of dissemination of the tumor):

Younger patients (under 8 years):
- For younger patients, regardless of their metastatic stage, chemotherapy can be considered as the first adjuvant treatment. Response assessment should be done with scans at six months following the start of treatment and six monthly thereafter until completion of therapy.
- In selected small tumors highly focussed radiotherapy may be considered, if the radiation dose to normal brain can be substantially reduced by this technique.
- Following tumor progression after primary response to Carboplatin/Vincristin chemotherapy in children that are still young, the recommended strategy is a second trial of chemotherapy with alternative drugs before radiotherapy is considered.
- If, during or after second line chemotherapy, the tumor progresses or if disseminated disease develops during or after chemotherapy and the patient is still in the young age category, consideration should be given to entering the patient into a phase II trial of novel agents or the use of alternative chemotherapy strategies from the published literature. Radiotherapy options may be discussed with the national radiotherapy reference center.
- Craniospinal irradiation may be considered for progression of disseminated disease during or following chemotherapy, if no further chemotherapy options are available.

Older patients (8 years and older):
- In older children without disseminated disease radiotherapy is the preferred first adjuvant therapy. Highly focussed fractional techniques should be employed to limit irradiation of uninvolved tissues, where possible. Radiotherapy options should be discussed with the national radiotherapy reference center.
- At the patient / parent / physician’s preference entry to the chemotherapy study may be an option for this patient group.
- In older children with disseminated disease beyond conventional involved radiation field boundaries for the primary tumor, or in multifocal disease, chemotherapy should be tried and response assessment should be done with scans at six months and six monthly thereafter until completion of therapy.
- Craniospinal irradiation should be considered for progression of disseminated disease during or following chemotherapy.

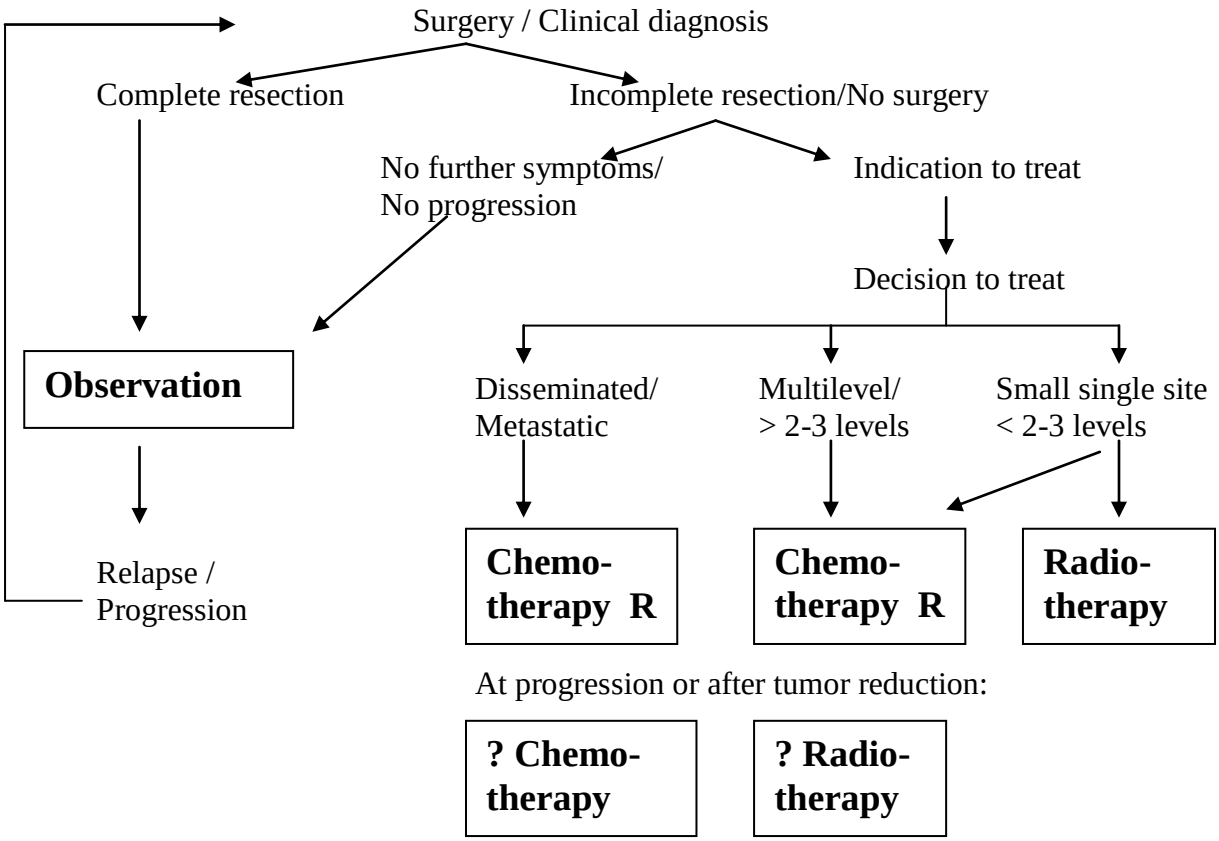
I. Treatment strategy for children unaffected of NF I (NF I-ve) with low grade cortical, cerebellar and brain stem tumors



*: In cortical tumors epilepsy controlled by anti-epileptics is not initially considered "symptomatic disease".
IF: involved field.

R: Randomisation of Induction chemotherapy as in 12.1.:
Vincristin/Carboplatin vs. Vincristin/Carboplatin/Etoposide

II. Treatment strategy for children unaffected of NF I (NF I-ve) with low grade spinal tumors:



R: Randomisation of Induction chemotherapy as in 12.1.:
Vincristin/Carboplatin vs. Vincristin/Carboplatin/Etoposide

Treatment modalities:

A. Surgery

I. Surgery at diagnosis
The extent of surgical removal has to be discussed in view of tumor location and local or distant tumor extension.

II. Second surgery
If there is the chance for a more complete tumor resection following primary tumor resection, or during observation or during the course of non-surgical therapy, this possibility should be discussed within the local treatment team, with the national study chairman and/or with the reference surgeon. Although tumor resections are recommended, the child should never be endangered by surgical intervention or suffer from additional severe neurologic impairment postoperatively.

Adjuvant treatment is offered to patients with inoperable relapse after complete resection or progression of a residuum not amenable to complete resection.

B. Chemotherapy

In large tumors and/or in young children a trial of chemotherapy should be considered for low grade glioma necessitating non-surgical therapy. Chemotherapy may be given to replace irradiation, but also to reduce the volume of tumor to be irradiated or to make the residual tumor operable.
Children, for whom there is an indication to be treated by chemotherapy and for whom the decision has been made to actually start treatment, shall be randomized and receive either standard induction treatment with Vincristin and Carboplatin or intensified induction with Vincristin and Carboplatin plus Etoposide (see section 14. for details).

> **Note:** Neuroimaging should be obtained prior to start of therapy at an interval less than 4 weeks !

I. Standard Induction:
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

II. Intensified Induction:
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).
Etoposide is given as an intravenous 1-hour infusion at a dose of 100 mg/m²/day on day 1 to 3 of week 1, 4, 7 and 10. (no dose adaptation for children < 10 kg body weight).

III. Consolidation
All children will receive consolidation therapy up to week 81 with ten 6-week cycles of Vincristin and Carboplatin. Cycles start in week 25, 31, 37, 43, 49, 55, 61, 67, 73 and 79.
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each cycle (maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of each cycle (dose for children < 10 kg body weight: 18,3 mg/kg/day).

IV. Allergy
In case a patient develops allergy to Carboplatin during consolidation, therapy shall be continued with alternative drug combinations (Cisplatin/Vincristin and Cyclophosphamide/Vincristin) maintaining treatment intervals and total treatment time. A maximum of 5 cycles with both drugs should not be exceded to limit cumulative doses.
Allergy during induction treatment is a rare event, further treatment should be individually planned following discussion with the national study center.

Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each cycle (maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Cisplatin is administered at 30 mg/m² as a 3-h infusion on day 1 and 2 of each cycle (dose for children < 10 kg body weight: 1 mg/kg/day).
Cyclophosphamide is given at 1500 mg/m² as a 1-h infusion on day 1 of each cycle (dose for children < 10 kg body weight: 50 mg/kg/day).

V. Recommendation in case of early progression
In case progressive disease is diagnosed and the commencement of radiotherapy shall still be deferred, the recommended chemotherapy is the use of Cisplatin/Vincristin and Cyclophosphamide/Vincristin as in the case of allergy.

C. Radiotherapy

When adjuvant treatment is indicated, radiotherapy can be the first line treatment in case of a small residuum amenable to stereotactic or conformal irradiation.
Older children, who upon indication for non-surgical therapy will receive external beam radiotherapy, will be irradiated with 54 Gy tumor dose conventionally fractionated at 1,8 Gy given on five days per week. The specific aims of the radiotherapy study are a maximal sparing of organs at risk by applying highly focussed radiotherapy with modern planning and technical equipment (see section 15.).

In case, that it is necessary to give radiotherapy to younger children, it is recommended to contact the national study chairmen for radiotherapy details.

A trial of prior chemotherapy could be considered to reduce the volume of a larger tumor.

D. Central neuroradiologic evaluation

Within the chemotherapy arm of the study central neuroradiologic assesment is mandatory and scans have to be sent in at definite time points (see section 8.5.):
- in order to validate radiological criteria for tumor progression and to confirm radiological or diagnostic imaging criteria (time point 1 and 2).
- to validate the response and assess the distribution of response at week 24 following induction treatment (time point 3),
- to define the point, when the “best response” throughout treatment is reached (time points 3 to 5)
- to compare subsequent scans (time point 6) where progression was deemed to have occurred in order to validate the time of progression.
Scans following radiotherapy will be assessed in a comparable pattern.

Qualitative changes of contrast enhancement will be described and correlated with response. See section 8.5. for radiodiagnostic guidelines and section 16. for tumor response and remission criteria.

E. Treatment of Pure Optic Nerve Tumors

Where there is symptomatic or progressive tumor associated with demonstrable visual deterioration, and there is a strong need to initiate treatment to control symptoms and attempt to preserve vision, highly focussed radiotherapy should be considered. Primary chemotherapy may be an additional option. Children receiving chemotherapy for an isolated optic nerve glioma will not be eligible for randomization, yet.

F. Treatment recommendations following tumor progression

Despite all efforts to prevent tumor progression by primary therapy, a significant number of children will suffer from progression during or after first line therapy. Thus, the treatment strategy for low-grade gliomas has to incorporate recommendations for second (and third) line treatment approaches. In each case the possibilities for a meaningful surgical intervention should be checked, as well.

I. Progression during chemotherapy (early progression) in a young child (< 8 years)
Chemotherapy in these children is started to postpone radiotherapy. So, if PD occurs at the first evaluation at week 24 or later during consolidation and the child is still young, it is recommended that therapy be continued with the alternative chemotherapy regimen as in the case of Carboplatin allergy (section 14.1.3.). The two drug combinations of Cis-Platin/Vincristin and Cyclophosphmid/Vincristin are expected to offer an effective treatment.

II. Progression during chemotherapy (early progression) in an older child (≥ 8 years)
In case of progression at the first evaluation at week 24 or later during consolidation in a child older than 8 years, it should be assessed, if radiotherapy can be applied as second line therapy. If radiotherapy is no option, the alternative chemotherapy regimen (14.1.3.) should be used.

III. Progression following the end of chemotherapy
For children, who experience tumor progression following the end of therapy, several points have to be considered:

- age: Children still in the young age group, in whom radiotherapy should be further postponed, should receive second line chemotherapy.
  Children still in the young age group, in whom highly focussed radiotherapy appears possible, can go on to receive radiotherapy.
  Children in the older age group receive radiotherapy as second line therapy.
- time since the end of chemotherapy: If the first chemotherapy has been completed for more than a year, and the child has not had Carboplatin allergy, restart of standard Carboplatin/Vincristin chemotherapy may be taken into account. The alternative chemotherapy (14.1.3.) can be used as well.
  If the intervall between the end of first chemotherapy is shorter than a year and/or the child has had Carboplatin allergy, the use of the alternative regimen (14.1.3.) is recommended. The national chairman should be contacted to plan details for the "induction" phase.
- previous allergy: If first line chemotherapy has already been complicated by Carboplatin allergy and the alternative drug combinations thus have already been applied and second line chemotherapy is indicated, it is recommended to contact the national chairman for the investigation of Phase II-treatment protocols. A trial with Vinblastin will be offered by the Phase II coordinators of the study.

IV. Progression following radiotherapy

For all children, who have received radiotherapy as their first treatment, chemotherapy is the first option in case of tumor progression. They will not be randomized and receive standard induction and consolidation with Vincristin and Carboplatin.

12.3. Study overview: Children affected by NF I (NF I+ve) with low grade glioma of all sites. SIOP LGG 2004

Within this trial all children affected by NF I and necessitating non-surgical therapy will receive the historical, but extended regimen with Vincristin / Carboplatin, regardless of their age at presentation. They should not be irradiated unless chemotherapy and surgery options have failed.

Preconditions to be stratified into this patient group:

Tumor location: All tumor locations

Histology: Low grade glioma according to section 9.
Histologic diagnosis is primarily made by the local pathologist, yet central pathologic review is strongly recommended.

Alternatively:

Clinical diagnosis: Neuroradiologic criteria for tumors of the optic pathways/chiasmatic-hypothalamic region fulfilled according to section 8.5.
Neuroradiologic criteria have to be fulfilled for all children not biopsied and central neuroradiologic review has to be obtained.

Surgery: Any extent of primary surgery

Neurofibromatosis I: present.

It should be noted that in very young children the signs of NF I may not be apparent and it is necessary in patients with tumors compatible with Neurofibromatosis that the patient is repeatedly re-evaluated in the first five to seven years of life for signs of emerging criteria (careful examination of skin is recommended).
Standard reassessment will be requested during follow-up at the age of six years.

Diagnosis of NF I
Diagnostic criteria for NF I are met in an individual, if two or more of the following are found (Definition of neurofibromatosis by NIH consensus statement 1988, Listernick 1997):

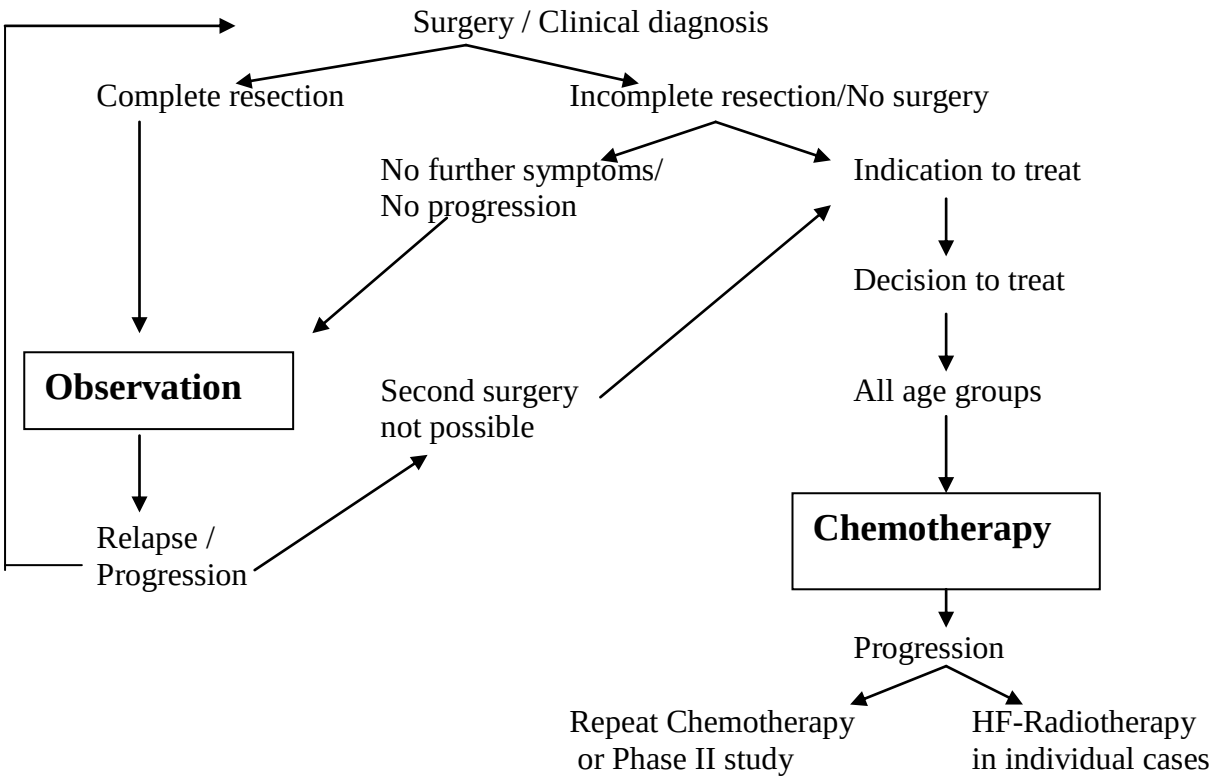
- Six or more café-au-lait macules of over 5 mm in greatest diameter in pre-pubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals.
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal region.
- Optic pathways glioma
- Two or more Lisch nodules (Iris hamartoma) (Lisch 1937, Lubs 1991)
- Distinctive osseous lesion such as sphenoid dysplasia or thinning of the long bony cortex with or without pseudarthrosis
- A first degree relative (parent, sibling or off-spring) with NF I by the above criteria

Metachronous tumors – Patients with NF I are at risk to develop multiple (brain) tumors, especially if they presented with optic pathway glioma (Friedman 1997). Such metachronous

tumors have to be distinguished from secondary dissemination of a LGG. Thus, these tumors have an indication to therapy on their own. Contact with the national study chairman is recommeded.

Age eligibility: For patients with Neurofibromatosis age should not be used as a criteria for primary treatment stratification, since the restrictions for the use of primary radiotherapy apply to all ages.

Treatment strategy for children affected by NF I (NF I+ve) with low grade gliomas of all sites:



HF: highly focussed.

Treatment modalities:

A. Surgery

I. Surgery at diagnosis
The extent of surgical removal has to be discussed in view of tumor location and local or distant tumor extension and the risk of neurologic sequelae.

II. Second surgery
If there is the chance for a more complete tumor resection following primary tumor resection, or during observation or during the course of non-surgical therapy, this possibility should be discussed within the local treatment team, with the national study chairman and/or with the reference surgeon. Although tumor resections are recommended, the child should never be endangered by surgical intervention or suffer from additional severe neurologic impairment postoperatively.

B. Chemotherapy

Children, for whom there is an indication to be treated by chemotherapy and for whom the decision has been made to actually start treatment, shall receive standard induction and consolidation treatment with Vincristin and Carboplatin:

> **Note:** Neuroimaging should be obtained prior to start of therapy at an interval less than 4 weeks !

I. Standard Induction:
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg, dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

II. Consolidation
All children will receive consolidation therapy up to week 81 with ten 6-week cycles of Vincristin and Carboplatin. Cycles start in week 25, 31, 37, 43, 49, 55, 61, 67, 73 and 79.
Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each cycle (maximum single dose: 2 mg; dose for children < 10 kg body weight: 0,05 mg/kg/day).
Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of each cycle (dose for children < 10 kg body weight: 18,3 mg/kg/day).

III. Allergy
In case of Carboplatin allergy in children with NF I, the individual strategy for continuation of chemotherapy should be discussed with the national study chairman. Reasons that have substantiated the “chemotherapy only” strategy without randomisation of VP 16 still apply, so the choice of alternative chemotherapy should be cautiously made.

IV. Progression
If, during or after first line chemotherapy, the tumor progresses or if disseminated disease develops during or after chemotherapy and the patient is still in the young age category, consideration should be given to entering the patient into a phase II trial of novel agents or the use of alternative chemotherapy strategies from the published literature.

C. Radiotherapy

Note: The use of radiotherapy in NF I+ve patients is associated with increased risk of involved field short term and long term toxicity. If radiotherapy is considered, e.g. in older children with progression following chemotherapy, external beam radiotherapy will be applied with 54 Gy tumor dose conventionally fractionated at 1,8 Gy given on five days per week. The specific aims of the radiotherapy study are a maximal sparing of organs at risk by applying highly focussed radiotherapy with modern planning and technical equipment.

In case, that it is unavoidable to give radiotherapy to younger children, it is recommended to contact the national study chairmen for radiotherapy details.

D. Pure Optic Nerve Glioma

Where there is symptomatic or progressive tumor associated with demonstrable visual deterioration, and there is a strong need to initiate treatment to control symptoms and attempt to preserve vision, highly focussed radiotherapy or primary chemotherapy should be considered.

E. Treatment recommendations following tumor progression

Despite all efforts to prevent tumor progression by primary therapy, a significant number of children will suffer from progression during or after first line therapy. Thus, the treatment strategy for low-grade gliomas in children with NF I has to incorporate recommendations for second (and third) line treatment approaches. In each case the possibilities for a meaningful surgical intervention should be checked, as well.

Chemotherapy in these children is started to avoid or at least postpone radiotherapy. So, if PD occurs at the first evaluation at week 24 or later during consolidation or after the end of therapy, it is recommended that therapy be continued/restarted as chemotherapy either with the alternative chemotherapy regimen as in the case of Carboplatin allergy (section 14.1.3.) or with a Phase II-therapy. A trial with Vinblastin will be offered by the Phase II coordinators of the study.

If first line chemotherapy has already been complicated by Carboplatin allergy and the alternative drug combinations thus have already been applied and second line chemotherapy is indicated, it is recommended to contact the national chairman for the investigation of Phase II-treatment protocols.
If radiotherapy seems appropriate for older children, techniques of highly focussed irradiation should be used.

12.4. Study overview: SIOP LGG 2004 Disseminated low grade glioma

Multicentric manifestation of low grade glioma is not infrequent at diagnosis or later during follow-up. All age groups are affected, but nearly one third of the patients is even younger than 1 year. Children with NF I do not seem to be affected, but may present metachronous primary tumors. Pilocytic astrocytomas (PA) with a primary tumor in the chiasmatic-hypothalamic region dominate. The slow-growing potential of PA probably persists even with multicentric spread.
For the purpose of this protocol this variant will be termed disseminated low grade glioma and the diagnosis be based upon MRI criteria and cytology (see 8.5. and 16.1.).
Routine spinal staging procedures are recommended in case of multifocal intracranial tumors, or cervical lesions found on cranial MRI or symptoms relating to spinal metastases.

Patients will be included into strategic group 1, 2 or 3 according to location of the primary tumor and absence or presence of NF I. They will be included in the analysis of the respective groups.

Tumor location: All primary tumor locations

Histology: Low grade glioma according to section 9.1.
Histologic diagnosis is primarily made by the local pathologist, yet central pathologic review is strongly recommended.

Alternatively:

Clinical diagnosis: Neuroradiologic criteria for tumors of the optic pathways/chiasmatic-hypothalamic region fulfilled according to section 8.5.
Neuroradiologic criteria have to be fulfilled for all children not biopsied and central neuroradiologic review has to be obtained.

Surgery: Any extent of primary surgery

Staging: Dissemination according to section 8.5. and 16.1.

Neurofibromatosis I: absent or present, although no dissemination has been reported in NF I patients in SIOP-LGG 1.

It should be noted that in very young children the signs of NF I may not be apparent and it is necessary in patients with tumors compatible with Neurofibromatosis that the patient is repeatedly re-evaluated in the first five to seven years of life for signs of emerging criteria.
Standard reassessment will be requested during follow-up at the age of six years.

Treatment strategy

A. Surgery
If possible, singular lesions should be removed surgically, however: multplicity of deposits or the presence of leptomeningeal lining will limit this approach.

Biopsy of disseminated lesions is encouraged however, especially to investigate histopathologic parameters, which might be associated with leptomeningeal seeding.

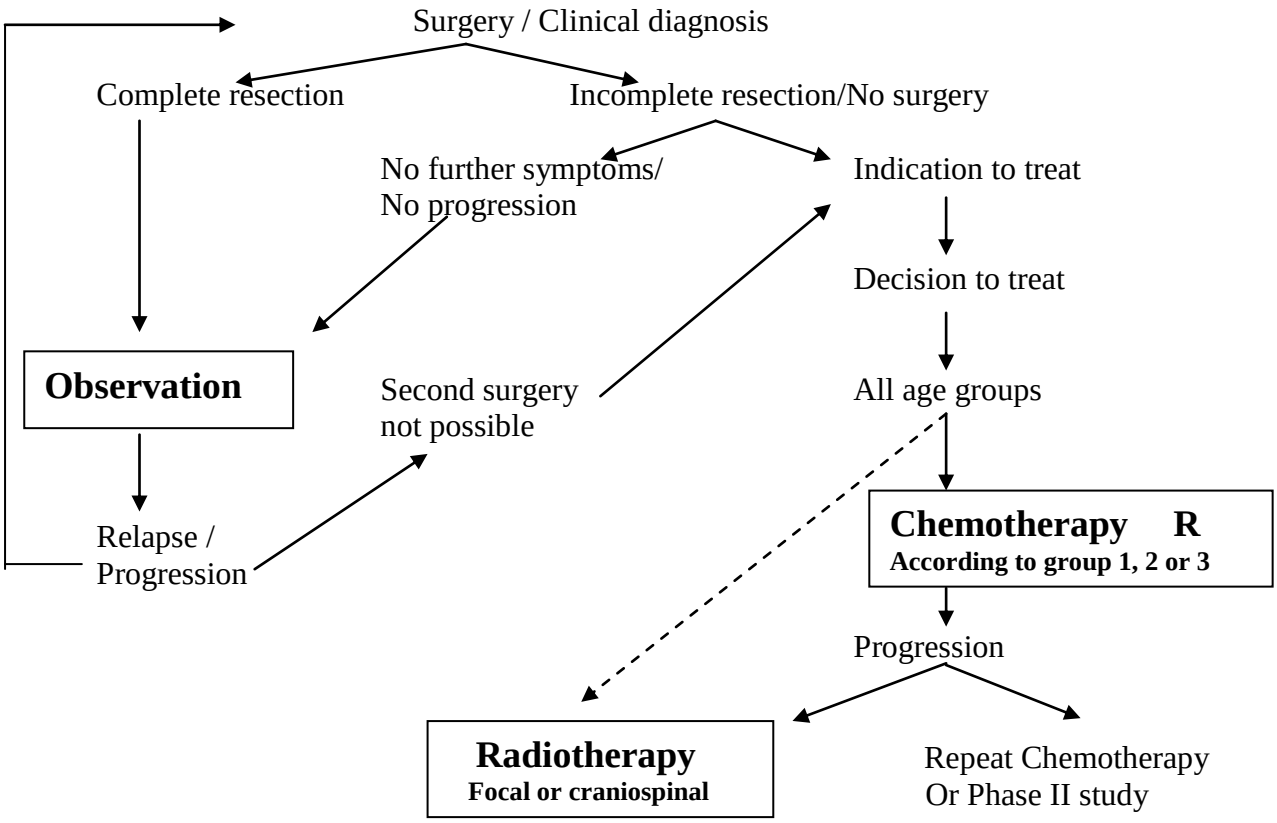
B. Non-surgical therapy

The question whether to proceed with radiotherapy or chemotherapy currently remains open and must consider the age of the patient, whether the patient has undergone radiotherapy for the primary tumor, and if so, the interval since the previous irradiation.
The presence of symptomatic multicentric disease at diagnosis or the emergence of multifocal tumors or their progression is considered to be an indication for non-surgical therapy (section 10.).

- Treatment with Vincristin and Carboplatin as scheduled within the SIOP - LGG 1996 protocol achieved response rates and progression free survival comparable to the sum of previous literature experiences. Considering the age of most patients primary chemotherapy for disseminated tumors along the principles applied to all other LGG is recommended.
  Prolonging therapy will probably prevent early progression, the effect of intensifying induction has to be investigated.

- In case of tumor progression following chemotherapy radiotherapy should be considered. Focal radiotherapy follows general guidelines. The concept of cranio-spinal irradiation for selected cases will be investigated. Doses and fractionation are detailed in section 15.

Treatment strategy for children affected by disseminated low grade gliomas:



R: Randomisation of induction in treatment group 1 and 2.

13. Surgical guidelines SIOP LGG 2004

It is beyond the scope of this chapter to provide a comprehensive description of surgical approaches for low grade gliomas in different areas of the brain and spinal cord.

Treatment of low grade gliomas in different areas of the child's brain with different biological characteristics is still a challenging task for both: the neurosurgeon and the oncologist. With todays knowledge some guidelines can be established for treatment approaches. Nevertheless there still remain some surgical strategies based on individual decision. However, some recommendations may be useful to define the role of surgery within the treatment concept.

From the oncological point of view the strong association between the extent of resection and progression free survival favors radical surgery, at least for hemispheric, cerebellar and intramedullary tumors (section 3.2.). But, a number of low grade gliomas, like dysembryoplastic neuroepithelial tumors and gangliogliomas, remain quiescent even after incomplete resection. The striking difference in overall outcome between children and adults with low grade gliomas probably results from biologic differences, not well understood yet. Thus the more favorable outcome of children may be due to biological characteristics rather than to aggressive surgical interventions.

Recommended considerations:

1. During the surgical procedure tumor tissue should be sampled not only for conventional histology, but for the tumot tissue bank for future biologic investigations as well (see section 8.3. and details according to national procedures in the addendum 21.10.).

2. Early postoperative imaging is important to determine the extent of resection and has to be secured by the oncological team (see section 8.5. and 16.2.).

3. If postoperative imaging discloses that a potentially resectable lesion has been incompletely removed, second surgery has to be considered for gross total removal before proceeding with any adjunctive therapy.

4. To reduce surgical morbidity the use of technical adjuncts, like intraoperative ultrasound, frameless stereotaxy and neurophysiological methods, which facilitate tumor localization and intraoperative management, is strongly recommended.

13.1. Low grade glioma of the supratentorial midline in children not affected by Neurofibromatosis NF I (NF I-ve)

Management for tumors of these locations still is controversial, but the surgical procedure is determined by the answers to the following questions:

1. Can the tumor be classified by neuroradiological criteria with respect to location (located within the visual pathways) and thus to the possible low grade histology (no unusual findings pointing towards a tumor of higher malignancy) ?
2. Is the tumor potentially resectable without deterioration of the clinical symptoms and without inacceptable late effects ?

3. Is the space-occupying effects mainly determined by a cystic part of the tumor ?
4. Is the interruption of the circulation of cerebrospinal fluid due to the mass effect of the tumor ?

With regard to the location of the main tumor bulk and its potential origin this group of tumors will be divided into tumors originating within the visual pathways and tumors of the hypothalamus, basal ganglia and thalamus.

Tumors of the visual pathways
Extensive resection of optic pathway gliomas are burdened with substantial surgical morbidity with respect to vision and endocrine deficits and severe hypothalamic disturbance. Indications to perform surgery in this group of tumors may be

- to verify a low grade glioma histologically in cases not allowing a definite neuroradiological classification prior to the start of non-surgical therapy. Especially germinoma, Langerhans-cell histiocytosis and craniopharyngioma, but other histologies as well have to be excluded.
- to perform a primary partial resection in cases with a symptomatic exophytic portion of the tumor, which often is partially cystic, with mass effect and hydrocephalus: e.g. from the 3rd ventricle in case of hydrocephalus or from the temporal lobe in case of epilepsy.
- to perform a secondary partial resection or a biopsy upon progression during or following chemotherapy or before radiotherapy.

Tumors restricted to the optic nerve (anterior, intraorbital portion)
Resection of unilateral optic nerve glioma should only be performed in the presence of a blind eye and progressive exophthalmus. Otherwise a cautious wait-and-see policy should be followed and non-surgical options be preferred.

Tumors of the hypothalamus, basal ganglia, thalamus and mesencephalon
In case of a radiologically circumscribed tumor there is a definite indication to perform primary surgery. However, limiting factors for the extent of resection are a bilateral extension of hypothalamic tumors, the localization of a thalamic tumor within the dominant hemisphere or bithalamic involvement. In these cases only a biopsy or limited partial resection are feasable.
Focal tumors of the mesencephalon are often resectable, at least subtotally.
In tectal gliomas of typical radiologic appearance presenting with hydrocephalus due to stenosis of the aqueduct a third ventriculostomy should be performed as primary intervention. An attempt of tumor resection in typical tectal glioma is not indicated. However, if other mesencephalic tumors show progression during radiologic follow-up, histologic verification of a low grade glioma before non-surgical therapy is strongly recommended.

13.2. Low grade glioma of the all other sites in children not affected by Neurofibromatosis NF I (NF I-ve)

The resectability of low grade gliomas of the cerebral hemispheres, the cerebellum, the caudal brain stem and the spinal cord is determined by the exact location and the radiological growth characteristics (diffuse versus focal). For well circumscribed lesions a gross total resection should be the operative goal, if it can be achieved without major risk. Conversely, if following information from imaging, history and symptoms the differential diagnoses include the presence of a lesion not necessitating radical excision, primary stereotactic biopsy may be indicated to verify the histologic nature of the process.

Cortical and subcortical hemispheric tumors
In these locations primary complete surgery should be the goal. Pre- and intraoperative definition of functionally important cortical regions and subcortical tracts should be integral part of the planning procedure.

Deep hemspheric tumors extending towards the basal ganglia
The potential resectability depends upon the extension into adjacing tracts.

Cerebellar tumors
Complete resection is the goal of primary surgery, which, however, may not always be possible in lesions extending into the brain stem and the cerebellar peduncles.
Besides well known coordinative and motor tasks, the cerebellum actively contributes towards high mental function by processing cognitive and linguistic or emotional and social behavior. Surgical approaches to cerebellar tumors should take these facts into account, as well.

Tumors of the caudal brain stem
MR-classification has subdivided tumors of the brain stem into diffuse, focal, exophytic and cervico-medullary brain-stem gliomas. Complete resection should be discussed for focal lesions which may be reached without inacceptable morbidity.
- Focal tumors of the pons are rarely surgically accessible without severe surgical morbidity.
- Dorsally-exophytic lesions are focal tumors typically growing out of the medulla oblongata, extending into the cavity of the 4th ventricle, from where they can be resected.
- In non-exophytic, focal tumors of the medulla oblongata avoidance of permanent functional impairment has absolute priority. Even modern neurophysiologic monitoring during the surgical procedure cannot assure functional integrity in an attempted radical excision.
- Dorsally exophytic tumors of the cervico-medullary junction can often undergo gross total resection with excellent long-term prognosis even concerning morbidity.

Diffuse, intrinsic brain-stem gliomas are “non-surgical” tumors, in case of typical MRI-morphology there is no need for a biopsy. Since these tumors are considered of high-grade malignancy regardless of the exact histologic diagnosis, children and adolescents with such tumors are excluded from the protocol (see section 9.2.).

Spinal tumors
The majority of spinal intramedullary tumors in children are low grade gliomas. In the presence of focal tumors an attempt of radical resection may be performed. Multilevel laminotomy is needed for some of these extended tumors to avoid postoperative severe kypho-skoliosis. Intra-operative electrophysiological monitoring and ultrasonic aspiration of intramedullary tumors should be employed to reduce surgical morbidity.

13.3. Low grade glioma of any location in patients affected by Neurofibromatosis NF I (NF I+ve)

Considering the possible diagnostic categories for tumors in various locations the following recommendations can be made:

Visual pathway gliomas
There is no indication for a biopsy in lesions restricted to the visual pathways. Surgical resection has to be considered with even more reserve than in children without NF I, except in rare cases with space occupying lesions.

Tumors restricted to the optic nerve (anterior, intraorbital portion)
Resection of unilateral optic nerve glioma should only be performed in the presence of a blind eye and progressive exophthalmus. Otherwise a cautious wait-and-see policy should be followed and non-surgical options be preferred. Since an optic nerve glioma in a NF I patient may only be the initial manifestation of a more extensive involvement of the visual pathwas, resection may not prevent progression.

Tumors of all other locations
In case of primary contrast enhancing lesions of any other location, resection should be envisaged for all resectable or potentially life-endangering lesions, e.g. of the Foramina Monroi. Since outside the visual pathways children with NF I may develop tumors of all possible histologies, biopsy or resection have to be performed prior to the start of any non-surgical therapy.

In lesions without contrast enhancement radiological observation is recommended and surgical intervention (biopsy) should only be performed in case of unequivocal progression (MRI and/or MR-spectroscopy).

14. Chemotherapy SIOP - LGG 2004

14.1. Chemotherapy guidelines

14.1.1. Induction
- 14.1.1.1. Induction I.: Vincristin / Carboplatin
- 14.1.1.2. Induction II.: Vincristin / Carboplatin / VP 16

14.1.2. Consolidation: Vincristin / Carboplatin

14.1.3. Consolidation following allergy or early progression

14.1.4. Cumulative drug doses

14.2. Drug information

14.2.1. General guidelines for dosing and application of cytostatic drugs

14.2.2. Effects and side effects of cytostatic drugs, used in this protocol

14.2.3. Toxicity and dose modifications

14.2.4. Specific Organ Toxicities

14.2.5. Allergy to Carboplatin

14.3. Supportive care

14.1. Chemotherapy - Guidelines

- For all children chemotherapy consists of an **induction period** with a more compact schedule **from week 1 to 10** and a less compact phase **from week 13 to 21** and a prolonged **consolidation** therapy starting at **week 25 up to week 81**.
- Due to the facts that tumor response to chemotherapy occurs at a slow pace in low grade glioma with a median time to best response of 5,1 months (range: 0,9 - 25,3 months) in the previous study, determined for a cohort of 84 German patients (Gnekow 2000), and that objective tumor regression occurs even after an initial, often cystic, clinically asymptomatic tumor enlargement, the relevant **response assessment to induction therapy is timed at week 24**.

Week:	1 to 10 Induction	+	13 to 21	*24 Response assessment*	25 to 81 Consolidation

- Induction therapy is randomized between Vincristin / Carboplatin and Vincristin / Carboplatin / VP 16:

Group 1: children unaffected by NF I with low grade glioma of the supratentorial midline (see 12.1.).
Group 2: Children unaffected by NF I with low grade cortical, cerebellar, brain stem and spinal glioma (see 12.2.).

- **Group 3**: Children affected by NF I with low grade glioma of all sites.

All children with NF I receiving chemotherapy will not be randomized and are to be treated with Vincristin / Carboplatin chemotherapy for induction (Induction I) and consolidation.

- **Disseminated low grade glioma**: Children with DLGG are part of one of the three treatment groups according to the location of the main/primary tumor and the absence or presence of NF I.

14.1.1 Induction therapy

14.1.1.1. Induction Therapy I - Vincristin / Carboplatin

Standard induction consists of Vincristin weekly and Carboplatin three-weekly for ten weeks as in the previous SIOP-trial. Following the 10 week-induction treatment the combination of Vincristin and Carboplatin is given three times at four week intervals to allow for recovery from hematologic and/or neurologic side effects of the induction phase.
Patient's clinical status evaluation (section 8.3.) should be performed regularly. Tumor status evaluation can be done upon individual decision at week 11 to 12, but moderate increments of the tumor dimension especially with regard to tumor cysts can be observed during the first weeks of therapy. Treatment response evaluation by neuroimaging has to be performed at week 24, deciding on the final response to this initial part of therapy and consequently on the subsequent treatment.

Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg, dose for children < 10 kg body weight: 0,05 mg/kg/day).

Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

1	2	3	4	5	6	7	8	9	10		13	17	21		24	week
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**			
C			**C**			**C**			**C**		**C**	**C**	**C**			
															MRI	

V	**Vincristin**	1,5 mg/m² (max. 2 mg)	iv-bolus - d 1
C	**Carboplatin**	550 mg/m²	1h infusion - d 1
MRI	**Neuroradiologic assessment of response by MRI**		

14.1.1.2. Induction Therapy II - Vincristin / Carboplatin / VP 16

Intensified induction consists of Vincristin weekly and Carboplatin three-weekly for ten weeks as in the previous SIOP-trial. Additionally VP 16 is given on day 1 to 3 of week 1, 4, 7 and 10 following the application of Carboplatin (d1 only). Following the 10 week-induction treatment the combination of Vincristin and Carboplatin is given three times at four week intervals to allow for recovery from hematologic and/or neurologic side effects of the induction phase.
Patient's clinical status evaluation (section 8.3.) should be performed regularly. Tumor status evaluation can be done upon individual decision at week 11 to 12, but moderate increments of the tumor dimension especially with regard to tumor cysts can be observed during the first weeks of therapy. Treatment response evaluation by neuroimaging has to be performed at week 24, deciding on the final response to this initial part of therapy and consequently on the subsequent treatment.

Vincristin is given once weekly as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 and then week 13, 17 and 21.
(maximum single dose: 2 mg, dose for children < 10 kg body weight: 0,05 mg/kg/day).

Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 1, 4, 7 and 10, and then week 13, 17 and 21 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

Etoposide is given as an intravenous 1-hour infusion at a dose of 100 mg/m²/day on day 1 to 3 of week 1, 4, 7 and 10 (no dose adaptation for children < 10 kg body weight).

1	2	3	4	5	6	7	8	9	10		13	17	21		24	week
V	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**	**V**		**V**	**V**	**V**			
C			**C**			**C**			**C**		**C**	**C**	**C**			
Ex3			**Ex3**			**Ex3**			**Ex3**							
															MRI	

V	**Vincristin**	1,5 mg/m² (max. 2 mg)	iv-bolus - d 1
C	**Carboplatin**	550 mg/m²	1h infusion - d 1
E	**Etoposide**	100 mg/m²	1h infusion - d 1 - 3
MRI	**Neuroradiologic assessment of response by MRI**		

14.1.2. Consolidation Therapy

As in the study SIOP/GPOH LGG 1996 consolidation is achieved by the continuous, simultaneous application of Vincristin and Carboplatin. However, treatment is prolonged up to week 81 by extending treatment intervals to 6 weeks, and Vincristin is given at a more intense schedule on day 1, 8 and 15 of each cycle.

Vincristin is given as an iv-bolus at a dose of 1,5 mg/m²/day on day 1 of week 25 to 27, 31 to 33, 37 to 39, 43 to 45, 49 to 51, 55 to 57, 61 to 63, 67 to 69, 73 to 75 and 79 to 81. (maximum single dose: 2 mg, dose for children < 10 kg body weight: 0,05 mg/kg/day).

Carboplatin is given as an intravenous 1-hour-infusion at a dose of 550 mg/m²/day on day 1 of week 25, 31, 37, 43, 49, 55, 61, 67, 73 and 79 (dose for children < 10 kg body weight: 18,3 mg/kg/day).

25	31	37	43	49	54	week
55	61	67	73	79	85	
VVV	**VVV**	**VVV**	**VVV**	**VVV**		
C	**C**	**C**	**C**	**C**		
					MRI	

V	**Vincristine**	1,5 mg/m² (max. 2mg)	iv-bolus d1, 8, 15 of each 6 week cycle
C	**Carboplatin**	550 mg/m²	1h infusion d1 of each 6 week cycle
MRI	**Neuroradiological assessment of tumor size / response**		

14.1.3. Consolidation therapy following allergy or early progression

Due to its allergic potential prolonged treatment with Carboplatin may not be possible. Since on the other hand, an extended treatment period may carry the potential for an extended progression free interval total treatment time shall be maintained, thus avoiding the necessity for early radiation. Alternative chemotherapy combinations shall be tested within such a continuation schedule. The drug-combinations have been studied for low grade glioma in various previous protocols (section 3).

The two combinations shall be given to a maximum of 5 times, to limit cumulative doses.
Vincristin is given as an iv-bolus at a dose of 1,5 mg/m²/day on day 1, 8 and 15 of each 6 week cycle starting with the first cycle post manifestation of allergy (i.e. weeks 1, 7, 13, 19, 25, 31, 37, 43, 49, and 55)
(maximum single dose: 2 mg, dose for children < 10 kg body weight: 0,05 mg/kg/day).

Cisplatin is given as an intravenous 3-hour-infusion at a dose of 30 mg/m²/day on day 1 and 2 of week 7, 19, 31, 43 and 55 (dose for children < 10 kg body weight: 1 mg/kg/day).

Cyclophosphamide is given as an intravenous 1-hour infusion at a dose of 1500 mg/m²/day on day 1 of week 1, 13, 25, 37 and 49 (dose for children < 10 kg body weight: 50 mg/kg/day).

Week post manifestation of allergy or early progression (maximum 5 cycles each):

1	7	13	19	25	31	37	43	49	55
VVV	**VVV**	**VVV**	**VVV**	**VVV**	**VVV**	**VVV**	**VVV**	**VVV**	**VVV**
Cyc	**Cisx2**	**Cyc**	**Cisx2**	**Cyc**	**Cisx2**	**Cyc**	**Cisx2**	**Cyc**	**Cisx2**

V: **Vincristine**	1,5 mg/m² (max 2 mg)	iv-bolus	d1, 8, 15 of each 6 week cycle
Cis: Cisplatin	30 mg/m²	3h infusion	d1 and 2 of each cycle
Cyc: Cyclophosphamide	1500 mg/m²	1h infusion	d1 of each cycle

14.1.4. Cumulative drug doses

Projected cumulative drug doses/m² for the entire length of chemotherapy are listed with respect to the different induction and consolidation regimens.

	Induction I	**II**	**Post-Allergy Induction I**	**II**
Vincristine (1,5 mg/m² iv)	64,5 mg	64,5 mg	64,5 mg	64,5 mg
Carboplatin (550 mg/m²/1h iv)	9350 mg	9350 mg	variable	variable
Etoposide (100 mg/m²/1h iv d1-3)	0 mg	1200 mg	0 mg	1200 mg
Cisplatin (30 mg/m²/3h iv d1+2)	0 mg	0 mg	300 mg maximum	300 mg maximum
Cyclophosphamide (1500 mg/m²/1h iv d1)	0 mg	0 mg	7500 mg maximum	7500 mg maximum

14.2. Drug Information

This section lists the most relevant drug actions and side effects, information for application and supportive measures. Side effects are mentioned only as far as they can be expected at doses used in this protocol according to current knowledge.
These guidelines do not exempt the treating physician from his/her obligation to inform himself/herself about the latest experiences with the respective drugs by use of the most recent publications and the information material provided by the drug companies, especially concerning the range of possible drug interactions.
The basic recommendations for the application of chemotherapy within the setting of this study may differ from local procedures. It is acknowledged that locally standardised procedures for the combination therapy of this protocol exist to which the details of this protocol may be adopted.

14.2.1. General guidelines for dosing and application of cytostatic drugs.

Despite the fact that chemotherapy within this protocol is designed primarily to postpone the early use of radiotherapy, its use for young children and for children with NF I has a profound impact upon their general prognosis. Especially those with diencephalic syndrome most often present as severely ill children. Thus, the intensity of this protocol is justified, but requires a responsible monitoring to avoid an inadequte amount of side effects.
On the other hand: indiscriminate dose reduction and unnecessary delay of chemotherapy has to be avoided. Each patient should receive the maximum recommended and tolerable dose of drugs at the appropriate time.

Dose modifications

I. by age and weight:
No randomised studies have been conducted to assess the relevance of dose adaptions for infants. Yet, it is considered appropriate that infants with a body weight below 10 kg should receive drug doses based upon body weight with a calculation of 1 m² body surface area equalling 30 kg:

Carboplatin	18,3	mg/kg
Vincristine	0,05	mg/kg
Cisplatin	1,0	mg/kg
Cyclophosphamide	50,0	mg/kg

For children below the age of 6 months further dose reduction of 1/3 is recommended. In case they do not experience relevant toxicity, dose adaption to dose/kg body weight can be considered.
Pharmacologic data for Etoposide have been explored demonstrating that drug reduction for young children above the age of 3 months even when weighing less than 10 kg are not necessary, so dosing as per m² of body surface area is safe (Boos 1992 and 1995).

Note: Infants are at a higher risk of Cis-Platin induced electrolyte imbalances and consequently regular electrolyte monitoring is particularly important in this age group. Correspondingly, the amount of hydration fluid has to be adjusted according to infants' weight and age.

II. by toxicity

The NCI Expanded Common Toxicity Criteria will be used for purposes of grading of toxicity (see Appendix 21.11.). Reqirements for starting therapy at normal dose and schedule are given for each drug below as well as dose modifications according to the extent of toxicity (section 14.2.3.). Yet recommendations within this protocol do not substitute for the responsibility of each treating physician to decide for each individual patient on site.
The national study chairman has to be contacted for any life threatening, lethal unexspected or unusual toxicity within 24 hours (For definition see section 16.4., report form in Addendum 21.12.).

Treatment intervals

Within the protocol treatment intervals lengthen gradually. They should therefore be maintained, if no undue toxicity intervenes. Postponing an element for 1 week is possible without modification. If intercurrent complications necessitate deferral for more than 2 weeks, dose reductions should be foretaken. In case of unexspected toxicity the national study center should be contacted.

Requirements to start therapy

- All elements: υStable general condition.
  (exception: infants with diencephalic syndrome may be treated initially despite poor general condition, since only chemotherapy offers the chance to ameliorate their status.)
  υChildren with a body weight less than or equal to the 3rd percentile at the time of starting therapy must have adequate enteral or parenteral nutrition.
  υNo significant infection.

- Carboplatin: No allergy to Carboplatin ≥ grade 2 (alternatives: section 14.2.5.)
  Leucocytes >2,0/nl, Neutrophils >0,5/nl
  Thrombocytes >100/nl (rising)
  No hearing loss above 10-20 dB within the frequency range of 1-4 kHz.
  Normal renal function, nephrotoxicity not >grade 1.

- Cisplatin: Leucocytes >2,0/nl, Neutrophils >0,5/nl.
  Thrombocytes > 80/nl (rising)
  Ototoxicity not above grade 2
  Nephrotoxicity not >grade 1, Kreatinin-clearance not < 70 ml/min/1,73m²
  Peripheral neuropathy not >grade 2.

- Cyclophosphamide: Leucocytes >2,0/nl, Neutrophils >0,5/nl
  Thrombocytes >80/nl (rising)
  Nephrotoxicity not >grade 1

- Etoposide: Parameters of blood count as for Carboplatin.

- Vincristine: Peripheral neuropathy ≤ grade 2.

14.2.2. Effects and side effects of the cytostatic drugs, used in this protocol

Carboplatin (C)

Non-classical alkylating agent, impairment of DNA-synthesis by intra-strand and inter-strand bridging. Reacts as well with RNA, proteins and cell membranes.

Dose: 550 mg/m²/day as a 1 hour infusion
(dose for children < 10 kg body weight: 18,3 mg/kg/day).

Application:
- intravenous infusion in 200 ml Glucose 5 %/ m² for 1 hour
- a concommitant hydration pre- and postinfusion of the drug with 2000 3000 ml/m²/24 h is recommended with regard to the individual patient and allows to record the development of allergic reactions during the hospital stay
- sufficient hydration with careful monitoring of electrolytes, body weight and urine output is essential in infants with diencephalic syndrome
- sufficient antiemetic coverage

Side effects:
Dose dependent, cumulative myelosuppression with a nadir between day 15 to 21 (Thrombocytopenia is more pronounced than Leucocytopenia)
Nausea, vomiting
Nephrotoxicity
Neurotoxicity
Ototoxicity
Allergy (see below)
Loss of Magnesium.

Interactions:
Dexamethasone probably inhibits the effect of Platinum compounds in glial cells.

Monitoring:
Severe nephrotoxicity has not been reported during Carboplatin-therapy. Yet, since elimination for the unmetabolised substance relies on glomerular filtration, renal function has to be monitored periodically (reduction of GFR to less than 50 % is less frequent than with Cisplatin). In case of a reduction in GFR the dose of Carboplatin can be calculated according to Calvert's formula: dose in mg = target AUC x (GFR+25). In most instances target AUC is 5-7 mg/ml/min (Calvert 1989).
Audiogramm
Blood count.
Substitution of Magnesium between treatments as with Cis-Platin.

Cisplatin (Cis)

Non-classical alkylating agent. DNA-cross-linkage and -point mutation, inhibition of DNA-repair, alkylation of RNA and proteins. Induction of apoptosis.

Dose: 30 mg/m²/day as 3 hour-infusion on day 1 and 2
(dose for children < 10 kg body weight: 1 mg/kg/day).

Application: ♦ Diuresis 3000 ml/m² from 6-12 hours before the first until 24 hours after the second dose of Cisplatin with adequate substitution of Mg and Ca
♦ Mannitol-bolus 40 ml/m² Mannit 20 % as a 10-15 min.-infusion before each dose of Cisplatin, parallel-infusion of Mannit 20 % 40 ml/m²/24 h to enforce adequate diuresis, avoid Furosemide
♦ Substitution of Magnesium 7 mg/kg/day p.o. for 2 to 4 weeks following Cisplatin
♦ sufficient antiemetic coverage

Side effects: Tubular-interstitial nephropathy
Neurotoxicity, especially irreversible high frequency auditory impairment, peripheral poly-neuropathy
Nausea, vomiting
Hypocalcemia, hypomagnesemia
Inappropriate secretion of ADH (SIADH)
Coombs-positive hemolytic anemia
Anaphylactic reactions.

Interaction: Synergistic cytotoxicity with Etoposide and other cytotoxic agents.
Dexamethasone probably inhibits the effect of Platinum compounds in glial cells.

Monitoring: Renal function
Audiogram
Neurologic status
Electrolyte (Mg, Ca)- and fluid- balance.

Cyclophosphamide (Cyc)

Alkylating agent, Oxazaphosphorin.
Cytotoxic during S-Phase of the cell cycle, liver metabolism to 4-OH-Cyclophosphamid, Phospharamidmustard and Acrolein (urotoxic), metabolites can form covalent bonds to DNA or proteins.

Dose: 1500 mg/m²/day as a 1 hour infusion in 0,9 % NaCl
(dose for children < 10 kg body weight: 50 mg/kg/day).

Application: ♦ Diuresis and prophylaxis of hemorrhagic cystitis: 3000 ml/m² for 24 h
♦ Mesna 500 mg/m² per dose iv., before and 4 and 8 hours after the start of the Cyclophosphamide infusion
♦ 6 hourly registration of fluid balance, Furosemide 0,5 mg/kg iv, if needed
♦ controlling for hematuria (every portion of urine), in case of positive analysis for erythrocytes or dysuria the development of hemorrhagic cystitis is possible: increase hydration, increased/prolonged application of Mesna and pain therapy
♦sufficient antiemetic coverage

Side effects: Myelosuppression (especially Granulocytopenia and Lymphopenia)

Hemorrhagic cystitis (Mesna !)
Renal water retention, tubular (Fanconi-syndrome) and glomerular nephropathy
Nausea, vomiting
Mucositis
Alopecia
Cytotoxic alveolitis
Cardiotoxicity
Changes of taste
Syndrome of inadequate secretion of ADH (SIADH)
Anaphylaxis, bronchospasm, dermatitis, Stevens-Johnson-syndrom,
Neurotoxicity
Liver toxicity.

As possible late effects infertility (disturbances of spermatogenesis and ovarian dysfunktion) and the development of secondary cancer (carcinogenic agent) have to be mentioned, but are unusual at low cumulative doses.

Interactions: Allopurinol, Cimetidin, Paracetamol, Barbiturates: increase of Cyc-effect and toxicity.
Amphotericin B: hypotension, bronchospasm
Insulin: increase of insulin-effect
Narcotics: increase of effect of narcotics.

Monitoring: Renal function.
Blood count.

Etoposide / VP 16 (E)

Epipodophyllotoxin
Inhibitor of the Topoisomerase II leading to single- and double strand DNA-breaks, reducing the capacity of DNA repair.

Dose: 100 mg/m²/d as a 1 hour infusion on day 1, 2, 3
(no dose adaption for children < 10 kg body weight)
Etoposide-phosphate can be given instead of Etoposide
(113,6 mg Etoposide phosphate equals 100 mg Etoposide).

Application : ♦ 1 hour infusion in normal saline (Na Cl 0,9 %) at a minimum dilution of 0,4 mg Etoposide/ml
♦ during and for 3 hours following the infusion the patient's blood pressure and heart rate should be monitored carefully
Decrease of the blood pressure and cardiac arhythmia can occur during VP 16 infusion. If this occurs, the infusion should be stopped and NaCl 0,9 % be given to restore normal blood pressure. Once symptoms resolve, the patient can be further challenged with VP 16 prolonging the infusion time
♦ sufficient antiemetic coverage

Side effects: Reversible bone marrow depression
Gastrointestinal: nausea and moderate vomiting

Mucositis,
Alopecia,
Rarely mild peripheral neuropathy
Rarely allergic reactions, blood pressure lowing in case of rapid infusion.
At high cumulative doses (above 5 g/m²) the risk for secondary myeloid leucemia is enhanced.

Interactions: Increased clearance at comedication with enzyme-inducing anticonvulsive drugs
Reduced clearance when given with high-dose Carboplatin.

Monitoring: Blood count
Integrity of mucous membranes
Blood pressure, monitoring for skin or respiratory signs of allergic reaction during infusion

Vincristine (VCR)

Vinca-alcaloid, extract from the evergreen Vinca rosea.
Blocking agent during M-phase of the cell cycle, inhibition of intracellular synthesis of tubulin. Disturbance of DNA and RNA-synthesis. Induction of apoptosis.

Dose: 1,5 mg/m²/day, maximum single dose: 2 mg,
(dose in case of body weight < 10 kg: 0,05 mg/kg/day)

Application:
- ♦ strictly intravenous bolus-injection, necrosis upon paravasation.
- ♦ ensure regular defecation.
- ♦ sufficient antiemetic coverage (if necessary)

Side effects: Peripheral neuropathy (reduction of peripheral tendon reflexes), paresis, myopathy, neuralgic pain, paralytic ileus, obstipation
Fever
Inadequate secretion of ADH (SIADH)
Cerebral convulsions
Myelosuppression
Alopecia
Cardiovascular disturbances
Photosensitation
Headache
Dysphagia, polyuria, dysuria
Dysfunction of cranial nerves, rarely atrophy of the optic nerve with amaurosis and transient cortical blindness.

Interactions (some are case reports only):
Cyclosporin A: increased neurotoxicity
Barbiturates: increased clearance of Vincristine
Histamin-2-antagonists: decelerated elimination of Vincristine
Itraconazol: increased polyneuropathy
Etoposide: synergistic effect, increased neurotoxicity (supposed)
Acetyldigoxin: reduced effect of Digoxin

Isoniazid: increased neurotixicity (single cases)
Metronidazol: increased neurotoxicity (case report)

Contraindication: Charcot-Marie-Tooth-syndrome.

Monitoring: Neurologic status (deep tendon reflexes, sensory neuropathy, bowel immotility).

14.2.3. Toxicity and dose modifications

Carboplatin:	Leucocytes <2,0/nl or Neutrophils <0,5/nl or Thrombocytes <100/nl at start of treatment	delay treatment for 1 week; if requirements are not met after 1 week delay: 25 % dose reduction for the next dose of Carboplatin.
	repeat sepsis during neutro-penia	25% dose reduction for the next dose of Carboplatin.
	progressive Ototoxicity at 1-4 kHz (> grade 2)	omit Carboplatin.
	Nephrotoxicity > grade 1	dose calculation according to the modified Calvert's formula
Cisplatin:	Leucocytes <2,0/nl or Neutrophils <0,5/nl or Thrombocytes <80/nl at start of treatment	delay treatment for 1 week; if requirements are not met after 1 week delay: 25 % dose reduction for the next dose of Cisplatin.
	Ototoxicity >grade 2 or Nephrotoxicity >grade 1 or Kreatinin-clearance: < 70 ml/min/1,73 m²	replace Cisplatin by Carboplatin
Cyclophosphamide:	Leucocytes <2,0/nl or Neutrophils <0,5/nl or Thrombocytes <80/nl at start of treatment	delay treatment for 1 week; if requirements are not met after 1 week delay: 25 % dose reduction for the next dose of Cyclophosphamide.
	Nephrotoxicity >grade 1	25 % dose reduction for the next dose of Cyclophosphamide.
Etoposide:	Hypotension	Prolong infusion time to 2-3 hours, Premedication with antihistamines.
Vincristine:	Peripheral neuropathy grade 3 or 4	omit the following dose/course of VCR; if neuropathy ameliorates resume therapy at 1,0 mg/m² VCR.

	Convulsions SIADH	omit the following dose/course of VCR, if no further convulsions or symptoms of SIADH occur, resume therapy at 1,0 mg/m² VCR (continuing any concurrent anticonvulsive treatment). If no further convulsions occur, following doses of VCR can be given according to schedule at 1,5 mg/m² (max. 2 mg)

Convulsions during chemotherapy generally need a diagnostic work-up including neuroimaging to rule out non-neurotoxic etiologies like bleeding or sinus vein thrombosis or tumor progression.

All drugs:	following severe neutropenia (ANC < 0,5/nl) associated with fever and sepsis or severe infection and/or severe thrompocytopenia (< 10/nl for > 5 days)	decrease dose 25 % for the next course consider G-CSF for acute severe infection, but routine G-CSF is not recommended (see 14.3.)

14.2.4. Specific Organ Toxicities

Ototoxicity – The grading system for hearing loss proposed by P.R. Brock et al (1991) will be used in SIOP/GPOH LGG 2004 (Table 28). Careful monitoring of children by an expert audiologist and by serial audiometry throughout the treatment with Carboplatin and Cisplatin is recommended. To monitor ototoxicity in infants oto-acoustic emissions, when available, are a preferable technique to BEAR (brainstem evoked auditory response). Pure tone audiometry is the method of choice in children older than 3 years of age. If a child starts to show signs of high frequency hearing loss then he/she should be followed more carefully than the minimum requirement of this protocol. If grade 3 or 4 ototoxicity is documented Cisplatin should be withdrawn and replaced by Carboplatin, but if hearing continues to deteriorate, Carboplatin should be omitted as well.

Grading system for Cisplatin-induced bilateral high-frequency hearing loss

Bilateral hearing loss	Grade	Designation
< 40 dB at all frequencies	0	None
> 40 dB at 8,000 Hz only	1	Mild
> 40 dB at 4,000 Hz only	2	Moderate
> 40 dB at 2,000 Hz only	3	Marked
> 40 dB at 1,000 Hz only	4	Severe

Renal toxicity

a) Glomerular toxicity – Nephrotoxicity of CDDP in children (as in adults) is dose-related and sometimes severe. Plasma creatinine measurements and creatinine clearances are not reliable guides to the degree of CDDP-induced renal damage, particularly in children. Careful measurement of Glomerular Filtration Rate (GFR) by isotope clearance is more accurate. DTPA and other scans are useful for national comparative studies, but for the purpose of this study GFR should be documented. It should not be done when a child is receiving iv.-hydration. The same technique for assessing GFR should be used at every time point in an individual child.
A standard endogenous creatinine clearance requires a 24 hr urine collection. If the urine collection is not complete, then please repeat it. Cr51 EDTA GFR is the preferred technique during CDDP treatment and involves obtaining the isotope, injecting it into the child and taking 4 blood samples at hourly intervals from an indwelling catheter. It entails less irradiation to the child than daily natural sources. The technique is well described by Chantler et al (Clin Sci 1969; 37:169-180 and Arch Dis Child 1972; 47:613-617).

In cases of severe reduction in CR-51-EDTA GFR (<60ml/min/1.73 m²), discontinue CDDP and use Carboplatin. If GFR falls below 2 SD of the expected GFR according to age in infants, Carboplatin should be substituted for CDDP.

b) Tubular toxicity – A way of monitoring tubular function is by phosphate clearance and phosphate reabsorption and by pattern of protein excretion and by β2-Micro-globulin.
Renal loss of Magnesium and consequent hypomagnesemia is expected in nearly all children on this study and oral Magnesium supplementation is recommended for all children entered into study. Hypomagnesemia is <u>not</u> a reason to stop CDDP. Children can develop other manifestation of <u>renal tubulopathy</u> at the same time as the GFR is improving. Thus, careful electrolyte monitoring is essential in all children exposed to CDDP treatment. Hypomagnesemia may persist years after stopping therapy.

14.2.5. Allergy to Carboplatin

As a whole 18 (14.5%) of 124 patients of the SIOP - LGG study cohort had allergic reaction to Carboplatin at a time interval between the beginning of chemotherapy and "allergy" ranging from 1 to 45 weeks (median 27 weeks). However, this could be an underestimation of the real incidence of the problem; in fact among the Italian patients 15 out of 35 children (40%) actually manifested allergic reaction to Carboplatin. Changes in the strategy of the present study may reduce the incidence of allergy, but clinicians should be alert at each dose of Carboplatin, that there is a possibility for severe reactions, even if previous doses have been tolerated well.

For hypersensitivity reactions to Carboplatin, reactions of grade I on one occasion would permit the repeated administration of Carboplatin subsequently with close surveillance, pre-medication with anti-histamine and hydrocortisone and slowed infusion rate (e.g. 4 hours). If grade II (or above) reactions occur, Carboplatin should not be used thereafter:

Grade I	Mild rash	Grade III	Bronchospasm
Grade II	Urticaria	Grade IV	Allergic shock

Consolidation therapy following Carboplatin allergy:

- In case of relevant hypersensitivity the study committee discourages the attempt to continue therapy by methods of desensitisation.
- Instead, since in most cases allergy will develop during consolidation, it is recommended to omit Carboplatin and to continue treatment by alternating the two elements Vincristine/Cyclophosphamide and Vincristine/Cisplatin.
- If possible, **total treatment time should be maintained**, however cumulative doses should be observed to avoid untolerable organ toxicity. A maximum of 5 cycles each of Cisplatin and Cyclophosphamide, respectively, shall not be exceeded.
- The following **sequence of cycles** is recommended (for details see 14.1.3.):

1	**7**	**13**	**19**	**etc.**	week post manifestation of allergy
VVV	**VVV**	**VVV**	**VVV**		**V**: **Vincristine** 1,5 mg/m² iv-bolus (max. 2 mg) - d1, 8, 15 of each 6 week cycle
Cyc	**Cis**	**Cyc**	**Cis**		**Cis: Cisplatin** 30 mg/m² 3h infusion - d1+2
					Cyc: Cyclophosphamide 1500 mg/m² 1h infusion, d1

- Another alternative is the substitution of Carboplatin by **Actinomycin D** according to the protocol used by Packer (Packer 1988b), but care should be taken to avoid the occurrence of veno-occlusive disease (see below).

Actinomycin D

Antibiotic
Inhibition of DNA synthesis by intercalation, blocking of replication and transcription of the DNA-template. May also cause topoisomerase-mediated single strand breaks in DNA.

Dose: 15 µg / kg / d as iv.-bolus injection on day 1 to 5

Application: υ Intravenous bolus injection
υ Sufficient antiemetic coverage

Side effects: Gastrointestinal irritation (nausea vomiting, diarrhoea, ulcerative stomatitis, gastroenteritis)
Hepatotoxicity (venoocclusive disease (VOD), particularly in young children)
Bone marrow depression
Alopecia
Exanthema
Extravasation may cause severe local and regional ulceration

Interactions: Radiation sensitizer and radiation recall effect.

Monitoring: Hepatic function and portal vein blood flow
Blood count

14.3. Supportive Care

All treatment here, even if tolerated well by the individual patient, has to be considered potentially intense and aggressive. Hence, treatment according to the guidelines of this protocol should be restricted to institutions, who are familiar with the administration of intensive aggressive combination chemotherapy and where the full range of supportive care is available.

Antiemetic therapy
All the chemotherapeutic agents, but VCR, can cause severe nausea and vomiting. Thus an appropriate antiemetic coverage is necessary before instituting therapy and at least for 24 hours after the end of therapy.
Antiemetic therapy should be administered according to institutional policy, e.g. odansetron 5 mg/m² (maximum single dose 8 mg) p.o./i.v. every 12 hours. Especially following the application of Cisplatin late emesis should be considered and the application should be prolonged.

Infection prophylaxis
Pneumocystis carinii prophylaxis is mandatory according to the recommendation of the national groups, which will be most often the prescription of Trimethoprim/ Sulfmethoxazol (5-6 mg/kg TMP or 30 mg/kg SMZ) on two to three days per week.

Central lines
The use of central lines is recommended, especially for small children.

Blood component therapy
Due to the risk of graft versus host reactions in infants as well as in patients under chemotherapy all blood products should be irradiated with at least 20 Gy (regularly 30 Gy) prior to transfusion, according to national policies. The use of leukocyte filters for leucocyte depletion is advised (in CMV negative patients), if there is no in-line filtration at the time the blood is taken.

Granulocytes colony stimulating factors (G-CSF)
The use of Granulocytes stimulating factors is not routinely recommended in children treated according to the protocol.
However, in case of a delay of one or more additional weeks in meeting the hematologic criteria for starting therapy instead of decreasing dosage by 25 % for the next course the use of granulocytes colony stimulating factors can be considered.
Similarly, if a course of chemotherapy is complicated by fever and sepsis or severe infections the use of G-CSF is suggested.
Routine dosage for this purpose is 5 µg/kg body weight sc. Filgrastim or 150 µg/kg body weight sc. Lenograstim. It is suggested to proceed until a stable absolute neutrophil count > 5,0 / nl is documented.

Endocrine function monitoring
Due to the location of the supratentorial midline low grade gliomas a significant portion of patients will either exhibit endocrine disturbances upon diagnosis or develop such during treatment or later follow-up. Regular assessments especially for thyroid function and corticosteroid secretion should be ensured during chemotherapy (section 8.4.).

Contraception
Pregnancy has to be prevented in fertile adolescent girls during chemotherapy by reliable anticonceptive methods, e.g. by hormonal anticonception.

Psycho-social support
Qualified psycho-social support for patients and their families should be an integral part of the treatment strategy. Faced with a tumor that may endanger life not immediately, yet rather throughout many years, but that carries along the risk for severe functional impairment, many adaptive processes have to be coped with. Especially loss of vision necessitates profound educational and rehabilitative measures. Moreover, social issues must be dealt with.Thus, continuous support should be offered to the patient and all other familiy members in cooperation with the medical staff.

15. Radiotherapeutic guidelines SIOP LGG RT 2004
Cooperative, prospective therapy protocol

NATIONAL REFERENCE CENTERS for RADIOTHERAPY:

United Kingdom:
Roger Taylor
Department of Radiotherapy
South West Wales Cancer Centre
Singleton Hospital
Swansea
SA2 8QA
Tel.: ++44 1792 285319
Fax: ++44 1792 285826
e-mail: Roger.Taylor@Swansea-tr.wales.nhs.uk

Germany:
Rolf - D. Kortmann.
Department of Radiotherapy
University of Leipzig
Härtelstr. 16
D - 04107 Leipzig
Tel.: ++49 (0)341 9718542
Fax: ++49 (0)341 9718549
e-mail: rolf-dieter.kortmann@medizin.uni-leipzig.de

Spain
Gordi Giralt
Oncologica radiotherapica
Pg Vall d'Hebron 135
E - 08035 Barcelona – Spain
Tel: ++34 93 27 48 086
Fax: ++34 93 274 60 59
e-mail: giralt@hg.vhebron.es

France
Christian Carrie
Radiotherapy Department
Centre Léon Bérard, 28, rue Laënnec
F - 69373 Lyon
Tel: ++33 4 78 78 28 85
Fax: ++33 4 78 78 26 26
e-mail: carrie@lyon.fnclcc.fr

Italy
Giovanni Scarzello
Department of Radiotherapy
Padua General Hospital
Via Giustiniani 2
I - 35100 Padua
Tel.: ++39 0498212960
Fax : ++39 049 8212957
e-mail : g.scarzello@unipd.it

Austria
Karin Dieckmann
Department of Radiotherapy
Universitätsklinikum Wien
Währinger Gürtel 18-20
A - 1090 Wien
Tel.: ++43 1 404 00 96 65
Fax ++43 400 26 90 / 93
e-mail : Karin.Dieckmann@str.akh.magwien.gv.at

Brachytherapy
Prof. Dr. C. Ostertag
Neurochir. Universitätsklinik
Department of stereotactic Neurosurgery
Neurozentrum
Breisacherstr. 64
D - 79106 Freiburg
Tel.: ++49 761 270 5063
Fax: ++49 761 270 5010

15.1. Introduction and Background SIOP LGG RT 2004

15.1.1. ROLE OF RADIATION THERAPY

The role of post-operative radiotherapy in adult low grade glioma now appears clearer following a report from the EORTC study showing that an improvement in progression-free but not overall survival is obtained after immediate post-operative radiotherapy [Karim et al., 2002]. However, a reliable identification of prognostic factors supporting the use of immediate postoperative radiotherapy is still lacking for children. Presently, it is recommended to employ radiotherapy in progressive disease only [Listernick et al., 1997]. In younger children chemotherapy is preferred to defer radiotherapy until further progression. For modern treatment techniques such as fractionated conformal techniques. preliminary data exist though with limited patient numbers yielding promising results [Merchant et al., 2002b;Debus et al., 1999].
For all locations extent of resection of a low grade glioma is the factor associated most strongly with progression-free survival favoring complete tumor removal (see section 3.2.). Following complete tumor removal radiotherapy does not seem necessary.

15.1.1.1. Glioma of the cerebral hemispheres

Disease progression is rarely observed after complete resection of low grade gliomas of the cerebral hemispheres in children [Fisher et al., 2001;Forsyth et al., 1993;Pollack et al., 1995;Sutton et al., 1995], so these children do not need radiotherapy.
However, even with incomplete tumor removal prolonged progression-free survival is commonly achieved [Forsyth et al., 1993].
Radiotherapy is reserved for tumor progression and non-resectable relapse. It offers an additional benefit by improving focal neurological deficits. In the series of Fischer et al. 9 of 15 children demonstrated focal neurological disorders before receiving radiotherapy and 7 of these 9 patients showed significant improvement [Fisher et al., 1998].

15.1.1.2. Cerebellar glioma

Complete surgical resection, as judged by postoperative neuro-imaging and operative record , appears possible in 84 to 90 % of all patients [Gajjar et al., 1997]. Incomplete removal is associated with tumor extension into the brainstem, leptomeningeal infiltration and for tumors encircling cranial nerves. Though extended periods of stable disease, and sporadic cases of tumor regression, following partial resection are reported for small numbers of patients, residual tumor tends to progress over long periods of time, mostly within 4-5 years after initial operation, and progression free survival rates are between 29 to 80 % and 0 to 79 % at 5 and 10 years [Dirven et al., 1997; Garcia et al., 1989; Gjerris et al., 1978; Schneider, Jr. et al., 1992; Smoots et al., 1998]. Small numbers of children have been irradiated with progressive or relapsing tumors only.

15.1.1.3. Gliomas of the supratentorial midline (visual pathways and hypothalamus)

Several series have demonstrated a poor outcome in patients with chiasmal tumor managed conservatively without radiation, demonstrating a survival advantage for children receiving irradiation.. In the report by Tenny et al. only 3 of 14 (21 %) survived.
after biopsy or exploration only compared to 28 of 44 (64 %) who received radiotherapy [Tenny et al., 1982]. In the series of Montgomery et al. of 16 patients undergoing radiation

therapy, 12 patients were alive without evidence of disease at a mean follow up of 6.3 years [Montgomery et al., 1977] (Table 29).

Table 29: Visual function / visual field after radiotherapy of gliomas of the optic pathway

Author	N	Total dose (TD) Daily fraction (FD)	Improved	Stable	Worse
Taveras et al., 1956	22	8 to 15 Gy	Vision 11 (50%)	8 (36.4%)	3 (13.6%)
Montgomery et al., 1977	12	TD 35 - 65 Gy (almost all 50 Gy) FD n.m.	Vision 3 (25%)	9 (75%)	0
Hoyt and Baghdassarian, 1969	28	n.m.	Acuity 4 (14.3%)	18 (28.6%)	6 (21.4%)
Dosoretz et al., 1980	9	TD 37-55.8 Gy FD 1.0-2.0 Gy	Vision 1 (11.1%)	8 (88.9%)	0
Kalifa et al, 1981	39	TD : 50 – 60 Gy FD : n.m.	Vision 7 (19.9%)	30 (76.9%)	2 (5.1%)
Horwich and Bloom,1985	23	TD 45-50 Gy FD 1.8-2.0 Gy	Acuity (23) 10 (43%) Vis.field (23) 4 (18%)	11 (48%) 19 (82%)	2 (9%) 0
Danoff et al, 1980	18	TD 50 – 60 Gy FD 1.8-2.5 Gy	Vision 6 (33%)	8 (44%)	4 (22%)
Weiss et al., 1987	12	TD : 40 – 56 Gy FD : n.m.	Vision 3 (25%)	9 (75%)	0
Flickinger et al.,1988	22	TD 38-56.86 Gy FD 1.4-2.0 Gy	2 (9%)	14 (77%)	3 (14%)
Wong et al., 1987	17	TD 35-61 Gy FD 1.5-2.0 Gy	6 (35%)	9 (53%)	2 (12%)
Pierce et al., 1990	23	TD 45-56,6 Gy FD 1.8-2.0 Gy	23 (30%)	14 (61%)	2 (9%)
Rodriguez et al., 1990	15	TD 43 – 60 Gy FD : n.m.	Vision 3(20%)	8 (53.3%)	1 (6.6%)
Bataini et al., 1991	44	TD 40-60 Gy FD 1.45-2.15 Gy	Acuity 25 (57%) Vis. Field 19 (61%)	16 (36%) 11 (35%)	3 (7%) 1 (3%)
Tao et al., 1997	29	TD : 50.4.-55.8 Gy FD : 1.8-2.0 Gy	Vision 7 (24.1%)	14 (48.3%)	5 (17.2%)
Erkal et al., 1997	13	TD 40-60 Gy FD 1.8-2.0 Gy	9 (34%)	14 (54%)	3 (12%)
Grabenbauer et al, 2000b	25	TD 45-60 Gy FD (1.6 – 2.0 Gy)	Acuity (25) 9 (36%) Vis. Field (20) 3 (15%)	13 (52%) 16 (80%)	3 (12%) 1 (5%)

n.m = not mentioned; Vis. field = visual field

Impact on visual function

Radiotherapy has become a standard treatment of optic nerve and chiasmatic gliomas since Taveras et al. reported improvement in visual acuity in 11 of 22 patients without noting any

morbidity associated with irradiation [Taveras et al., 1956]. Numerous reports over the years consistently support the high efficacy (90 %) of radiotherapy in stabilizing and improving visual function (Table 29). In contrast to these studies Dutton in his analysis of 1136 patients failed to confirm a benefit of radiotherapy [Dutton, 1994]. Among 511 patients treated with radiotherapy and followed for up to 10 years, 354 (69 %) showed stable or improved vision. 203 similar patients were followed without radiotherapy. 156 (77 %) showed visual stability or improvement. In this study it can be assumed, that a conservative approach without treatment was taken in the majority of patients with clinically stable tumors, whereas the proportion of patients with progressive tumors probably was higher in the cohort undergoing radiotherapy. This supports the "wait and see"-policy for non-progressive tumors.
The data on visual outcome are often difficult to judge as standards for evaluation are not existing and the description on visual function were cursory only in the majority of series. These shortcomings mandate a standardized approach in evaluating visual function both when deciding for treatment and at the time of assessing response to treatment.

15.1.1.4. The role of brachytherapy

Interstitial brachytherapy is a useful alternative in selected cases (Ostertag, 1989). The purpose of interstitial brachytherapy is to deliver a focal necrotising radiation dose within the tumor while sparing normal surrounding tissue. There is a steep dose gradient at the periphery thereby leaving a high cumulative dose around the implanted radioactive seeds, most commonly Iodine-125 (Ostertag, 1989). The largest series of interstitial brachytherapy in childhood and adult low grade glioma was published by Kreth et al. [Kreth et al., 45]. A total of 455 patients with low grade glioma were treated by using I-125 either as permanent or temporary implants. The 5- and 10-year survival rates in 97 patients with pilocytic astrocytoma were 85 % and 83 % and in patients with WHO grade II astrocytomas (250 patients) 61 % and 51 %, respectively. One hundred and twenty four of 455 patients were children and adolescents, 54 had a WHO grade II glioma, 70 a pilocytic astrocytoma. A 5 year survival rate of 84 % was obtained in astrocytoma WHO II and 90 % in pilocytic astrocytomas. Clinical stability was reported to be maintained throughout the survival time in all children. However, the data were not specifically analysed with respect to the pediatric cohort within this series. Voges treated 19 children with deep seated glioma, 13 of whom had low grade histology. (Voges et al., 1990). Tumor shrinkage could be seen on CT scans in all children and the estimated 4.5 year survival probability was 92%. Transient radiation induced edema was seen in 5 children. Although it is nearly impossible to define precisely which tumors are suitable for interstitial brachytherapy, with the available data it seems that small, circumscribed deep seated tumors with a diameter of less than 4 cm in locations other than the optic nerve and chiasm are preferred cases for interstitial radiosurgery.

15.1.1.5. The role of proton therapy

The major advantage of proton therapy over conventional radiation techniques is the high degree of dose conformity around the tumor that can be achieved, since protons have no exit dose beyond the target. Only one report has been published. The working group of Loma Linda treated 27 pediatric patients with progressive or recurrent gliomas at various sites [Hug et al., 2002](Table 4). Target doses were between 50.4 and 63.0 CGE (Cobalt Gray Equivalent) at 1.8 Gy per fraction. At a mean follow-up period of 3.3 years 6 patients experienced local failure and 4 died of disease. By anatomic sites these data translated into rates of local control and survival of 87%/93% for midline tumors, 71 % / 86 % for hemispheric tumors and 60 % / 60 % for brainstem tumors. The authors stated that their results were very encouraging especially for larger, irregular shaped tumors along the visual

pathway, where dose conformity is of particular importance. The limited access to proton therapy is the major disadvantage. However, intensity modulated radiotherapy will achieve similar dose conformity and it is most likely that this modern technique can be performed in the majority of institutions in not too distant future.

15.1.2. TIMING OF POSTOPERATIVE RADIOTHERAPY

Several retrospective studies have indicated an advantage for immediate postoperative radiotherapy regarding overall survival and progression - free survival in adults [Garcia et al., 1985;Shaw et al., 1989;Shibamoto et al., 1993], although there are opposite observations [Grabenbauer et al., 2000a]. Recent results of an EORTC/MRC study have shown that immediate postoperative radiotherapy in low grade glioma improved progression-free survival over that seen with observation only (5-year progression-free survival rates : 44% versus 37%, p=0.02). This benefit, however, was not translated into an improvement in overall survival [Karim et al., 2002].

15.1.2.1. Hemispheric and cerebellar low grade glioma

Forsyth et al. observed that immediate postoperative radiotherapy had an impact on overall survival in 39 patients with supratentorial pilocytic astrocytoma [Forsyth et al., 1993]. A policy of surveillance alone after surgical management was retrospectively analyzed in most series. In the series of Fisher tumor progression occurred in 12 of 48 patients (25 %) receiving immediate postoperative irradiation after incomplete resection, whereas the rate of progression was 42 % among 55 patients in whom radiotherapy was deferred (Fisher 2001). Postoperative radiotherapy has been employed for patients with residual, progressive or recurrent cerebellar astrocytoma in a rather unsystematic pattern. Garcia et al. noted that of 21 patients locally controlled after incomplete resection 16 were irradiated [Garcia et al., 1989]**.** In a previous analysis on the same patients, the cohort of 26 patients receiving immediate radiotherapy experienced a prolonged progression-free survival which was translated into a trend towards a better overall survival as compared to 16 patients undergoing surgery alone (70 % versus 60 % survival rate) [Garcia et al., 1990]. In other series, however, this observation could not be confirmed [Dirven et al., 1997;Gjerris et al., 1978;Schneider, Jr. et al., 1992;Smoots et al., 1998].

Table 30: Impact of immediate, delayed or no radiotherapy on progression or overall survival.

Author	**N (age)**	**Tumor location**	**Extent of resection**	**Result**
Pollack et al 1995	49	Cerebral hemisphere	Subtotal	10 y PFS 82 % immediate RT (n=33) 40 % no RT (n=16) p 0,014
Fisher et al 2001	128 <18y	Cerebral and cerebellar hemisphere (median follow-up: 7,3 y)	Complete (25) Subtotal (103)	PFS 5y 100 % OS 5y 100 % RT deferred postOP (N: 55 48) PFS 5y 69 81 % 10y 55 68 % OS 5y 87 81 % 10y 83 73 %

Thus, it is justifiable to defer radiotherapy for cerebral and cerebellar tumors until non-resectable relapse or tumor progression is observed.

15.1.2.2. Low grade gliomas of the supratentorial midline (visual pathway)

Jenkin et al. addressed this question in a retrospective analysis [Jenkin et al., 1993]. For thirty-eight patients receiving postoperative radiotherapy and 49 patients undergoing surveillance. No difference in progression free and overall survival rates could be detected (65 % versus 65 % and 69 % versus 80 % at 15 years), although more residual disease in the radiotherapy group may have adversely influenced outcome. In the study from St Jude's hospital, radiotherapy was used only in case of progressive disease [Gajjar et al., 1997]. One hundred and seven out of 142 children with tumors of all sites were observed, while 31 patients received radiotherapy and 4 patients chemotherapy (they were younger than 5 years of age), respectively, when showing progressive disease. The progression-free survival and overall survival rates of all patients were 70 % and 90 %, respectively, whereas the overall survival rate was only 65 % at 4 years in children after treatment for progressive disease. By contrast, in the series of 29 patients reported by Tao et al the policy to treat with radiation therapy as determined by clinical progression or increase in tumor size on imaging achieved a better result with a 15 year progression-free survival rate of 82.1 % and overall survival rate of 85.1 % [Tao et al., 1997]. The strategy to postpone the necessity for radiotherapy until time to progression was investigated in the SIOP / GPOH LGG trial 1996. Children 5 years of age and older received radiotherapy as first line non-surgical treatment, whereas children younger than 5 received chemotherapy in progressive disease. Preliminary data in 96 patients show that a 3 year progression – free survival rate of 87.1 % and an overall survival rate of 95.7 % can be obtained by radiotherapy [Kortmann et al., 2000b].

15.1.2.3. Radiotherapy following chemotherapy

The effect of radiotherapy after chemotherapy has failed is unclear. In the series of Janss et al. 46 children under the age of 5 years received first line chemotherapy [Janss et al., 1995]. Seventeen children finally received radiotherapy because of progressive disease. Seven of 17 children who required radiation after chemotherapy have incurred a third progression and the second progression free survival was 29 % at 10 years. It appears that this subset of patients represents a cohort with biologically more aggressive tumors and the additional question of whether chemotherapy renders the tumors more radio-resistant needs to be considered. By contrast, in an interim analysis of the SIOP - LGG trial a reduced efficacy after chemotherapy could not be observed [Kortmann et al., 2000b]. In this study 23 of 96 patients received radiotherapy after chemotherapy had failed. Although the follow-up was too short to draw reliable conclusions the progression free survival and overall survival rates did not differ from patients having received radiotherapy as first line treatment (91.3 % versus 87.3 % and 100% versus 96.8 %).

15.1.3. DOSE-RESPONSE EFFECTS

The optimum dose for radiation therapy in childhood low grade glioma has not been well established (Table 31). In children, no prospective randomized studies of radiotherapy dose/response have been performed. Retrospective analyses are rare comprising small patient numbers and very heterogeneous dose prescriptions and the selection of dose prescriptions was strongly influenced by patient age, extent and site of tumor with a tendency to a lower dose in younger children with larger tumors (larger treatment portals).
Although it is difficult to define an adequate dose prescription, the recently recommended and generally accepted dose prescription ranges between 45 and 54 Gy in 1.8 Gy fractions depending on age at treatment, extent of disease and location of tumor.

Table 31 : Progression-free survival in children and adults with low grade glioma / dose - response relationship.

Author	patients	total dose	Fractionated dose	PFS (5 years)	PFS (10 years)	p-value
Karim et al., 1996	171 172	45.0 Gy 59.4 Gy	1,8 Gy	47% 50%	Not reached	p : n.s.
Montgomery et al., 1977	 7 9	 </= 42 Gy >/= 50 Gy	n.m.	Overall 43% 100%	n.m.	n.m.
Sung et al., 1982	 13 29	 35 - 45 Gy 50 - 60 Gy	n.m.	Relapse rate : 11 / 13 8 / 29	n.m.	n.m.
Alvord, Jr and Lofton, 1988	52 62	> 45.0 Gy < 45.0 Gy	n. m.	80% 65%	65% 55%	n. m.
Flickinger et al., 1988	12 12	> 45.0 Gy < 45.0 Gy	Calculation according nominal standard dose	100% 75%		P=0.045
Kovalic et al., 1990	3 30	< 40.0 Gy > 40.0 Gy	n. m.	0 90%	0% 79%	<0.0001
Garcia et al., 1990	8 17	< 40 Gy =/> 40 Gy	n.m.	4/8 recurred 2/17 recurred	n.m.	n.m.
Jenkin et al., 1993	19 15	> 50.0Gy < 50.0 Gy	n. m.	88% 72%	88% 57%	0.37, n.s.
Grabenbauer et al., 2000b	9 16	44 – 45 Gy 45.1 - 60 Gy	1.6 – 2.0 Gy	87% 90%	36% 85%	0.04

n.s. : not significant, n.m. : not mentioned, PFS : progression – free survival

15.1.4. TUMOR VOLUME RESPONSE TO RADIATION

Radiologically determined response of low grade gliomas to radiotherapy has not been well documented because it has been assumed that they are indolent and unresponsive to radiotherapy. The typical biological behavior of a delayed tumor regression assessed clinically and by imaging investigations has often been disregarded. It can be suggested that low grade gliomas in children can demonstrate shrinkage on radiographic studies in response to radiotherapy, but that such shrinkage is not directly related to tumor control or improvement of symptoms.

Table 32: Response assessment following radiotherapy of residual tumor:

Author	N/type of tumor	Dose of RT	Results
Gould et al 1987	20 Optic glioma		10 regression 9 SD 1 PD
Furuya et al 1986	1 Chiasmatic glioma	RT 51,4 Gy	Regression over 2,5 years
Bataini et al 1991	3/57		3 CR at 6 months after RT
Grabenbauer et al, 2000b	6/25	RT 44-60 Gy	Regression of ≥ 50 % after 6 to 24 months
Fisher et al, 1998	19/80 low grade glioma		10 tumor volume reduction 5/10 response at 1st follow-up scan median time to response 3,3 months

			CR: 4 (21%) at 7, 12, 15m, 5y ≥ 50 %: 5 (26%) ≥ 25 %: 8 (43%)≥
Tao et al, 1997			Great variability in time to response 56 % SD over the whole period of follow-up; 24 % PR median time to maximal 16 % CR response: 62 months, maximum > 10 years.

A great variability in time to (maximal) response was observed. Response to radiation can be very slow taking years in some cases and is therefore not necessarily detectable on the first follow up scan. Many patients continue to display visible residual tumor on imaging many years after therapy. Treatment related changes on MRI imaging might be misleading and should be distinguished from tumor progression. Bakardjiev et al. followed patients with MR imaging at close time intervals between 3 and 26 months after stereotactic fractionated radiotherapy with a total dose between 52.2 and 60 Gy [Bakardjiev et al., 1996]. Twelve of 28 patients developed an increased size of the lesions between 9 and 12 months after radiotherapy which was not accompanied by clinical symptoms. The changes resolved or decreased by 15 to 21 months.

Table 33 : Stereotactic fractionated and proton therapy in childhood low grade gliomas (hemispheric and midline location).

Author	Technique	Patients	Outcome	Follow-up
Dunbar et al., 1994	fractionated convergence therapy (5x 1.8 –2.0 Gy / 45 –54 Gy) + dose escalation 60 Gy	11 (initial RT) 9 (recurrence)	No acute side effects 1 CR 19 PR / SD Overall survival 100%	16 months
Bakardjiev et al., 1996	fractionated convergence therapy (5x 1.8 –2.0 Gy / 52.2 – 60.0 Gy)	28	Overall survival 100% 15 pat decrease of tumor size 1 pat. Stable tumor size 13 pat. Increased tumor size (transient (15-21 months))	24 months
Benk et al., 1999	Hypofractionated convergence therapy (median total dose 39 Gy – 18.0 – 42.0 Gy- in 6 – 10 fractions)	8	1 edema, 1 edema + tumor necrosis, 1 tumor necrosis 5 year progression-free survival 60% 0verall survival : 100%	42 months
Debus et al., 1999	Fractionated conformal radiotherapy Median total dose 52.4 Gy / 1.6-2.0 Gy fractionated dose	10	Progression-free survival at 5 years 90%, overall survival 100% No acute toxicity	12-72 months
Merchant et al., 2002 [	Fractionated conformal radiotherapy Median total dose 54 – 59.4 Gy / 1.8 Gy fractionated dose	38	4 failures (3 within CTV and one immediate outside)	17 months (3-44 months)
Hug et al., 2002	Proton therapy 50.4 – 63.0 CGE (Cobalt Gray Equivalent), 1.8 Gy fractionated dose	Total 27 pat. Hemispheric 7 pat. Dienceph. 15 pat. Brainstem	Local control survival rate Hemispheric 71% 86 % Dienceph. 87% 93%	3.3 years (0.6-6.8 y.)

		5 pat.	Brainstem 60% 60%	

15.1.5. TREATMENT FIELDS

Advances in neuroimaging enabled new approaches in the management of childhood low grade glioma relating to diagnosis, decision on surgery and treatment planning for radiotherapy as well as assessing response to therapy or for follow-up. An advantage of contemporary (CT/MR-era) over earlier (pre-CT/MR era) seems to lie in better delineation of the tumor site/size. This has led, at least in part, to a significant improvement in survival of adults treated in the CT-era probably due to fewer marginal misses [Kortmann et al., 2000a]. Especially in pilocytic astrocytomas a sharply demarcated contrast enhancing lesion is often seen on imaging. These tumors only rarely infiltrate normal surrounding tissue and it can be anticipated that macroscopic tumor is precisely delineated. Since 60-70% of all low grade gliomas may be non-enhancing on CT it is to be expected that MRI would lead to better and earlier diagnosis, and may also be used for treatment planning [Kortmann et al., 2000a]. Computer assisted (preferable 3D) treatment planning is mandatory because it will reduce possible acute morbidity and late sequelae by reducing the volume of normal tissue exposed to a high RT dose. Whenever feasible image fusion of diagnostic MR and CT scans should be used to determine the target volume. Conformal treatment techniques will also help further reduce irradiation of normal tissue.

Although it has been shown using stereotactic biopsies that tumor cells can extend beyond imaging abnormalities which may suggest wider radiotherapy treatment fields, data from adult patients accumulated over decades support the use of localized fields to treat low grade gliomas [Kortmann et al., 2000a]. In childhood low grade glioma local failure is the predominant feature in progressive or recurrent disease and leptomeningeal spread is a rare event (less than 5%) [Pollack et al., 1995;Pollack et al., 1994]. This implies that treatment fields encompassing the tumor are appropriate in contrast to large lateral opposed fields predominantly used in the pre-CT area. Safety margins for the clinical and planning target volume should be defined according to anatomic borders and the reproducibility of field alignment. It is not necessary to encompass large zone of possible infiltration like in high grade glioma. With the identification of isolated tumor cells beyond the margin of a tumor on a T2 weighted MR image, the appropriate clinical target volume should include the MRI indicated extent of the tumor with a close margin of surrounding brain tissue with respect to anatomical boundaries. Debus et al. (1999) used three-dimensional conformal external beam radiotherapy to treat 10 patients. The clinical target volume included the visible tumor in CT and MRI plus 5 mm, the planning target volume consisted of the clinical target volume plus 2 mm safety margin. With these restricted treatment volumes the median target volume was 14.7 cm^3. No treatment failure was observed suggesting that limiting the high dose volume did not cause an increase in marginal or out-of-field failure rate. Merchant et al. (2002b) concluded that normal tissue sparing through the use of advanced radiation therapy treatment planning and delivery techniques should be beneficial to pediatric patients, if the rate and patterns of failure are similar to conventional techniques at a longer follow-up.
The currently recommended standardized approach is based on the ICRU 50 / 62 report. The clinical target volume (CTV) encompasses the visible tumor as seen on MR (T2 weighted images) with an additional margin of 0.5 cm. If surgery was performed, postoperative delineation of residual disease will be used for treatment planning. The preoperative scans are used to identify regions of possible tumor infiltration. It is not necessary to entirely encompass areas of cerebral edema. The planning target volume (PTV) encompasses the CTV with an additional margin according to the precision of treatment technique (0.2 - 0.5 cm if

rigid head fixation and 0.5 - 1.0 cm if a conventional face masks/head shell is used) depending on the departments policy [Kortmann et al., 1994;Kortmann et al., 1999] (Table 34).

Table 34*:* Geometric precision of current treatment techniques in irradiation of primary tumor site

Author	**Technique**	**Fixation system**	**Precision (linear Deviations -mm-)**
Kortmann et al., 1994	conv. 2-D therapy	thermoplastic face mask	2,5mm / max. 5mm
Warrington et al., 1994	fractionated convergence therapy	Gill-Thomas-Cosman Ring	1mm / max 2,3mm
Kortmann et al., 1999	Conformal radiotherapy	rigid face mask (cast)	0,9mm /max.3,0mm

15.1.6. MONITORING OF INTEGRAL DOSE TO TUMOR AND ORGANS AT RISK

Radiation induced growth hormone deficiencies seem to depend on a dose / volume relationship and the corresponding integral dose distribution. Adan et al. investigated growth hormone (GH) deficiency caused by cranial irradiation during childhood in cohorts of 18, 24, 30 to 40 and 45 to 60 Gy (optic glioma). Growth hormone levels were significantly lower after 18 to 40 Gy (whole brain irradiation) as compared to 45 to 60 Gy (limited volume irradiation) [Adan et al., 2001]. Decrease correlated with dose but not with age at treatment. The relationship between irradiated volume and dose prescription is both a difficult and important issue when attempting to reduce the risk for radiation induced endocrinopathies. Merchant et al. addressed this question in an analysis on growth hormone deficiency in 25 children with primary brain tumors requiring local treatment fields only [Merchant et al., 2002a]. The baseline was normal in all patients. Peak GH levels were modeled as a function of time after radiotherapy and volume of the hypothalamus receiving a dose within the specified intervals of 0-20 Gy, 20-40 Gy, and 40-60 Gy. GH deficiency was observed in 11 children at 6 months and a total of 20 children at 12 months. The effects appeared to depend on hypothalamic dose-volume relationship and may be predicted on the basis of a linear model that sums the effects of the entire distribution of dose. These calculations may in future allow to predict or reduce the risk for endocrine disorders.
MR imaging is a new method and measures tissue spin-lattice relaxation time (T1) with respect to spatial distribution of structural changes. It is sensitive to subtle changes below the resolution of conventional MR imaging. The working group of St. Jude Hospital assessed the effect of ionising radiation to the brain in 29 pediatric patients undergoing fractionated conformal radiotherapy of brain tumors [Steen et al., 2001]**.** Mapping showed that white matter exposed to less than 20 Gy and gray matter to less than 60 Gy does not undergo pathologic changes. The results indicate that conformal techniques, although delivering dose over a larger area of the brain offers a substantial benefit for children.

15.1.7. LOW GRADE GLIOMA OF THE SPINAL CORD

Low grade astrocytomas of the spinal canal are rare, accounting for less than 10 % of spinal cord tumors. They predominantly arise in the intramedullary region and exhibit a typical growth pattern often spanning many vertebral segments resulting in them having an apparent ‘pencil shape’. Because of the lack of prospective trials with sufficient follow-up treatment strategies are based on those for intracranial tumors on the assumption that the pathobiologic behavior is comparable. With the ongoing advances in imaging, surgical skills and radiation

techniques it becomes difficult to assess the value of each therapeutic intervention. Tumor extension often precludes complete tumor removal, and thus the role of radiotherapy has to be defined with respect to preservation or improvement of neurological function, site and extent of disease, surgical resectability, age and recently chemotherapy.
Prognostic factors are difficult to define. Abdel-Wahab et al. found in a multivariate analysis that involvement of more than five segments of the vertebral column was associated with a significantly inferior outcome [Abdel-Wahab et al., 1999]. Minehan et al. noted in his series comprising 79 children and adult patients that patients with pilocytic astrocytoma fare significantly better than those with diffuse fibrillary astrocytoma, WHO grade II [Minehan et al., 1995]**.** For all patients, the 5 and 10 year survival rates were 55 % and 50 %, respectively. In pilocytic astrocytoma a 5 and 10 year survival rate of 80 % could be achieved as compared to 15 % in fibrillary astrocytoma. There was a trend towards a better survival rate in patients receiving radiotherapy for pilocytic astrocytoma (85 % versus 75 % after surgery alone) and a significant advantage for non pilocytic astrocytoma. The extent of tumor resection did not reveal an impact on survival. However, a more aggressive surgical approach was associated with a poorer outcome as compared to biopsy only [Minehan et al., 1995]. The most favorable outcome was observed by O'Sullivan et al. in 12 patients younger than 17 years suggesting a better prognosis for children [O'Sullivan et al., 1994]. Independent of the extent of surgical resection the 10 and 20 year progression – free and overall survival rates were 83 % and 71 %, respectively. In this analysis, however, the histological subtypes were not clearly stated and the contribution of pilocytic astrocytoma which are associated with a survival advantage as it was demonstrated in the series of Minehan et al., is unknown. In the series of the Princess Margaret Hospital comprising adult and pediatric patients postoperative radiotherapy achieved a 5-year overall, cause-specific, and progression-free survival rates of 54 %, 62 %, and 58 %, respectively [Rodrigues et al., 2000]. Factors predicting improved outcome on univariate analysis were age < 18 years, low grade histology, and length of symptoms prior to diagnosis > 6 months. Bouffet et al. retrospectively analysed 49 consecutive patients with spinal cord astrocytoma [Bouffet et al., 1998]. Twenty-one patients received radiation therapy and achieved a 10 year survival rate of 83 % as compared to 70 % after surgery alone (21 patients) indicating a possible advantage of postoperative radiotherapy. However, the criteria for selecting treatment modalities was not clear in the report.
Control of neurological deficits is a major option for the selection of treatment but due to the paucity of data in the literature the impact of radiotherapy on neurological function is difficult to estimate. In a retrospective analysis of Jyothirmayi et al. 23 patients who received radiotherapy were followed for a mean of 51 months. Partial excision was achieved in 10 patients and surgery was limited to biopsy in 10 patients [Jyothirmayi et al., 1997]**.** At six months after radiotherapy 12 patients had improvement of neurological deficits, 9 had stable disease status and only 2 had deteriorated indicating a benefit of radiotherapy.

15.1.7.1. Treatment volume / dose prescriptions

In the majority of cases spinal low grade glioma recur locally and metastatic spread is a rare event. In all published series radiotherapy to the tumor site was performed. Chun et al. and Linstadt et al. assessed the pattern of relapse and observed no CSF seeding or relapse outside the treatment portals [Chun et al., 1990;Linstadt et al., 1989]**.** With the use of MR imaging the gross tumor volume according to the ICRU – 50/62 report can be accurately delineated and a safety margin in cranio-caudal direction of one vertebral body is recommended in the literature [Chun et al., 1990;Linstadt et al., 1989]. Although difficult to assess because of small patient numbers and a presumed shallow dose – response curve it appears that doses in excess of 45 Gy are sufficient for tumor control [Linstadt et al., 1989]. Doses less than 40 Gy may be associated with an increased failure rate [Chun et al., 1990]. Two of three patients

died of locally recurrent disease after doses between 20 and 38 Gy. Also, beyond 50 Gy no additional benefit in terms of progression – free survival was observed by Minehan [Minehan et al., 1995]. With respect to the presumed dose - response relationship of their intracranial counterparts doses between 45 and 54 Gy are currently recommended.

15.1.8. Conclusion

Current knowledge about the use and effect of radiotherapy in childhood low grade glioma results from small series, in which indication to therapy, doses and fields were highly variable. Nevertheless the results allow to define guidelines for its employment. But improvement of treatment techniques allow to spare normal tissue more consequently. Thus it shall be investigated, if these advances translate into a benefit for the patients. The aims can only gain clinical importance if the follow-up will be closely monitored in terms of assessment of quality of survival.

15.2. Aims of the Radiotherapy protocol

The following aims will be addressed in the protocol.

- To utilize modern treatment techniques to reduce the integral radiation dose given to normal tissue compared with the previous protocol.
- To record and monitor the integral dose to tumor and normal tissue as a basis for future assessment of quality of life of long term survivors
- To assess response of tumor and clinical symptoms to radiotherapy (intracranial and spinal tumors) with respect to primary treatment or after chemotherapy has failed.
- To assess the pattern of relapse, when using modern treatment techniques
- To assess the efficacy of cranio-spinal irradiation in metastatic disease
- To assess clinical outcome after brachytherapy
- To assess efficacy of brachytherapy

15.2.1. Rationale to maintain dose perscription

RT is an effective treatment for LGG in children. In the previous SIOP trial the irradiation of the tumor site in case of progressive disease revealed response rates in excess of 90% on imaging at a dose of 50.4 to 54.0 Gy at a median follow-up of 48 months. In view of these high response rates it seems to be justified to attempt to modify treatment, aiming to reduce acute side effects and late sequelae of treatment. Data on dose response effects are conflicting. In children they are essentially based on heterogeneous patient cohorts with small numbers. A lower dose has often been used in larger tumors and younger children. Although the data for adults might be promising (in the prospective, randomized EORTC study no difference was seen between 45.0 and 59.6 Gy in terms of survival). Data in children suggest, that a dose level of 54 Gy appears to be more effective than lower dose prescriptions [Karim et al., 1996;Horwich and Bloom, 1985]. Taking into consideration potentially hazardous effects on the developing central nervous system, it appears to be more important to reduce the dose to normal tissue rather than to lower the dose to tumor.

15.2.2. Rationale to introduce modern treatment techniques

Data on long term effects caused by radiotherapy are based on patient series who were treated in the sixties to the seventies in the majority of cases. Precise delineation of tumor was not possible and treatment techniques available then mainly comprised large portals given as an isocentric oposed fields. It could not be avoided to irradiate large areas of normal tissue. Additionally, high single doses were often used [Chadderton et al., 1995]. The development of modern imaging and treatment techniques in radiotherapy (“stereotactic radiotherapy”) opened the approach to effectively conform the dose to tumor while sparing normal surrounding tissue. Today stereotactic facilities are widely spread and allow an application of stereotactic radiotherapy in all children, who will go on to radiotherapy according to the entry

criteria. Although some experience has been acquired for stereotactic radiosurgery given with a high single or hypofractionated schedule, the conventionally fractionated approach is more convincing because the previously performed dose prescription can be continued and larger tumors can be treated better. The new techniques are able to reduce the integral dose to normal tissue. Consequently, it s indispensable to record and monitor the integral dose to tumor and normal tissue to obtain information as to what extent the dose to normal tissue can be reduced and as to whether the dose reduction will be reflected by an acceptable acute and long term toxicity.
Exception : Interstitial radiotherapy (Brachytherapy) can also be applied in selected cases. Patients treated with this technique will undergo a separate surveillance.

15.2.3. Rationale for monitoring of integral dose to tumor and organs at risk

Radiation induced endocrine disorders and structural changes of brain parenchyma seem to depend on a dose / volume relationship and the corresponding integral dose distribution. These calculations may allow to predict such late effects and appropriate selection of adequate plans will help to reduce the risk for their development.
IMRI and Protontherapy are also allowed (see documentation forms)

15.2.4. Rationale to monitor tumor response to radiotherapy

Since the response of tumor size and clinical symptoms to radiotherapy are known only in very few patients (see 15.1.5.), it is therefore important to obtain detailed information about the natural course of disease after end of treatment and to assess the impact for subsequent supportive care.
Increase in size after end of treatment seems to be not an uncommon effect and it appears that an increase in size is not accompanied by clinical signs and symptoms. However, increase in size might nevertheless be misleading and misinterpreted as recurrent disease.

15.2.5. Rationale to perform cranio – spinal irradiation in metastatic disease

Although reports on the efficacy and feasibility of cranio-spinal irradiation are scarce in the literature and this therapy has been given in very different settings and with varying dose prescriptions, there are convincing data that a positive effect can be expected. It is therefore necessary to assess acute toxicity and progression-free and overall survival as well as long-term toxicity prospectively with a definite dose prescription.

15.2.6. Rationale for brachytherapy

The role of brachytherapy has until now only be retrospectively investigated in single institutions often including adult patients. Data for children in larger cohorts are lacking. It is therefore intended to prospectively investigate the role of brachytherapy in the management of low grade glioma and to obtain information in terms of tumor control and side effects. The choice for brachytherapy is not depending on the eligibility criteria within the chemotherapy and radiotherapy study. The therapeutic decision will be made at the discretion of the participating institution. Biometric evaluation, however will be subject to the statistical analysis described in section 17. In case of progressive disease after brachytherapy the decision on subsequent treatment (fractionated, external radiotherapy or chemotherapy according to this protocol) should be made after contact with the national coordinating center.

15.3. Endpoints of trial

Primary endpoint
is the assessment of progression-free survival

Secondary end-points are :

- Overall survival
- Assessment of integral dose to tumor and normal tissue and evaluation on the impact on long – term toxicity
- Assessment of tumor response to radiotherapy by imaging and clinical investigations
- Assessment of progression-free and overall survival, acute and long-term toxicity of cranio – spinal irradiation in metastatic disease.

15.4. Eligibility criteria for Radiotherapy

1. Eligibility criteria for this study are listed in section 9., the indications to start non-surgical therapy are detailed in section 10. The indications to start radiotherapy are identical with the criteria to start chemotherapy respecting the age-related strategy.
Detailed information upon treatment strategies for the therapy groups 1 to 3 is given in section 12.

2. All children with the age of eight years or older with a histologically proven low grade glioma of intracranial and spinal sites, fulfilling the criteria for the start of non-surgical therapy, and for whom patients/parents and physician decide to give radiotherapy as non-surgical therapy, will be included. Diagnoses made by imaging is also allowed for chiasmatic-hypothalamic tumors, provided, that imaging, clinical course of disease and tumor location make the diagnosis of a low grade glioma most probable (section 8.5.).

3. Children younger than eight will also be included upon individual indication, e.g. if (successive) chemotherapies have failed and the children reveal signs of progressive disease clinically or on imaging.

4. Children with disseminated disease may be irradiated upon individual indication. These cases should be discussed with the national study coordinators.

5. Exception : brachytherapy
Indication for treatment with brachytherapy is at the discretion of participating institution irrespective of the indications for treatment as defined in section 10. However the specific limitations of brachytherapy as described in paragraph 15.1.1.4. should be observed.

15.5. Specific and technical outlines for Radiotherapy — SIOP LGG 2004

15.5.1. Pretherapeutic imaging

In order to assess the precise extent of tumor growth MR scanning including contrast enhanced T1 and T2 weighted imaging is necessary. Areas of blood brain barrier disruptions should be recorded and monitored during follow-up, as these areas might indicate malignant transformation. For treatment planning preoperative and postoperative imaging is necessary. For spinal tumors MR imaging pre- and postoperatively is indispensable to delineate extent of disease.

15.5.2. Treatment technique / intracranial and spinal sites

15.5.2.1. Intracranial sites :

When aiming to reduce possible acute morbidity and late sequelae it is necessary to reduce the volume of normal tissue exposed to a high RT dose. Computer assisted treatment planning is therefore mandatory. Three dimensional treatment planning should be used if possible. Conformal treatment techniques will help to further reduce irradiation of normal tissue. In addition, the dose to critical organs must be recorded (see documentation sheets). Whenever feasible image fusion of diagnostic MRI and CT-scans should be used to determine the target volume.

15.5.2.2. Spinal sites

Computer assisted treatment planning should be used in order to obtain a reproducible dose distribution.

15.5.3. Target volumes

Target volumes will be defined according to the ICRU 50/62. The clinical target volume (CTV) encompasses the visible tumor as seen on MR (T2 weighted images) with an additional margin of 0.5 cm. If surgery was performed, postoperative delineation of residual disease will be used for treatment planning. The preoperative scans are used to identify regions of possible tumor infiltration. It is not necessary to entirely encompass areas of cerebral edema. The planning target volume (PTV) encompasses the CTV with an additional margin according to the precision of treatment technique (0.2 - 0.5 cm if rigid head fixation and 0.5 - 1.0 cm if a conventional face masks/head shell is used) depending on the departments policy (Kortmann et al., 1994, 1999). When defining the clinical target volume anatomical borders must be considered.
For spinal sites the safety margins to visible tumor in cranio-caudal direction should be the lenght of one vertebral body. It is not necessary to entirely encompass a syrinx if present or the entire zone of edema. Postoperative imaging should be used in case of surgical resection. Laterally the filed border should encompass the pedicles.

15.5.4. Dose specification

RT dose is specified according to the ICRU 50/62 report. The ICRU reference point by definition is located in the center of the target volume (100 %). Dose inhomogeneity within the target volume should not exceed the tolerance limits of 95 % and 107 %.

For spinal sites dose specification should be located at the dorsal border of the vertebrae.

15.5.5. Dose prescription

For cranial sites a total dose of 54.0 Gy should be administered in a fractionated dose of 1.8 Gy, 5 times per week. All fields should be treated daily. For spinal sites the dose is limited to 50.4 Gy.

Table 35: Dose prescription for radiotherapy of low grade glioma

Target volume	Number of fractions	Dose per fraction	Total dose	Duration (weeks)
Intracranial tumor site	30	1.8Gy	54.0Gy	6
Spinal tumor site	28	1.8	50.4 Gy	5 ½

In case children under 5 years shall be irradiated, the national radiotherapy coordinator should be contacted. Doses should be limited to 45,0 Gy at 1,8 Gy per fraction.

15.5.6. Patient positioning

It is recommended that an individualized face mask (head shell) is used to guarantee the reproducibility of head positioning. If possible a rigid head fixation should be used to reduce the planning target volume (Kortmann et al., 1999).

15.5.7. Cranio-spinal irradiation (CS-RT)

Planning CT is strongly recommended for definition of the target volume for the cranio-spinal axis, posterior fossa and tumor bed volumes. It is recommended that the CT slice thickness should be no greater than 0.5 cm in the region of the cribriform fossa, base of skull, posterior fossa and cranio-cervical field junction, and no greater than 1.0 cm elsewhere within the cranio-spinal axis. TVs and OAR shall be outlined:

Target Volumes (TVs)	Organs At Risk (OAR)
Craniospinal axis Metastatic deposits	Eyes Pituitary Inner ear Hypothalamus Optic chiasm

Dose Volume Histograms (DVHs), if available should be constructed for the planning target volumes (PTVs) and OAR.
If the spinal field is treated with electron beams the dose along the entire spinal axis should be calculated with an appropriate correction for tissue heterogeneity.
If CT planning is not available then conventional planning of the target volumes is acceptable. Planning CT exam is strongly recommended, particularly for the posterior fossa and tumor bed target volumes.

15.5.7.1. Three-dimensional planning

It is strongly recommended that 3-D planning should be used to determine the target volume

for metastatic deposits. Some centres may wish to consider 3-D planning for determination of CS-RT target volume.

15.5.7.2. Treatment volume anatomical description and dose

Craniospinal Axis:
The clinical target volume (CTV) for CS-RT comprises the whole brain as well as the spinal cord and thecal sac.

Whole Brain Volume
The whole brain CTV should extend anteriorly to include the entire frontal lobe and cribriform plate region. The superior orbital tissue should be included in the treatment volume, but not the posterior globe. The treatment volume should extend at least 0.5 cm inferiorly below the cribriform plate and at least 1 cm elsewhere below the base of the skull (paying particular attention to the margin around the inferior aspect of the temporal lobes). The margin between the shielding and the anterior border of the upper cervical vertebrae should be 0.5 cm. The lower border of the cranial fields should form a precise match with the upper border of the spinal field.

Cervical Spinal Volume
As much as possible of the cervical spinal volume is included in the lateral cranial fields with the junction between the cranial and spinal fields kept as inferior as possible. This is advised for two reasons:
Avoidance of as much thyroid tissue irradiation as possible, by shielding this within the cranial volume.
To minimise the risk of the junction being close to the primary tumor and thus the risk of a 'cold spot' in this region the spinal field should extend superiorly to form an accurate match with the lower borders of the cranial fields.

Dorso-Lumbar Spine Volume
The inferior limit of the spinal CTV must be determined by imaging the lower limit of the thecal sac on a spinal MR scan and will usually extend inferiorly to at least the lower border of the second sacral vertebra.

Width of the Spinal Volume
The aim is to include the entire subarachnoid space including the extensions along the nerve roots as far as the intervertebral foramina. The spinal CTV should extend laterally to cover the intervertebral foramina with at least 1 cm margin on either side. The use of a 'spade' shaped field to treat the lumbo-sacral spine is not recommended.

Metastatic deposits
It is strongly recommended that the CTV for metastatic deposits should be determined on a planning CT. For PTV, an additional margin should be allowed according to departmental policy. This will generally be a margin of 0.5 cm. The field arrangement will be chosen to provide a high conformity index, avoiding OAR where possible.

15.5.7.3. Dose Specification

Dose Definition **:** All doses will be specified according to ICRU 50/ICRU 62.
Reference Point:

Brain
If the brain is treated by a pair of parallel opposed fields, the dose should be defined at the midpoint of the central axis.

Spine
The dose to the spine should be prescribed along the central axis at a depth representing the posterior margin of the vertebral bodies.
In the case of electron RT to the spine the anterior border of the target volume (posterior aspect of the vertebral bodies) must be encompassed within the 85% isodose.

Metastatic deposits
The prescription point should be in the center of the target volume, i.e. at the intersection point of oblique fields or along the central axis of the opposed beams, midway between the two entrance points.

Table 36: Total Treatment Dose

Brain :	35.2 Gy in 22 fractions of 1.60 Gy
Spine :	35.2 Gy in 22 fractions of 1.60 Gy
Metastatic deposits :	55.0 Gy cumulative dose , 1.8 Gy fractionated dose
(Intracranial sites)	
Metastatic deposits :	49.6 Gy cumulative dose , 1.8 Gy fractionated dose
(spinal sites)	
Dose restriction (maximal cumulative dose) > 50% intracranial volume and or > 2/3 of spinal canal : 45 Gv	

15.5.8. Documentation

It is mandatory to document the field alignment using simulator films and polaroid photographs. At the start of radiotherapy verification films should be obtained of each irradiated field.
Portal films should be repeated once a week. Precise application of radiotherapy is essential for both tumor control and reduction of side-effects.
To develop recommendations for optimal treatment techniques it is necessary to analyze the radiation protocols, the prescription of target volumes, doses and the accuracy of treatment delivery. Therefore, it is requested that the following data (copies) be sent to the reference center for radiotherapy.

-Radiation protocols
-Simulation films
-Portal films
-Computer assisted treatment plans
-Polaroid pictures of patient positioning and field allignment
-Evaluation forms (Addendum 21.9.) Patient data
Toxicity
Treatment technique / dose prescription

15.5.9. Acute treatment related toxicity

Steroid prophylaxis of cerebral edema is not mandatory during radiotherapy. If cerebral oedema occurs dexamethasone should be given orally or iv, if necessary.
The acute maximal toxicity during irradiation should be documented on the evaluation forms.

15.5.10. Routine laboratory tests during radiotherapy

- Red and white blood cell counts, platelet counts: 2x weekly in CXA, 1x weekly in limited volume radiotherapy..
- If the patient is receiving steroid medication: blood glucose 1x weekly.
- Before and at the end of radiotherapy: sodium, potassium, calcium, GOT, GPT, Gamma-GT, LDH, creatinine, BUN, hormones of the pituitary axis (TSH, growth hormone, ACTH, FSH/LH - see endocrine guidelines section 8.4.).

16. Definitions for: SIOP LGG 2004
Tumor staging
Extent of resection
Response and remission
Serious adverse event

16.1. Tumor staging

Primary solitary tumors and disseminated tumors

No validated **staging system** exists for childhood LGG. Thus, the assessment of tumor extension will be based on descriptive terms aiming to define:

- tumor site: Main region of the brain:
  1. cerebral hemispheres
  2. supratentorial midline
  3. cerebellum
  4. caudal brain stem
  5. spine

- structures involved – Definition of local extension (supplementing the main tumor site)
  - ad 1. exact hemispheric lobes,
  - ad 2. visual pathways: right and/or left optic nerve; chiasma; hypothalamus; right and/or left (posterior) optic tracts; basal ganglia, thalamus or other midline structures, midbrain
  - ad 3. cerebellar hemispheres, vermis, cerebellar-pontine angle
  - ad 4. upper/middle/lower pons, medulla
  - ad 5. region and number of spinal segments involved

- tumor "volume":
  1. 2 diameter surface area calculation or
  2. a third diameter creating an ellipsoid, giving an indication of volume (horizontal x vertical x sagittal x 0,5)

The relevance of "multi"-dimensional tumor volume assessment has been reviewed for tumors outside the central nervous system especially with respect to response assessment (Therasse et al., 2000). Within this study tumor "volume" should preferably be recorded by three dimensions, but to document two dimensions is the minimum requirement. For a given patient the documentation of tumor "volume" should always apply the same diameters in comparable MRI/CT planes (section 8.5.).

- evidence of leptomeningeal and/or sub-ependymal tumor dissemination
  1. number of lesions
  2. localisation within brain and spine
  3. morphologic description and size of multifocal tumor

Classification of leptomeningeal dissemination:

In an attempt to classify meningeal dissemination the classification of Chang (Harisiadis and Chang 1977) will be adopted. It will be investigated whether this staging system is appropriate for low grade glioma:

M 0: no dissemination

M 1: positive proof of tumor cells in the lumbar cerebro-spinal fluid, more than 14 days following an operative intervention, but no concurrent meningeal enhancement on MRI or CT. If possible, immunohistochemical staining (GFAP) should be performed

M 2: meningeal dissemination in the cerebral area in form of
a. laminary thickening
b. nodular deposits or very thick laminary layers

M 3: meningeal dissemination in the spinal canal in form of
a. laminary thickening
b. nodular deposits or very thick laminary layers

M 4: extraneural metastases (related to shunt or not)

16.2. Extent of resection

The minimal modified criteria to define extent of resection and response as elaborated by the Brain Tumor Sub-Committee are adopted for the study (Gnekow 1995).
The classification of the extent of resection should be based upon the results of the surgical report and of the postoperative neuroradiologic assessment, but be primarily a radiological classification aided by the surgeon's report. Four categories have been defined for each field:

Extent of resection – Surgical judgement

S1 - Total resection, no recognizable residues
S2 - Remaining tumor of less than 1,5 cm^3, possible local invasion
S3 - Residual tumor of more than 1,5 cm^3
S4 - Tumor volume unchanged, biopsy

Extent of resection – radiological judgement
(on early (24 to max. 72 h) post-operative MRI or CT without and with contrast enhancement)

R1 – No visible tumor ("Total")
R2 – Rim enhancement at the operation site only ("RIM")
R3 – Residual tumor of a measurable size (product of two/three diameters – "Lump")
R4 – No significant chance to preoperative tumor size ("minimal change")

Extent of resection combining surgical and radiological judgement:

	Radiology	Surgery
I "Total"	R1 - Total	S1 - Total
II Near Total	R1/R2 - Total or Rim	S2 - Small residue ? localised invasion
	R2 - Rim	S1 - Total
III "Partial"	R3 - Distinct lump	S1/S2/S3 - Any residual disease
IV "Biopsy"	R4 - Minimal change	S4 – Biopsy

A **total resection** can only be stated, when surgical and radiographic judgement agree (S1-R1).

Near total resection - Leaving a small residual of tumor behind, which may be invading, can result in a rim enhancement at radiologic investigation or not be visible (S2 - R1/2, R2-S1).

Partial Resection - In case the post-surgical scan reveals measurable tumor of any size the surgical estimate may agree or may not (S1/2/3 - R3).

Biopsy - In case only a biopsy is performed, the surgical report and radio-diagnostic finding should be identical (S4 – R4).

Thus the **definitions of the extent of resection** will be as follows

Total resection / near total (subtotal) resection = no visible tumor is left at the time of surgery (according the neurosurgeon' s operative note) and this is confirmed by post-operative contrast enhanced CT or MRI scan performed within 48-72 hours from the operation. The presence of tumor at the margins of the resection specimen will be noted.

Incomplete resection/ partial resection = any residual tumor after surgery which is confirmed by post-operative contrast enhanced CT or MRI scan performed within 48-72 hours from the operation. In this case the extent of tumor removal must be established by comparing the pre- and post-contrast enhanced CT or MRI scan.

Biopsy = when the surgical procedure is done for the sole purpose of establishing the pathological diagnosis. Depending upon the site of the tumor and other relevant individual circumstances, biopsies can be taken during an "open" operation or via stereotactic approaches.

16.3. Response and Remission

16.3.1. General assessment of response

To evaluate tumor response in low grade glioma is a complex endeavor. It involves the objective clinical responses to therapy, measured according to criteria suggested below, as well as tumor size/volume changes, measured by the conventional neuroradiological techniques, which will be carefully monitored during therapy. A descriptive multifactorial

system will be adopted to cover the scope of possible combinations of tumor response to therapy. Since up to now no study has followed clinical and ophthalmological findings in relation to radiological response, there are no data to substantiate the relevance of clinical (ophthalmological and other symptoms) and radiologic response or progression. The following components to measure treatment effects will be monitored:

Clinical findings – in particular body weight changes in children presenting with diencephalic syndrome, and the ophthalmologic parameters will be studied along with any relevant neurological and endocrinological signs. Significant visual deterioration (confirmed at two consecutive exams) must be considered as a clear signal for progression.

Lumbar CSF cytologic findings – At the level of current knowledge, lumbar cytologic CSF findings can not be considered a criteria for judging tumor response; however - if previously positive in case of disseminated LGG – it is recommended to follow this parameter during treatment, including the protein level, absolute cell count and cellular morphology on cytospin preparations.

Neuroradiological findings – Changes in tumor size/volume, especially concerning involvement of adjacent structures (right and/or left optic nerve; chiasm; hypothalamus; right and/or left posterior optic tracts; midbrain; others) and evidence of leptomeningeal and/or sub-ependymal tumor dissemination will be monitored to measure and describe neuroradiological tumor response. Changes of the intensity of post-gadolinium contrast enhancement will be recorded, but not used as a parameter to judge response.

Table 35: Definitions of response with respect to:

	Parameters to be studied	**Definition**
CLINICAL FINDINGS	body weight changes in children presenting with diencephalic syndrome neurological signs	Gain Stable Loss Better Stable Worse
OPHTALMOLOGICAL FINDINGS	Visual acuity Visual field	Better Stable Worse
CYTOLOGY	Lumbar CSF: number of tumor cells	Decrease Stable Increase
NEURORADIOLOGICAL INVESTIGATIONS	MRI without and with Gadolinium enhancement for primary tumor and/or multifocal lesions	Tumor size/volume change see definition below

16.3.2. Criteria of neuroradiologic response of primary tumor and of disseminated lesions

Complete response : No radiological evidence of tumor on contrast enhanced CT or MRI scan. Disappearance of multifocal lesions and tumor cells from the CSF in the case of disseminated disease.

Partial response : Reduction of the size of the solid parts of the tumor of more than 50% (product of the two largest perpendicular diameters) radiographically. A calculation according to the formula axial x coronal x sagittal /2, referring to the largest diameter in every direction will be performed centrally, but is not directly comparable. If the tumor consists of solid and cystic parts they should be evaluated separately. In significantly polycyclic tumors separate representative nodules should be added to one volume to make the calculation as exact as possible.
In disseminated disease, the distant lesions show reduction in size or a stable size and there is no appearance of new tumor lesions or development of malignant cells in the CSF.

Objective response : Reduction in size of unequivocal residual tumor manifestation between 50 and 25% (product of the two largest perpendicular diameters) radiographically referring to last evaluation. A calculation according to the formula axial x coronal x sagittal /2, referring to the largest diameter in every direction will be performed centrally, but is not directly comparable. If the tumor consists of solid and cystic parts they should be evaluated separately. In significantly polycyclic tumors separate representative nodules should be added to one volume to make the calculation as exact as possible.

There is no tumor progression and no appearance of new tumor lesions or development of malignant cells in the CSF.

Stable disease : Reduction of the size of the solid parts of the tumor of less than 25% (product of the two largest perpendicular diameters) radiographically. A calculation according to the formula axial x coronal x sagittal /2, referring to the largest diameter in every direction will be performed centrally, but is not directly comparable. If the tumor consists of solid and cystic parts they should be evaluated separately. Several tumors should be added to one volume to make the calculation to be as exact as possible.
There is no tumor progression of more than 25 % and no appearance of new tumor lesions or development of malignant cells in the CSF.

Tumor progression : Enlargement of the primary of more than 25 % (product of the two largest perpendicular diameters) radiographically or appearance of new tumor manifestations such as new lesions or tumor cells in the CSF. A calculation according to the formula axial x coronal x sagittal /2, referring to the largest diameter in every direction will be performed centrally, but is not directly comparable.

Complete, partial, objective responses and stable disease will be considered positive responses in this protocol.

16.3.3. Considerations for the neuroradiological assessment of response
Caution: Please be aware that:

♦ For the neuroradiological evaluation of tumor response the contrast behavior will not be taken into consideration, although a reduction in contrast uptake can often be seen following chemotherapy. Contrast behavior of a tumor is very much dependent upon the performance of imaging (dosage of contrast medium, time course after the application and

field strength of the magnet) and the relevance of enhancement for progression or regression in low grade glioma is not defined, especially not for grade I astrocytomas.

♦ Pilocytic astrocytoma can have a solid and cystic component of the tumor. Sometimes only the cystic components enlarge while the solid ones remain unchanged. The isolated enlargement of the cysts is not a secure evidence of tumor progression. It should not be considered for response, because the dynamics of cystic parts do not relate to the proliferative behavior of the tumor, even though the mass effect and the indication for its treatment might immediately be influenced by the cysts.

However, changes of cystic parts as well as contrast behavior should be registered on the evaluation forms/status forms (Addendum 21.8.4. response assessment, 21.13.1. patient status report) to increase information on the dynamics of tumor behavior during or after treatment.

♦ A moderate increment of the tumor dimension can be observed during the first weeks of therapy and more specifically between week 11-12. It is strongly recommended to await the definite treatment response evaluation performed between weeks 22-24 before deciding on the final response to this initial part of therapy and consequently on the subsequent treatment.

♦ Unequivocal progressive visual function deterioration even in face of an unchanged tumor volume, as determined by contrast enhanced brain studies (CT or MRI), has to be considered as tumor progression.

♦ The development of hydrocephalus in isolation without any other radiological evidence of tumor progression should not be taken necessarily as evidence of tumor progression.

♦ Tumor progression by either clinical, ophthalmological or radiological criteria is an indication to start therapy in a child who is observed (see section 10.) or to change therapy if the child is on chemotherapy or has received radiotherapy.

♦ Care should be taken in case of neurologic deterioration, which may be related to steroid withdrawal, coexisting systemic diseases, unrelated intracranial causes (e.g. sub – dural haematoma), delayed seizures or post-ictal findings.

16.4. Severe adverse events, including second malignant neoplasm.

1. All life-threatening treatment-related complications, i.e. WHO/CTC grade 4 toxicities, of the following categories are regarded as a serious adverse event (SAE):
- Peripheral nervous system
- Central nervous system
- Renal
- Hepatic
- Cardiac
- Skin

Additionally the following conditions are regarded as SAE:
- Permanent, relevant handicap following any other toxicity
- Drug overdose

2. The development of allergy to Carboplatin has to be closely monitored in all patients receiving Carboplatin. If early signs do go unnoticed, life-threatening allergic shock may manifest. This is regarded as a SAE, yet allergy is monitored separately from all other forms of toxicities.

3. WHO/CTC grade 4 hematologic toxicities have to be expected with the protocol presented here. If they resolve and do not have life-threatening consequences, they are not considered as a life-threatening event in the context of this protocol. They are documented routinely concommittant to regular therapy documentation.

4. Death under treatment will be considered an adverse event regardless of its cause. Death, other than death of disease, within 12 months from the end of treatment will be regarded as adverse event, unless it is proven that there is no relation to therapy (e.g. traffic accident).

5. Any solitary, and histologically distinct, malignant neoplasm occurring after the date of diagnosis of the initial tumor and not counting disseminated low grade glioma, is regarded as a secondary malignant neoplasm (SMN). This designation bears no implication for the possible causal mechanism, which especially in patients with NF I may be genetic, giving rise to (multiple) metachronous tumors. The development of SMN should be reported as a SAE as well.

Any serious adverse event must be reported immediately to the national data center, i.e. within the next working day, and followed-up by the treating institution, regardless of whether or not it falls within the categories listed above. The information must be forwarded to the international data center and be relayed to the other national data centers for further reporting according to GCP guidelines.
The documentation form from addendum 21.12. shall be used for the reporting of serious adverse events. Any additional important information should be included as copy.

17. Statistics SIOP LGG 2004

17.1. Chemotherapy Group

17.1.1. Low grade glioma of all sites in children not affected by Neurofibromatosis NF I (group 1 and 2 according to section 12.)

Design of the trial

The aim of the trial is to compare **standard induction therapy** with Vincristin and Carboplatin with the **intensified induction therapy** with Vincristin, Carboplatin and Etoposide in children, who are not affected by Neurofibromatosis (type NF I), with low grade glioma of all sites necessitating chemotherapy as non-surgical therapy (according to patient eligibility criteria (section 9.) and indication for non-surgical therapy (section 10.)).

This therapy optimization trial is multinational, multicenter, non-blinded, randomized and prospective.

The accrual period of the trial is 6 years followed by an observation period of 2 years.

Immediately upon the decision for chemotherapy as non-surgical intervention each child will be randomized to one of the two induction regimens.

For this multinational, multicenter trial randomization will be provided by Istituto Oncologico Veneto, Clinical Trials & Biostatistic Unit, "SIOP-LGG 2004", University Hospital of Padova, I-35128 Padova, Italy, by using blocks.
Randomisation will be stratified according to age (< 1 year, 1-8 years, ≥ 8 years) and primary tumor site (chiasmatic tumors (Dodge II and III), all other supratentorial midline tumors, tumors of all other sites outside the supratentorial midline).

End points

According to the different questions the following end points are defined:
For definition of progression and relapse referral is made to protocol section 16.3.

1. $\underline{PFS_R}$: Progression free survival measured from the time of randomization: Time from randomization up to an event:
   Definition of event:
   - death (for all reasons)
   - progression of a residual tumor (section 16.3.)
   - relapse following previous complete remission (section 16.3.)
   - appearance of new or progression of existing metastasis (section 16.3.)

2. Radiological response measured at week 24: Complete, partial, objective responses and stable disease will be considered positive responses in this protocol. Response definitions according to section 16.3. are used.

3. PFS_D: Progression free survival measured from the time of diagnosis: Time from diagnosis up to an event (definitions of event see 1.).

4. EFS_R: Event free survival measured from the time of randomization: Time from randomization up to an event.
   Definition of event:
   - death (for all reasons)
   - progression of a residual tumor (section 16.3.)
   - relapse following previous complete remission (section 16.3.)
   - appearance of new or progression of existing metastasis (section 16.3.)
   - severe adverse event / toxicity (not counting Carboplatin hypersensitivity and toxicity of regular protocol application) (section 16.4.)
   - appearance of secondary malignant neoplasm (section 16.4.)

5. EFS_D: Event free survival measured from the time of diagnosis: Time from diagnosis up to an event. (definition of event: see 4.).

6. OS_R: Overall survival measured from the time of randomization: Interval starting with the day of randomization and ending with the death of the patient independently of its cause.

7. OS_D: Overall survival measured from the time of diagnosis: Interval starting with the day of diagnosis and ending with the death of the patient independently of its cause.

Questions of the trial

By means of this trial the following questions shall be answered:

Main question of the trial

1. Does intensified induction therapy with additional Etoposide lead to a different progression free survival PFS_R measured form the time of randomization than the standard induction therapy?

Secondary questions:

2. Does the radiological response at week 24 depend on the type of induction therapy (standard or intensified induction) ?

3. Does induction therapy with additional Etoposide lead to a different PFS_D than the standard induction therapy?

4. Does induction therapy with additional Etoposide lead to a different EFS_R than the standard induction therapy?

5. Does induction therapy with additional Etoposide lead to a different EFS_D than the standard induction therapy?

6. Does induction therapy with additional Etoposide lead to a different OS_R than the standard induction therapy?

7. Does induction therapy with additional Etoposide lead to a different $\underline{OS_D}$ than the standard induction therapy?

Cox regression model

The following variables are checked with reference to their influence on the $\underline{PFS_R}$ and $\underline{EFS_R}$ with multivariable methods by Cox regression:

Histopathology
- Markers of proliferation (e.g. Ki 67 / MIB-1) (% positive cells)
- Molecular-pathologic markers (e.g. p 53 mutation) (% positive cells)
  (Quantification of markers is not standardized yet. The panel of pathologists will group these markers according to the current interpretation of their presence. See section 8.3.)

Tumor
- Tumor size preoperatively (two-/three dimensional, diameters in cm)
- Tumor size postoperatively (two-/three dimensional, diameters in cm)
- Extent of surgery (see section 16.2)
- Localization and extent within the supratentorial midline for visual pathway glioma (Dodge classification)

Dissemination
- primary/secondary
  (primary: present at diagnosis, secondary: diagnosis during follow-up)
- Type and extent of dissemination
  (nodular or leptomeningeal, descriptive extent (see section 16.1.))

Symptoms Severe, visual or neurologic symptoms relevant for the decision to start non-surgical therapy (see section 10.) will be described according to their presence or absence:
- Visual symptoms
- Neurologic symptoms
- Increased intracranial pressure
- Diencephalic syndrome

Age To investigate the „young“ and „older“ age groups according to the present strategy patients are divided into the following age groups:
- < 8 and ≥ 8 years (the young age group will be further divided into those younger than 1 year and those 1-8 years)
- To be comparable to previous trials patients are divided into the following age groups:
  < 1 year, 1 to 4, 5 to 10, > 10 years.
- Age will be analysed as a continuous variable also.

Sex
- male / female

Observation time following diagnosis before starting therapy (continuous variable)

The delay between diagnosis and the time to commence treatment has been the strongest prognostic factor in the previous trial in that those that were treated within a short period of time did worse than those that were treated after a period of observation. However, the decision to treat or not to treat was often arbitrarily taken and therefore this parameter will be studied prospectively, but will not be stratified.
In the present study the indications to start non-surgical therapy (see section 10.) shall be strictly observed, in order to avoid such inaccuracies. Analysis will consider whether start of protocol therapy was according to the indications or chosen arbitrarily.

Response at week 24

Adding "response at week 24" as a possible important factor for PFS_R for the Cox regression, its influence upon the PFS_R is tested. Thus it is tested, if the "response at week 24" is suitable for predicting PFS_R.
Response definitions according to section 16.3. are used.

Induction therapy (I or II) – main analysis at the time points defined

Statistical analysis

- The analysis will be done according to the intention-to-treat principle.
- Additionally, a per-protocol analysis will be performed for explorative reasons.

Per-protocol-patients are defined as follows:

Every child should receive the type of chemotherapy and the amount of chemotherapy to which it was allocated. Treatment-modifications or interruptions for toxicity are no violation of the protocol.
Children developing Carboplatin hypersensitivity will continue treatment according to protocol recommendations. This change in chemotherapy is no violation of the treatment assigned.
Premature termination due to toxicity is no protocol violation, but there should be no unreasonable or unexplained termination. Children who received more than 75 % of the possible doses are included as being treated "per protocol". Children who for other reasons than progression or toxicity have interrupted treatment early have to be censored.

- The main question will be analyzed on a significance level of α=0,05. The p-values corresponding to the secondary questions are regarded as explorative.

Additionally, the analyses will be performed separately for the group of children with chiasmatic tumors (Dodge II and III), for the group of children with all other tumors of the supratentorial midline and the group of children with tumors of all other sites outside of the supratentorial midline. These analyses are regarded as explorative.

According to the questions of the trial the following null hypothesis and test statistics follow:

1. Null hypothesis: The $\underline{PFS_R}$ of children on intensified induction does not differ from the $\underline{PFS_R}$ of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the $\underline{PFS_R}$, the quartiles of the $\underline{PFS_R}$ with the 95 %

confidence intervals, the PFS_R at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

2. Null hypothesis: The response at week 24 does not depend upon the type of preceding induction therapy (intensified or standard induction).
This hypothesis will be analyzed by a two-sided Chi squared test. For descriptive reasons the respective frequency table will be illustrated.

3. Null hypothesis: The PFS_D of children on intensified induction does not differ from the PFS_R of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the PFS_D, the quartiles of the PFS_D with the 95 % confidence intervals, the PFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

4. Null hypothesis: The EFS_R of children on intensified induction does not differ from the EFS_R of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_R, the quartiles of the EFS_R with the 95 % confidence intervals, the EFS_R at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.
For testing the null hypothesis, that the number of early progressions of the two induction therapies are not different, we will use the generalized Wilcoxon test (Breslow). The EFS_R at 24 weeks and the respective 95 % confidence intervals for both induction therapies will illustrate this.

5. Null hypothesis: The EFS_D of children on intensified induction does not differ from the EFS_D of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_D, the quartiles of the EFS_D with the 95 % confidence intervals, the EFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

6. Null hypothesis: The OS_R of children on intensified induction does not differ from the OS_R of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the OS_R, the quartiles of the OS_R with the 95 % confidence intervals, the OS_R at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

7. Null hypothesis: The OS_D of children on intensified induction does not differ from the OS_D of children on standard induction.
This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the OS_D, the quartiles of the OS_D with the 95 % confidence intervals, the OS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

Interim analyses and final analysis, stopping rule

Analyses will be performed after 1/3, 2/3 and all expected events occurred, unless the trial was stopped before. Both induction therapy arms are added up to evaluate the number of occurred events with respect to the expected number of events.

With an accrual period of 6 years, a follow-up period of 2 years, an accrual rate of 60 children per year, a 3-year $\underline{PFS_R}$ of 50% having standard induction therapy and 65 % having the intensified induction, a 5-year drop-out rate of 10% and the assumption of exponential distributed $\underline{PFS_R}$ and drop-out-times, a total number of 198 events is expected. Therefore the first interim analysis is scheduled to take place after 66 events and second after 132 events. The trial will be terminated after an interim analysis, if the main question can already be answered at this interim analysis or the chance to answer the main question is low while continuing the trial.
The criteria for stopping the trial after an interim analysis are given by a 3-step group sequential plan according to Pampallona & Tsiatis with the possibility to stop the trial in favor for the alternative and the null hypothesis [Jennison 2000]. The bounds of the 3-step group sequential design result from α=5%, power=90%, hazard ratio =1,609, event free survival rate after 3 years of 50% and 65% for the two groups and an α-spending approach according to O'Brien & Fleming [1979].

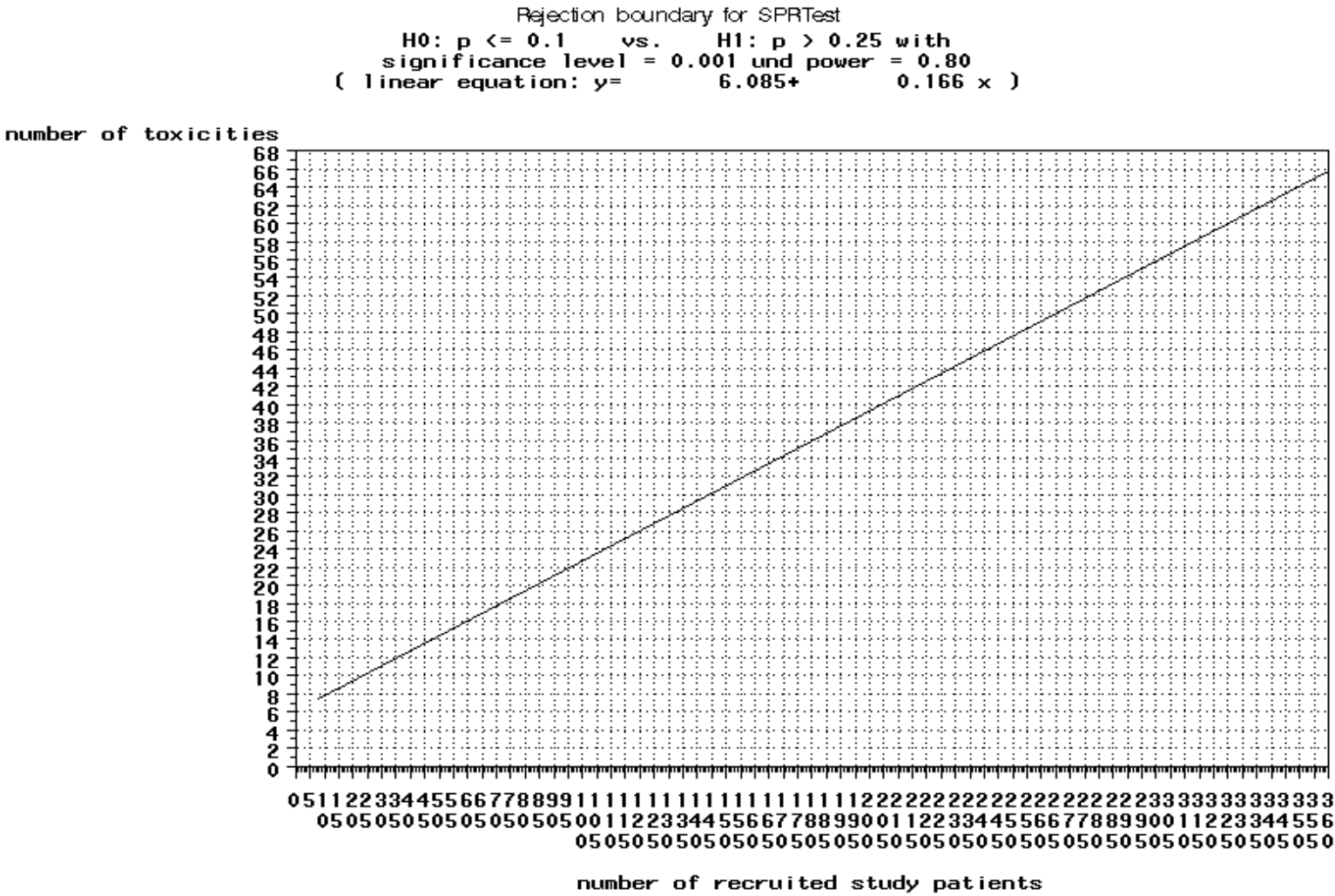
Stopping for toxicity and overall progression

Whenever a toxicity event occurs, the toxicity rate will be newly calculated. The toxicity rate will be computed as ratio of the number of study patients, which already had an event until this moment and the number of patients, which were recruited until this moment.
Relevant toxicities for this analysis are the WHO and / or CDC III° and IV° non-hematological organ-toxicities of the kidneys, the liver, the inner ear, and of the central and peripheral nervous system as well as death from toxicity.

The trial has to be stopped, if the probability for a toxic event exceeds 25 %. A probability for a toxic event of 10 % is acceptable. Having a sequential design according to Wald the trial shall be stopped, if the observed number of toxicities exceeds 6.085+0,166 x number of recruited patient. If 360 patients are recruited after 6 years, simulations show that the trial will be stopped in 99%, if the probability of a toxic event is 25%, and the trial will be stopped in 0.077% of the simulations, if the probability of a toxic event is 10 %.

This criterion has to be checked after each toxicity event.

Additionally, the $\underline{PFS_{CT}}$ (measured from the time of the start of chemotherapy) pooled over both randomized groups will be checked by an independent Data Monitoring Committee to identify a possible increase of progressions between the 6^{th} and 12^{th} month of chemotherapy, where therapy is given in 6-week cycles as compared to 4-week intervals as in the SIOP-LGG 1 study.
For this reason the Kaplan-Meier curves of the $\underline{PFS_{CT}}$ will be estimated. The estimates of the $\underline{PFS_{CT}}$ at 1/2 year and at 1 year will be compared with the 95 % confidence intervalls to the known $\underline{PFS_{CT}}$ at 1/2 and 1 year of the historical control groups, which were 90 % for the 1/2 year and 81 % for the 1 year point of time (Perilongo 2000).



Sample size calculation

By means of this trial the use of an intensified induction chemotherapy shall be investigated. The 3 year $\underline{PFS_R}$ for the standard induction chemotherapy is supposed to be 50%. The 3 year $\underline{PFS_R}$ for the intensified therapy is estimated to be 65%. With a significance level of 5 %, an accrual period of 6 years, a follow-up period of 2 years, a supposed drop-out rate after 5 years of 10% and on the assumption of exponential distributed $\underline{PFS_R}$ and drop-out times, 360 patients are necessary to obtain a power of 90% while performing a three step group sequential design according to Pampallona & Tsiatis explained above for the two-sided log-rank-test on difference. This corresponds with an annual recruitment rate of 60 patients. The sample size was calculated for an one-step design with nQuery Advisor 3.0 and the sample size was adapted to the 3-step group sequential design according to [1].

Estimated recruitment rate per year and country:

It is predicted that the annual recruitment rates for the participating national groups for children unaffected by NF I with glioma in and outside of the supratentorial midline would be:

Group 1:	Germany	15-20 per year
	United Kingdom	15
	Italy	10
	Nordic countries	5-10
Group 2:	approximately 30 % of the group 1	

No exact numbers can be calculated for the other participating countries.

Modifications of the protocol

The design of this trial may be changed, if necessary, in case of new important discoveries. Modifications of the protocol will be made only in form of written amendments and with agreement of the study committee. The respective ethic commissions have to be informed of the modifications. The patient information has to be changed according to the modifications of the protocol.

If an adaptation of the group sequential design is necessary – e.g. because of a low recruitment rate – the respective changes of the time points, number of interim analyses, maximal sample size and α-spending function will be done according to the conditional rejection error probability method by Schäfer und Müller [2001]. The modifications can be done during a planned or unplanned interim analysis on the basis of the observed data collected so far. The corresponding conditional rejection error probability functions are defined by Schäfer [2001]. If a design change is made the time point, the data file of the trial, all calculations and the description of the new group sequential design have to be recorded in the amendment.

17.1.2. Low grade glioma of all sites in children affected by Neurofibromatosis NF I (group 3 according to section 12.)

Design of the trial

Chemotherapy according to this protocol is applied to delay or obviate the start of radiotherapy compared with a historical control group.
In the trial SIOP - LGG 1 the NF1-patients younger than 5 years were treated with a 12 months chemotherapy, which was shorter than the 18 months chemotherapy of this protocol. For children older than 5 years primary radiotherapy was recommended, but only a small proportion of the older children did proceed with primary radiotherapy and had chemotherapy instead. This cohort is defined as the historical control group.

This therapy optimization trial is multinational, multicenter , prospective and historically controlled.
The accrual period of the trial amounts to 6 years, followed by an observation period of 2 years.

End points

Definitions of PFS, EFS and OS are according to section I.

1. $\underline{RFS_D}$: Radiotherapy free survival: Interval starting with the day of diagnosis and ending with the start of radiotherapy or death of the patient independently of its cause.For analysis of radiotherapy-free survival the event "death" is counted as an event as well.

2. $\underline{PFS_{CE}}$: Time from the end of the chemotherapy up to an event:
   Definition of event: death (for all reasons)
   progression of a residual tumor (section 16.3.)
   relapse following previous complete remission (section 16.3.)
   appearance of new or progression of existing metastasis
   This end point is only defined for those patients who will not have a progression until the end of the chemotherapy.

Questions of the trial

Explorative questions:

1. Does the prolonged chemotherapy (18 months) lead to a different $\underline{PFS_D}$ for the whole group of patients with NF1 - in comparison with a historical control group, who received radiotherapy or a shorter chemotherapy.

2. Does the prolonged chemotherapy lead to a different $\underline{EFS_D}$ for the whole group of patients with NF1 - in comparison with a historical control group, who received radiotherapy or a shorter chemotherapy.

3. Does the prolonged chemotherapy (18 months) lead to a different $\underline{RFS_D}$ - for patients with NF1 younger than 5 years - in comparison with a historical control group (NF I, younger than 5 years), who received a shorter chemotherapy (12 months).

4. Does the prolonged chemotherapy (18 months) lead to a different $\underline{PFS_D}$ - for patients with NF1 younger than 5 years - in comparison with a historical control group (NF1, younger than 5 years), who received a shorter chemotherapy (12 months)?

5. Does the prolonged chemotherapy leads to another $\underline{PFS_D}$ – for patients with NF1, with an age above 5 years – in comparison with a historical control group (NF1, age above 5 years), who received radiotherapy?

6. Does the prolonged chemotherapy (18 months) lead to a different $\underline{EFS_D}$ – for patients with NF I younger than 5 years – in comparison with a historical control group (NF I, younger than 5 years), who received a shorter chemotherapy (12 months)?

7. Does the prolonged chemotherapy (18 months) lead to a different $\underline{EFS_D}$ – for patients with NF I age above 5 years – in comparison with a historical control group (NF I, age above 5 years), who received radiotherapy?

8. What is the $\underline{RFS_D}$ of the whole group (NF1, all ages, only new trial) ?

9. Does the strategy of this protocol lead to a different $\underline{OS_D}$ for the children with NF I of all ages as compared to the previous protocol ?

10. Does the prolonged chemotherapy reduce / prevent the occurrence of progression after the end of the chemotherapy – for children with NF1 younger than 5 years – in comparison to a historical control group (NF1, younger than 5 years), who received a shorter chemotherapy?

Statistical analysis

It is anticipated that the SIOP-LGG 2004 strategy will maintain the good results for NF I children from the previous trials, with less therapy for the French children and only marginally more for the others.

The analysis will be done according to the intention-to-treat principle. Additionally there will be made a per-protocol analysis.
Per-protocol-patients are defined as follows: Children that received either intensified induction treatment and/or consolidation option B although recommendation for this treatment group is standard induction with consolidation option A. Aside the definitions from part I apply.

All analyses will be performed exploratively. Therefore the repective p-values are regarded as descriptive and no significance level is given.

According to the questions of the trial the following analyses will be done:

1. Null hypothesis: The $\underline{PFS_D}$ of children on the prolonged chemotherapy does not differ from the $\underline{PFS_D}$ of children of the historical control group, who received radiotherapy or a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the $\underline{PFS_D}$, the quartiles of the $\underline{PFS_D}$ with the 95 % confidence intervals, the $\underline{PFS_D}$ at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

2. Null hypothesis: The $\underline{EFS_D}$ of children on the prolonged chemotherapy does not differ from the $\underline{EFS_D}$ of children of the historical control group, who received radiotherapy or a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the $\underline{EFS_D}$, the quartiles of the $\underline{EFS_D}$ with the 95 % confidence intervals, the $\underline{EFS_D}$ at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

3. Null hypothesis: The $\underline{RFS_D}$ of children on the prolonged chemotherapy (younger than 5 years) does not differ from the $\underline{RFS_D}$ of children of the historical control group (younger than 5 years, NF1), who received a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the $\underline{RFS_D}$, the quartiles of the $\underline{RFS_D}$ with the 95 % confidence intervals, the $\underline{RFS_D}$ at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

4. Null hypothesis: The $\underline{PFS_D}$ of children on the prolonged chemotherapy (younger than 5 years) does not differ from the $\underline{PFS_D}$ of children of the historical control group (younger than 5 years, NF1), who received a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the $\underline{PFS_D}$, the quartiles of the $\underline{PFS_D}$ with the 95 % confidence intervals, the $\underline{PFS_D}$ at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

5. Null hypothesis: The $\underline{PFS_D}$ of children on the prolonged chemotherapy (older than 5 years) does not differ from the $\underline{PFS_D}$ of children of the historical control group (older than 5 years, NF1), who received radiotherapy.

This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the PFS_D, the quartiles of the PFS_D with the 95 % confidence intervals, the PFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

6. Null hypothesis: The EFS_D of children on the prolonged chemotherapy (younger than 5 years) does not differ from the EFS_D of children of the historical control group (younger than 5 years, NF1), who received a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_D, the quartiles of the EFS_D with the 95 % confidence intervals, the EFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

7. Null hypothesis: The EFS_D of children on the prolonged chemotherapy (older than 5 years) does not differ from the EFS_D of children of the historical control group (older than 5 years, NF1), who received radiotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the EFS_D, the quartiles of the EFS_D with the 95 % confidence intervals, the EFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

8. For descriptive reasons the Kaplan Meier curves of the RFS_D, the quartiles of the RFS_D with the 95 % confidence intervals, the RFS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

9. Null hypothesis: The OS_D of children on the prolonged chemotherapy (all ages) does not differ from the OS_D of children of the historical control group (all ages, NF1), who received radiotherapy or a shorter chemotherapy.
   This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the OS_D, the quartiles of the OS_D with the 95 % confidence intervals, the OS_D at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

10. Null hypothesis: The PFS_{CE} of children on the prolonged chemotherapy (younger than 5 years) does not differ from the PFS_{CE} of children of the historical control group (younger than 5 years, NF1), who received a shorter chemotherapy.
    This hypothesis will be analyzed by a two sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of the PFS_{CE}, the quartiles of the PFS_{CE} with the 95 % confidence intervals, the PFS_{CE} at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be illustrated.

17.2. Radiotherapy Group

17.2.1. Low grade glioma of all sites in children not affected by Neurofibromatosis NF I (group 1 and 2 according to section 12.)

Design of the trial

The aim of the trial is to assess outcome in children with low grade glioma of all sites necessitating radiotherapy as non-surgical therapy. (according to patient eligibility criteria (section 9.) and indication for non-surgical therapy (section 10.) as well as brachytherapy irrespective of these criteria).
This therapy optimization trial is multinational, multicenter, prospective and historically controlled.
The study patients of the SIOP-LGG 1996 study who received radiotherapy (primary or secondary radiotherapy) are defined as the historical control group.
The accrual period of the trial is 6 years followed by an observation period of 2 years.
It is expected that 240 patients will be recruited during 6 years.

End points

According to the different questions the following end points are defined:
For definition of progression and relapse referral is made to protocol section 16.3.

1. $\underline{PFS_{RT}}$: Progression free survival measured from the time of start of radiotherapy (brachytherapy): Time of start of radiotherapy (brachytherapy) up to one of the following events:
   - death (for all reasons)
   - progression of a residual tumor (section 16.3.)
   - relapse following previous complete remission (section 16.3.)
   - appearance of new or progression of existing metastasis (section 16.3.)

2. $\underline{PFS_{D}}$: Progression free survival measured from the time of diagnosis: Time from diagnosis up to an event defined in 1.

3. $\underline{EFS_{RT}}$: Event free survival measured from the time of start of radiotherapy (brachytherapy): Time of start of radiotherapy (brachytherapy) up to one of the following events:
   - death (for all reasons)
   - progression of a residual tumor (section 16.3.)
   - relapse following previous complete remission (section 16.3.)
   - appearance of new or progression of existing metastasis (section 16.3.)
   - severe adverse event / toxicity (section 16.4.)
   - appearance of secondary malignant neoplasm (section 16.4.)

4. $\underline{EFS_{D}}$: Event free survival measured from the time of diagnosis: Time from diagnosis up to an event defined in 3.

5. $\underline{OS_{RT}}$: Overall survival measured from the time of start of radiotherapy (brachytherapy): Interval starting with the day of start of radiotherapy (brachytherapy) and ending with the death of the patient independently of its cause.

6. $\underline{OS_D}$: Overall survival measured from the time of diagnosis: Interval starting with the day of diagnosis and ending with the death of the patient independently of its cause.

7. Radiological and clinical response (vision, neurological functions) measured after end of radiotherapy (brachytherapy) and at 6 and 12 months: Complete, partial, objective responses and stable disease will be considered positive responses in this protocol. Response definitions according to section 16.3. are used.

8. Time to maximal radiological and clinical response (vision, neurological functions).

   Subgroups:
   - Patients receiving external radiotherapy (excluding craniospinal irradiation)
   - Patients receiving brachytherapy
   - Patients receiving craniospinal irradiation

Questions of the trial

By means of this trial the following questions shall be investigated exploratively:

1. Does the use of modern treatment techniques in radiotherapy lead to a different PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_D, EFS_D, OS_D) in comparison with the radiotherapy of the historical control group (SIOP-LGG 1996)?
   (Subgroups: patients who receive external radiotherapy and patients who receive brachytherapy)

2. Is PFS_{RT} (EFS_{RT}, OS_{RT}, OS_D) different between patients who receive primary radiotherapy and patients who receive radiotherapy after chemotherapy has failed?
   (Subgroups: patients who receive external radiotherapy and patients who receive brachytherapy)

3. What is the PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_D, EFS_D, OS_D) of patients who started craniospinal irradiation after metastatic disease?

4. What are the rates of radiological and clinical response measured after 3 months (end of radiotherapy) and 6 and 12 months after end of radiotherapy?
   (Subgroups: patients who receive external radiotherapy, patients who receive brachytherapy and patients who receive craniospinal irradiation)

5. Is the radiological and clinical response (vision, neurological functions) measured after 3 months (end of radiotherapy (brachytherapy)) and at 6 and 12 months different between primary treatment or after chemotherapy has failed?
   (Subgroups: patients who receive external radiotherapy, patients who receive brachytherapy and patients who receive craniospinal irradiation)

6. What is the rate of maximal radiological and clinical response?
   (Subgroups: patients who receive external radiotherapy, patients who receive brachytherapy and patients who receive craniospinal irradiation)

7. What is the time to maximal radiological and clinical response for patients on primary treatment or for patients, who receive radiotherapy after chemotherapy has failed?

(Subgroups: patients who receive external radiotherapy and patients who receive brachytherapy)

8. Are modern treatment techniques associated with marginal or out of field treatment failures?

Cox regression model

The following variables are checked with reference to their influence on the $\underline{PFS_{RT}}$ and $\underline{EFS_{RT}}$ with multivariable methods by Cox regression:

Histopathology	Markers of proliferation (e.g. Ki 67 / MIB-1) (% positive cells) Molecular-pathologic markers (e.g. p 53 mutation) (% positive cells) (Quantification of markers is not standardized yet. The panel of pathologists will group these markers according to the current interpretation of their presence. See section 8.3.)
Tumor	Tumor size preoperatively (Product of the two largest diameters in cm) Tumor size postoperatively (Product of the two largest diameters in cm) Extent of surgery (see section 16.2) Localization and extent within the supratentorial midline for visual pathway glioma (Dodge classification)
Treatment	Radiotherapy as primary treatment / as salvage treatment Brachytherapy as primary / salvage treatment
Dissemination	primary/secondary (primary: present at diagnosis, secondary: diagnosis during follow-up) Type and extent of dissemination (nodular or leptomeningeal, descriptive extent (see section 16.1.))
Symptoms	Severe, visual or neurologic symptoms relevant for the decision to start non-surgical therapy (see section 10.) will be described according to their presence or absence: Visual symptoms Neurologic symptoms Increased intracranial pressure Diencephalic syndrome
Age	To investigate the „young“ and „older“ age groups according to the present strategy patients are divided into the following age groups: < 1 year, 1-8 years, ≥ 8 years To be comparable to previous trials patients are divided into the following age groups: < 1 year, 1 to 4, 5 to 10, > 10 years. Age will be analysed as a continuous variable also.
Sex	male / female

Observation time following diagnosis before starting therapy (continuous variable)

The delay between diagnosis and the time to commence treatment has been the strongest prognostic factor in the previous trial in that those that were treated within a short period of time did worse than those that were treated after a period of observation. However, the decision to treat or not to treat was often arbitrarily taken and therefore this parameter will be studied prospectively.

In the present study the indications to start non-surgical therapy (see section 10.) shall be strictly observed, in order to avoid such inaccuracies.

Last known response (before an event according to the definition of PFS_{RT} occurs)

Patients, in whom an event occurred before the first radiological examination to evaluate the response was given, will be censored.

Response definitions according to section 16.3. are used.

Statistical analysis

The analysis will be done according to the intention-to-treat principle. Additionally there will be made a per-protocol analysis.

Per-protocol-patients are defined as follows: Every child that received radiotherapy (or brachytherapy) according to the eligibility criteria. Treatment-modifications or interruptions for toxicity are no violation of the protocol. Premature termination due to toxicity is no protocol violation, but there should be no unreasonable or unexplained termination. Children who received a total dose which vary only less than 10% or more than 7% the defined dose prescriptions are included as being treated "per protocol".

All analyses will be performed exploratively. Therefore the respective p-values are regarded as descriptive and no significance level is given.

According to the questions of the trial the following analyses will be done:

1. Null hypothesis: PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_{D}, EFS_{D}, OS_{D}) of children treated according to protocol SIOP-LGG 2004 does not differ from PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_{D}, EFS_{D}, OS_{D}) of children treated according protocol SIOP-LGG 1996.
   This hypothesis will be analyzed by a two-sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_{D}, EFS_{D}, OS_{D}), the quartiles of PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_{D}, EFS_{D}, OS_{D}) with the 95 % confidence intervals, PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_{D}, EFS_{D}, OS_{D}) rates at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be given.
   These analyses will be done including all study patients treated according to protocol SIOP-LGG 1996 and SIOP-LGG 2004, who received radiotherapy. In a second step this analysis will be done separately for study patients, who received brachytherapy and for patients, who received external radiotherapy.

2. Null hypothesis: PFS_{RT} (EFS_{RT}, OS_{RT}, OS_{D}) of children on primary radiotherapy does not differ from PFS_{RT} (EFS_{RT}, OS_{RT}, OS_{D}) of patients who receive radiotherapy after chemotherapy has failed?
   This hypothesis will be analyzed by a two-sided log-rank test on difference. For descriptive reasons the Kaplan Meier curves of PFS_{RT} (EFS_{RT}, OS_{RT}, OS_{D}), the quartiles of PFS_{RT} (EFS_{RT}, OS_{RT}, OS_{D}) with the 95 % confidence intervals, PFS_{RT}

(EFS_{RT}, OS_{RT}, OS_D) rates at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be given.
These analyses will be done including all study patients treated according to protocol SIOP-LGG 1996 and SIOP-LGG 2004, who received radiotherapy. In a second step this analysis will be done separately for study patients, who received brachytherapy and for patients, who received external radiotherapy.

3. For the subgroup of patients, who receive craniospinal irradiation because of metastatic disease the following descriptive analyses will be done:
   For descriptive reasons the Kaplan Meier curves of PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_D, EFS_D, OS_D), the quartiles of PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_D, EFS_D, OS_D) with the 95 % confidence intervals, PFS_{RT} (EFS_{RT}, OS_{RT}, PFS_D, EFS_D, OS_D) rates at 24 weeks, 1 year, 3 years and 5 years with the 95 % confidence intervals will be given.

4. For descriptive reasons the frequencies of radiological and clinical response at month 3, 6 and 12 with 95 % confidence intervals will be illustrated. This analysis will be done separately for study patients who received brachytherapy, for patients, who received external radiotherapy, and for patients who received craniospinal irradiation.

5. Null hypothesis: The radiological and clinical response measured after 3 months (end of radiotherapy) and at 6 and 12 months after the end of radiotherapy does not differ between patients receiving primary radiotherapy and patients receiving radiotherapy after chemotherapy has failed.
   For each time of evaluation this hypothesis will be analyzed by a two-sided Chi-squared test. For descriptive reasons the respective frequency table and the corresponding 95 % confidence intervals will be given.
   This analysis will be done separately for study patients who received brachytherapy, for patients, who received external radiotherapy, and for patients who received craniospinal irradiation.

6. For descriptive reasons the frequencies of maximal radiological and clinical response measured in the first year (MRI at month 3, 6 12) after end of radiotherapy will be illustrated.
   This analysis will be done separately for study patients who receive brachytherapy, for patients, who receive external radiotherapy, and for patients who receive craniospinal irradiation.

Radiolog. Response	MRI 3 month	MRI 6 month	MRI 12 month	Best of MRI 3,6,12 month
CR				
PR				
OR				
SD				
PD				
	100%	100%	100%	100%

7. For the subgroup of patients who reach CR (PR, OR, SD, PD) as best response in the first year after the end of radiotherapy the frequencies of the time points when this response was reached will be given.

Best response	Reached	Reached at month 3 for the first time	Reached at month 6 for the first time	Reached at month 12 for the first time
CR				
PR				
OR				
SD				
PD				

This analysis will be done separately for patients on primary radiotherapy and for patients who receive radiotherapy after chemotherapy has failed.
Additionally this analysis will be done separately for patients who receive external radiotherapy and for patients who receive brachytherapy.

8. The rates of marginal or out of field treatment failures will be given.

Additionally, the analyses will be performed separately for the group of children with pure chiasmatic tumors (Dodge II), for the group of children with all other tumors of the supratentorial midline, the group of children with tumors of all other sites outside of the supratentorial midline.

Stopping for toxicity

The toxicity of children, who receive craniospinal irradiation because of metastatic LGG, will be observed.
Whenever a toxicity event occurs, the toxicity rate will be newly calculated. The toxicity rate will be computed as ratio of the number of study patients, who already had an event until this moment and the number of patients, who were recruited until this moment.
Relevant toxicities for this analysis are the WHO and / or CDC III° and IV° non-hematological organ-toxicities of the skin, mucosa, inner ear, and of the central and peripheral nervous system as well as death from toxicity.

The trial has to be stopped, if the probability for a toxic event exceeds 30 %. A probability for a toxic event of 10 % is acceptable. Having a sequential design according to Wald the trial shall be stopped, if the observed number of toxicities exceeds 1,706 + 0,186 x number of recruited patients. If 20 patients are recruited after 6 years, simulations show that the trial will be stopped in 69 %, if the probability of a toxic event is 30%, and the trial will be stopped in 4 % of the simulations, if the probability of a toxic event is 10 %.
This criteria has to be checked after each toxicity event.

Additionally, the trial has to be stopped, if more than one patient dies because of radiotherapy.

Since the effectiveness of the stopping rule given above depends on the recruited number of patients (which is small) the final decision to stop the trial is incumbent upon the study committee.

18. Organisational Issues SIOP LGG 2004

18.1. Institutional commitment

All institutions participating in the study must declare their commitment to do so according to the guidelines of the joined national study groups.
If individual centers from countries, whose national group does not take part as a whole, want to join the study, they shall link the national data center of one of the participating pediatric onocology groups.
All patients diagnosed with a low grade glioma by the participating institutions have to be registered and treated according to the guidelines of this protocol during the study period.

18.2. Study period

The study will be activated on April 1st 2004. Patient recruitment during the main study phase will extend for 6 years depending on the actual rate of enrolment. A two year follow-up phase is planned.

18.3. Protocol organisation

One common international protocol will be used by all national groups. This master protocol is written in English and is kept by members of the core committee. National groups or centers may provide translations of the English protocol.

Each national group is responsible to distribute the protocol to the members/institutions within their group.

Subsequent to finalisation, any amendments to the protocol must be agreed by all co-operative groups. The coordinating center and the core committee members will issue a revised version of the protocol, if and when required.
Addenda may be added independently by any groups to adress local needs, provided they have no bearing on the essential aims of the international protocol.

18.4. Study forms

One common set of forms will be used by all cooperative groups. The English language master version of the study forms will be held at the coordinating center and by the core committee members. Translations are within the responsibility of the national study centers.

The study center of each national group will be responsible for distribution of forms to institutions within that national group.

In case the international study does require additional information, amendments to forms have to be agreed upon by all cooperative groups. The central data center will be responsible to distribute the amended forms.
Additional forms may be produced within national study groups for data collections that are specific for that national group and exceed the international data set.

18.5. Documentation and data handling

Patients may be registered for the Low grade glioma study LGG 2004 only after he/she and/or his/her legal guardian has consented to registration and data saving. The appropriate forms for registration procedure from the addendum of this protocol have to be used by the institutions

and forwarded to the national data center. All forms must indicate the institution, name and signature of the physician responsible.

Each national group shall hold the database for its own patients and shall be responsible for data quality according to local practice. Forms returned from the treating institutions will be stored at the respective national data centers for time periods conformal to national law.
The content of the national database shall be identical to the data collected on the study forms.

All data from the national databases required for the conduct of the international study will be transferred by information transfer tecchniques to the international data center in 3-monthly intervals.
The International data base will be held at the Istituto Oncologico Veneto, Clinical Trials & Biostatistic Unit, "SIOP-LGG 2004", Busonera Hospital, I-35128 Padova, Italy.

It is most probable that future developments of information transfer will change the ways data are entered at the level of the participating institutions, the national study offices and the international study office during the currency term of this study. Especially the possibilities of remote data entry (RDE) will alter the traditional paper-based flow of data. If access to RDE is a realistic option, the national study members and the members of the core committee will discuss the implications of this technique and present the results to all national groups before action is taken.

If RDE is adopted, a high standard level of data confidentiality and security should be guaranteed.
In detail:

- The International common data base will not contain individual personal information
- All traffic with the server will be encrypted.
- Each user at each site will have its own User ID and Password.

The system will ensure:

- appropriate and regular backup on electronic media of all data, to permit restoration in case of loss or damage of the data base,
- operation tracking log (for each user: registration of any operation),
- electronic data audit trails (creation of a data base of original entries/modifications with identification of date, time, source and user identity),
- disaster recovery procedures.

18.6. Confidentiality of patient data

The use of patient names for identification on paper forms and in each data base will follow national practice. An abbreviated patient identifier will be used for data transfer and for the master database.

National and European legal rules concerning data handling will be observed.

18.7. Data quality control

On receipt of forms at each data center, common range and logical checks will be carried out on the data prior to entering into the national or to transfer into the international database. Criteria for this check or their changes/amendments will be agreed upon by the represented national groups
Errors noted in the national and/or master data base will be reported back to the center/institution of origin. Corrections can only be made using query forms.

18.8. Data analysis and monitoring

Reports on the international study progress will be prepared yearly, describing accrual of the patients, distribution among the strategy groups, local therapy modalities and toxicity of the treatments given. Data will be published as abstracts at each SIOP meeting.

The international study committee shall meet as appropriate to consider patient accrual, eligibility, treatment allocation and outcome and ensure a smooth conduct of the study.

Results of the interim analysis of response and progression free survival and of toxicity shall be reported to the International Data Monitoring Committee (IDMC) as scheduled by the protocol. The IDMC may recommend early stopping, continuation of or extension of the study to the international study committee.

18.9. Documentation of adverse events

Any life threatening event must be reported immediately by the treating physician to the national data center, i.e. within the next working day, and followed-up by the treating institution, regardless of whether or not it falls within the categories listed in section 16.4. The information must be relayed to the other data centers for further reporting according to GCP guidelines. Toxicity criteria are applied according to the publication of common toxicity criteria uniformly for all national groups.

18.10. Independent Data Monitoring and Safety Committee (DMSC)

An independent data monitoring committee composed of four international experts will monitor the progress of the study on ethical and scientific grounds.

The role of the IDMC will be:

- To review the accrual rate and to be involved with all interim analyses according to the statistical plan.

Each interim analysis will be reported to the DMSC. These interim analyses will remain confidential.
On the basis of these analyses the DMSC will recommend whether the study can continue, whether it has to be extended or changed or terminated prematurely.

- To monitor toxicity of all treatments, but especially toxicity of the chemotherapy arms and severe ad verse events.

Every 6 months a report of toxicity will be prepared by the international study center and the statistician of the study and circulated among the participating national groups and to the DMSC.
The DMSC will review these interim toxicity data and any relevant information will be forwarded to each study coordinator. Problems and patterns of major toxicity shall be analysed to prevent major toxicity endangering the conduct of the study.

- To compare the results of the on-going study to reports from other related study groups or institutions which may have implications for the aims of the study.

The DMSC will review reports of related studies performed by other groups or organisations to determine whether such information materially affects the aims or preliminary findings of

the trial. In case that interim analyses or the results of other studies implicate that the study questions have been answered, the DMSC has to decide in conjunction with the international study committee about the continuation of the current study.

- Other

The DMSC will be asked to review any major modification to the study proposed by the study committee prior to its implementation.

18.11. Follow-up

All registered patients shall be followed up by the national cooperative group study centers during and after completion of treatment according to the study. This also refers to patients off-study for any reason (e.g. toxicity).

18.12. Institutional/local ethical approval and patient's consent

Institutional / local ethical approval must follow national practice. The national and/or local ethics committee has to be contacted and a positive vote has to be obtained prior to starting patient recruitment. The ethics committee has to be informed about major toxic events (severe adverse events - study section 18.9., documentation of adverse events 16.4. severe adverse events, including second malignant neoplasm.)
Accepted national procedures for patient consent as documented are to be used.

The patient's and/or parent's written consent to participate in the study must be obtained after a full explanation has been given of the treatment options including the conventional and generally accepted methods of treatment and the manner of treatment allocation.
If the patient is a minor, the treatment must be explained to and consent received from his/her guardian. Additionally the child should receive an explanation as to his/her means of understanding and should give consent as well, if he/she is able to do so. Enough time and the opportunity to discuss participation before the decision for and start of treatment have to be given. The right of a patient to refuse to participate without giving reasons must be respected.

Consent for participation in the study and for data management will be obtained separately.

After the patient has entered the trial the physician must be free to give alternative treatment to that specified in the protocol at any stage, if he/she feels it to be in the best interest of the patient, but the reasons for doing so should be recorded, and the patient will need to remain in the study for the purpose of follow-up and data analysis according to the treatment option to which he/she had been allocated.
Similarly the patient must remain free to withdraw at any time from the study and the protocol treatment or to withdraw his/her data from the study without giving reasons and without prejudicing his/her further treatment.

All patients and/or their parents must give written consent to inclusion into the trial, data processing and – if applicable – to sending diagnostic material to reference institutions, which in all participating countries has to conform to the national data protection legislation. Administrative documents, consent forms and copies of the study documentation of a study patient have to be kept according to set archival terms.

This study will observe the rules for clinical research set out in the declaration of Helsinki in its latest form (Edinburgh, Scotland, 2000), the WHO and EC rules of "Good Clinical Practice" (ICH GCP: International Conference on Harmonisation – Good Clinical Practice, effective 17.01.1997), and the involved countries' laws.

18.13. Publication policy

Data relating to the present study SIOP - LGG 2004 must not be reported or published without prior consultation of the study chairmen, but side topics may be reviewed separately. Any publication arising from this study will have to acknowledge the contributing members/hospitals besides the regular listing of the authors of the paper. Additionally the specific requirements for listing of authors in different journals have to be respected.

A final report of SIOP - LGG 2004 will be provided within 5 years after the completion of the projected patient accrual by the “International Consortium on low grade glioma ” and all contributors be listed with their individual contributions in an appendix.

18.14. Associated research

Associated research is encouraged by the international and national study groups. Projects will mostly include limited numbers of patients or limited material, but hopefully will help to further understand the naturally erratic biologic behaviour of these tumors. Some projects are listed in this protocol, others may emerge during the conduct of the study. Participation in these studies is highly appreciated. Further information is available from the study centers.

19. Associated Research SIOP LGG 2004

SIOP

1. A phase II study of vinblastine sulphate injection in children with recurrent or refractory low grade glioma.
Investigator: Eric Bouffet, Toronto, Canada

2. Validation of methods of visual assessment in children with optic pathwa tumors.
Investigator: Ian Simmons, Alistair Fielder, Susan Picton, Adam Glaser, United Kingdom

Inquiry:
3. Analysis of tumor tissue of Disseminated low grade glioma by molecular genetic techniques (Comparative genomic hybridisation)
Investigator: Uri Tabori, Tel Hashomer, Israel

Germany

1. Atypical and clinically malignant pilocytic astrocytoma in children.
Investigator: O.D. Wiestler, T. Pietsch, H. Radner, Bonn

2. Treatment associated late effects following radiation therapy of malignancies in childhood and adolescents.
Investigator: N. Willich, A. Schuck, Münster

20. Literature SIOP LGG 2004

Besides all papers cited in the protocol, this list contains a number of references of additional interest for various aspects of low grade glioma that cannot be detailed in the frame of this therapy protocol.

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21.1. Common Toxicity Criteria SIOP - LGG 2004
Classification of acute side-effects according to CTC Page 1/4

Cancer Therapy Evaluation Program
Common Toxicity Criteria, Version 2,0
Publish Date: April 30, 1999

Blood

Grade	0	1	2	3	4
Hemoglobin (g/l)	WNL	<LLN - 100	80 - <100	65 - <80	<65
Leukocytes (mm³)	WNL	<LLN - 3000	≥2000 - <3000	1000 - <2000	<1000
Granulocytes (mm³)	WNL	<LLN - 1500	≥1000 - <1500	≥500 - <1000	<500
Platelets (mm³)	WNL	<LLN - 75,000	≥50,000 - <75,000	≥10,000 - <50,000	<10,000

Auditory/Hearing

Grade	0	1	2	3	4
Inner ear / hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Bilateral hearing loss *(Brock et al, 1991)*	< 40 dB at all frequencies	> 40 dB at 8000 Hz only	> 40 dB at 4000 Hz only	> 40 dB at 2000 Hz only	> 40 dB at 1000 Hz only

Neurology

Grade	0	1	2	3	4
Neuropathy-cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy-motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizure(s) of any type which are prolonged, repetitive of difficult to control (e.g., status epilepticus, intractable epilepsy)

Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

Infection

Grade	**0**	**1**	**2**	**3**	**4**
Infection	none	mild, no active treatment	moderate, localized infection, requiring antibiotic treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1,0 x 10^9/L)	none	38,0 - 39,0°C	39,1 - 40,0°C	>40,0°C for < 24 hrs	>40,0°C for >24 hrs

Renal

Grade	**0**	**1**	**2**	**3**	**4**
Hematuria	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Creatinine (x ULN)	WNL	> ULN - 1,5	> 1,5 - 3,0	> 3,0 - 6,0	> 6,0
Proteinuria (g/24 hrs)	normal or <0,15	1+ or 0,15 - 1,0	2+ to 3+ or 1,0 - 3,5	4+ or >3,5	nephrotic syndrome
Creatinine-clearance (ml/min + 1,73 m^2)	≥ 90	60 - 89	40 - 59	20 - 39	≤ 19

Nausea/Vomiting

Grade	**0**	**1**	**2**	**3**	**4**
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Vomiting (number of episodes/24 h)	none	1 over pretreatment	1-5 over pretreatment	≥ 6 over pretreatment; or need for IV fluids	requiring parenteral nutrition; or physiologic consequences requiring intensive care, hemodynamic collapse

Constitutional Symptoms

Grade	**0**	**1**	**2**	**3**	**4**
Weight loss	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Fatigue	none	increased fatigue over baseline, but	moderate (e.g., decrease in per-	severe (e. g., decrease in per-	bedridden or disabling

		not altering normal activities	formance status by 1 ECOG level or 20% Karnofsky or Lansky) or causing difficulty performing some activities	formance status by ≥2 ECOG levels) or loss of ability to perform some activities	
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition

Allergy

Allergic reaction / hypersensitivity	none	transient rash, drug fever <38°C (y< 100,4°F)	urticaria, drug fever ≥38°C (≥100,4°F) and/or asymptomatic bronchospasm	symptomatic brochospasm, requiring parenteral medication(s) with or without urticaria, allergy-related edema/angioedema	anaphylaxis

Gastrointestinal

Grade	**0**	**1**	**2**	**3**	**4**
Mucositis	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1,5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1,5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Stomatitus/pharyngitis	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers, but can eat or swallow	painful erythema, edema or ulcers requiring IV hydration	severe ulceration or requires parenteal of enteral nutritional support or prophylactic intubation
Diarrhea	none	increase of <4 stools/day over pre-treatment	increase of 4-6 stools/day or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care, or hemodynamic collapse
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon

Dermatology/Skin

Grade	**0**	**1**	**2**	**3**	**4**
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation ≥ 1,5 cm diameter and not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

Hepatic

Grade	**0**	**1**	**2**	**3**	**4**
Bilirubin (x ULN)	WNL	> ULN - 1,5	> 1,5 - 3,0	> 3,0 - 10,0	> 10,0
SGOT/SGPT (x ULN)	WNL	> ULN - 2,5	> 2,5 - 5,0	> 5,0 - 20,0	> 20,0

Pulmonary

Grade	**0**	**1**	**2**	**3**	**4**
Dyspnea	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support

Cardiovascular

Grade	**0**	**1**	**2**	**3**	**4**
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥24'% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline valuie; <24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
LV-EF Echocardiography	> 30%	26% - 30%	21% - 25%	16% - 20%	< 16%

Abbreviations:

LLN: lower limit of normal values
LV-EF: left ventricular ejection fraction
ULN: upper limit of normal values
WNL: within normal limits