Journal of Neuro-Oncology (2006) 78: 199–205
DOI 10.1007/s11060-005-9091-z
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Clinical–patient studies

Late sequela after treatment of childhood low-grade gliomas: a retrospective analysis of 69 long-term survivors treated between 1983 and 2003

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Key words: children, late effects, low-grade gliomas, outcome, treatment

Summary

The aim of the present study was to evaluate the spectrum of late effects in a large cohort of pediatric patients with low-grade gliomas (WHO grade I and II) during an observation period of 20 years. Eighty-seven patients with low-grade gliomas grouped according to tumor location (cerebellum: $n=28$; cerebral hemispheres: $n=21$; central midline: $n=15$; brainstem: $n=12$; tectum: $n=5$; other locations: $n=6$) were evaluated for tumor- and/or treatment-related late effects by analysis of medical and computer records, and personal interviews. Seventy patients underwent neurosurgery, 29 patients received additional radiotherapy and 20 additional chemotherapy. Median follow-up of survivors is 96 months with an overall survival of 79% (cerebellum: 89%; cerebral hemispheres: 95%; central midline: 80%; brainstem: 25%; tectum: 100%; other locations: 66%). Chronic medical problems (mild ataxia to multiple severe neuroendocrine deficits) are observed in 100% of patients with brainstem/central midline tumors and in 40–50% of patients with low-grade gliomas of other locations. Endocrine deficiencies were observed in 15/17 (88%) of long-term survivors who received radiotherapy. In contrast, none of the patients who underwent surgery only had endocrine deficiencies. Seven long-term survivors (10.1%) are severely disabled with permanent need of medical help. Tumor- and treatment-related late effects are common in patients with low-grade gliomas with the most severe occurring in patients with brainstem or central midline tumors. As long-term survival is excellent in patients with low-grade gliomas except for tumors located in the brainstem, future treatment studies should focus on avoiding long-term late effects.

Introduction

Low-grade gliomas (LGG) are a heterogenous group of slowly growing central nervous system (CNS) neoplasms accounting for approximately 40% of all childhood CNS tumors [1,2]. The clinical behavior varies remarkably and depends primarily on tumor location [3]. Patients with cerebellar or cerebral hemispheric LGG are frequently cured by total or gross total resection and generally do not need adjuvant treatment [4,5]. In contrast, radical surgical resection is not feasible for LGG at other sites such as central midline or brainstem tumors. Radiotherapy and/or chemotherapy are indicated for treatment of patients with central midline (hypothalamic/chiasmatic) LGG showing neurological symptoms or disease progression with chemotherapy being increasingly used in younger children to avoid or delay radiotherapy [6–12]. Mesencephalic tectal gliomas constitute a subgroup of brain stem gliomas which may remain stable over long time periods [13]. Conversely, patients with diffuse intrinsic pontine gliomas have an extremely unfavourable prognosis even after aggressive treatment [14–16]. Except for diffuse intrinsic pontine gliomas, long-term survival of $>80\%$ has been reported in patients with LGG [3–6,10,11]. Late effects in long-term survivors are either caused by the tumor itself or by the different treatment modalities used. The aim of the present retrospective study was to evaluate tumor- and/or treatment-related late sequela in a large cohort of long-term survivors after treatment of LGG.

Patients and methods

Between January 1983 and December 2003 289 patients with primary CNS tumors were referred to our institution. One hundred seventeen patients (40.8%) had LGG. Thirty patients were excluded from the present analysis. Twelve of these patients had diagnosis of neurofibromatosis or tuberous sclerosis. Eight patients, all of them admitted between 1983 and 1989 were excluded due to incomplete treatment and follow-up data. The remaining ten patients were excluded for the following reasons: admission for biopsy/surgery ($n=5$), gamma-knife radiosurgery ($n=1$) or second opinion ($n=1$) only, treatment continued at another institution due to geographical reasons with missing follow-up data ($n=1$), referral for salvage therapy ($n=2$). The remaining 87 patients form the basis of the present report (Table 1). The majority of patients ($n=70$; 80.5%) had

Table 1. Clinical characteristics of study patients according to tumor location

Characteristic	No. of patients (%)					
	Cerebellum	Cerebral hemispheres	Central midline[a]	Brainstem[b]	Tectum[b]	Others[c]
No. of patients	28	21	15	12	5	6
Gender						
Male	15	13	10	6	4	2
Female	13	8	5	6	1	4
Age at diagnosis (months)						
Median	71	145	64	71	123	72
Range	5–187	48–280	3–153	28–119	72–152	3–195
Histology	27	17	14	7	0	5
WHO grade I	22	7	12	1	0	3
WHO grade II	5	10	2	5	0	1
WHO I/II or grading inconclusive	0	0	0	1	0	1
Treatment						
Surgery						
Total resection	16	9	0	0	0	1
Near total resection	4	4	1	0	0	0
Partial resection	6	2	7	2	0	0
Biopsy	1	2	6	5	0	4
Radiotherapy (median dose)	3 (54 Gy)	5 (54 Gy)	8 (54 Gy)	11 (54 Gy)	1 (54 Gy)	1 (55.7 Gy)
Chemotherapy	0	0	6	9	1	4
Follow-up (months)						
Median	112	69	108	45	164	123
Range	24–246	18–235	39–185	27–62	31–211	57–193
Alive	25	20	12	3	5	4
Current remission status (of patients alive)						
Complete remission	18	15	2	0	0	1
Residual disease						
Non-progressive	5	4[d]	9	3	5	3
Progressive	0	1	1	0	0	0
True recurrence	2	0	0	0	0	0

[a]Including optic pathway/thalamic–hypothalamic LGG; [b]including diffuse intrinsic pontine and dorsally exophytic gliomas; [c]including spine and other locations; [d]including four patients with radiographically diagnosed LGG.

biopsy-proven LGG (WHO grade I and II). In the remaining 17 patients (19.5%) diagnosis of LGG was based on neuroimaging. Primary diagnostic evaluation included complete physical examination and pre- and postoperative contrast-enhanced magnetic resonance imaging (MRI) scans of the brain (± spine). Computed tomography scans were used for initial and follow-up evaluations until 1987. Follow-up MRI scans were performed at 3-month intervals for the first year after diagnosis, at 6- to 12-month intervals between the second and sixth year, and at 2–4 year intervals thereafter. Additional scans were done when clinical symptoms suggested disease progression. Tumor tissue specimens for histopathologic examination were obtained either by open tumor biopsy or by tumor resection. Histopathologic diagnosis was performed by local neuropathologists according to the WHO classification system for brain tumors [17] and included pilocytic astrocytoma I ($n=40$), fibrillary astrocytoma II ($n=19$), oligoastrocytoma II ($n=4$), others ($n=7$).

The extent of surgical resection was documented using the neurosurgeon's report and the immediate postoperative contrast-enhanced MRI. The criteria and definitions as published by the SIOP Brain Tumor Subcommittee were used to classify the extent of resection [18]. From 1996 adjuvant non-surgical treatment was performed according to the HIT-LGG 1996 multicenter trial of the German Society of Pediatric Oncology and Hematology (GPOH) [10]. Earlier patients with LGG were individually treated including surgery and radiochemotherapy depending on tumor location, extent of surgical resection and disease course. Patients with exophytic or diffuse intrinsic brainstem LGG were aggressively treated by simultaneous radiochemotherapy as described [16]. Evaluation of long-term tumor- and/or treatment-related late effects was done depending on tumor location and treatment. Patients with totally resected cerebellar or cerebral hemispheric LGG underwent routine neurological examinations in addition to follow-up neuroimaging only. Additional examinations in these patients were done in selected cases (e.g. after irradiation or in case of postoperative symptoms/deficits). Patients with central midline (hypothalamic/chiasmatic) or brainstem tumors and those who received radiochemotherapy following surgery underwent a detailed neuroendocrine and neurosensory (ophthalmological and audiological) evaluation. Endocrine evaluation included measurement of basal serum hormone levels and a combined stimulation test of the anterior pituitary function as described [19]. Simulation tests of the anterior pituitary function were primarily done before or after surgery and were repeated 6–12 months after discontinuation of radiochemotherapy and when clinically indicated (e.g. reduced growth rate). Replacement therapy was initiated in patients in whom clinical examination and biochemical tests

disclosed hormone deficiencies. The ophthalmological evaluation consisted of at least a fundus examination, assessment of ocular motility and, when feasible according to the patient's age, measurement of visual acuity and visual field determination. Audiological evaluation included standard audiometric techniques as well as behavioral and play audiometry under earphones.

Both ophthalmological and audiological examinations were performed by well-trained specialists of the respective departments. Late effects were categorized into two groups as previously described [20,21]. Group I consisted of 'significant' late effects (e.g. endocrine deficits requiring hormone replacement therapy or seizures requiring anticonvulsive medication), whereas group II included 'subclinical' findings (e.g. mild ataxia/hemiparesis, unsubstituted GH-deficiency). In patients who were not seen in our follow-up clinic for >2 years a brief semi-structured telephone survey was conducted. Survey questions addressed willingness to participate, time of last neuroradiographic evaluation, therapy since last visit, symptoms related to the underlying disease and/or therapy, self-reported health status, current medication and employment status.

Results

Basic clinical characteristics as well as response and treatment data are listed in Table 1. Late effects are summarized in Table 2. Median follow-up of all long-term survivors is 96 months with an overall survival (OS) of 79%.

Cerebellar tumors ($n=28$)

At a median follow-up of 112 months 25 patients are alive (OS: 89%). Eighteen patients are in complete remission. Presently, five patients have non-progressive residual tumors and two patients developed non-progressive recurrences after initial total resection. Tumor- or treatment-related late effects were found in 12 long-term survivors (48%). Three of them were assigned to late effects group I and nine patients to group II. Two patients are severely disabled with permanent need of medical help. The most common side effect was ataxia and was observed in seven patients. Cranial nerve palsies/hemiparesis and unilateral deafness are documented in three patients each. Visual impairment, GH deficiency, obesity and alopecia were found in one patient each, respectively.

Cerebral hemispheric tumors ($n=21$)

At a median follow-up of 69 months 20 patients are alive with an OS of 95%. Fifteen patients are in complete remission; one patient developed disease progression and underwent second surgery. The remaining four patients in whom diagnosis was based upon MRI scans have non-progressive tumors. A total of 10 patients developed late sequela (group I: 7; group II: 3). Seizures as a late effect were documented in seven patients; four of them are still requiring anticonvulsive medication. One of these seven patients underwent surgical seizure foci removal leading to complete disappearance of seizures and one patient presently does not need anticonvulsants. In the remaining patient no information is

Table 2. Chronic medical problems of long-term survivors according to tumor location

	No. of patients alive (%)					
	Cerebellum	Cerebral hemispheres	Central midline	Brainstem	Tectum	Others
No. of survivors	25	20	12	3	5	4
Chronic medical problems	12 (48%)	10 (50%)	12 (100%)	3 (100%)	2 (40%)	2 (50%)
Severely disabled	2	1	2	0	1	1
Category	No. of patients affected					
Endocrine[a]	1	4	8	2	1	1
GH-hormone deficiency	1 (s.)	3 (n.s.)	4 (s.: $n=1$; n.s.: $n=3$)	2 (n.s.)	1 (n.s.)	0
Hypothyroidism	0	1 (s.)	2 (n.s.)	1 (n.s.)	0	0
Anterior pituitary insufficiency	0	0	3 (s.)	0	0	1 (s.)
Amenorrhea	0	2 (s.: 1)	1 (s.)	0	1	0
Neurology[a]	9	7	8	3	1	2
Seizures	0	7	2	0	1	1
Ataxia/Extrapyramidal symptoms	7	0	2	1	0	0
Motor deficits (mono-hemiparesis, cranial nerve palsies)	3	2	5	2	1	1
Mental retardation	2 (preexisting)	0	0	0	0	1
Visual deficits						
Visual impairment	1	3	6	0	0	0
Hearing impairment						
Deafness (in one or both ears)	3	0	1	1	1	0
Others (including alopecia, obesity, shunts, second malignancies)	3	2	8	0	3	1

s.: substituted; n.s.: not substituted; [a]Since some patients had more than one of the late effects listed, the number of patients in one category (e.g. neurology) does not always equal the sum of the particular late effects.

available on anticonvulsive medication. Other late effects included mild visual impairment ($n=3$), GH deficiency ($n=3$), amenorrhoea ($n=2$) and motor deficits ($n=2$). Hypothyroidism, obesity and alopecia were observed in one patient each, respectively.

Central midline (hypothalamic/chiasmatic) tumors ($n=15$)

The OS in this group is 80% at a median follow-up of 108 months. During the disease course four patients were treated with radiotherapy, two patients with chemotherapy and four patients received both radiotherapy and chemotherapy. In seven patients ventriculo-peritoneal shunts were implanted. Only two patients are in complete remission. As a consequence of the tumor location and multimodality treatment all survivors are suffering from late sequela in various combinations. Eight patients developed endocrine deficits (hormone replacement therapy: $n=5$) and eight patients neurological deficits (Table 2). At the time of the last visit three patients were ≤10th percentile with regard to height; only four patients had a normal body weight and eight were obese (≥97th percentile), respectively. Visual impairment was found in six patients of whom two patients are completely blind. Four patients had optic nerve atrophy and disturbances of ocular motility ($n=2$), visual field defects ($n=1$), or optic nerve atrophy ($n=1$), respectively. Almost all patients were assigned to late effects group I ($n=11$). Two patients showed severe disabilities.

Brain stem tumors ($n=12$)

Nine patients with brainstem LGG received both local radiotherapy and chemotherapy and two patients radiotherapy only. All patients with diffuse intrinsic pontine gliomas died. Three patients are alive at a median follow-up of 45 months after diagnosis in good clinical condition with non-progressive residual tumors. With regard to late effects two patients were categorized into group II and one patient into group I (Table 2).

Mesencephalic tectal tumors ($n=5$)

In all five patients with focal gliomas involving the midbrain tectum and tegmentum diagnosis was based on neuroimaging. Three patients received ventriculoperitoneal shunts and one patient underwent ventriculostomy. At a median follow-up of 164 months all patients are alive with non-progressive disease, three of them without any sequela. The two patients with late effects were attributed to late effects group I. One patient who was treated with chemotherapy and conventionally fractionated local radiotherapy had severe combined neuroendocrine late effects. Another patient developed early onset of puberty, seizures and memory loss, but is currently without medication.

Tumors of other locations ($n=6$)

Four patients had spinal LGG and two of them died. In one patient each the tumor was located in the pinealis region and mid cerebral fossa, respectively. Three of the four patients alive had no ($n=2$) or only minimal neurological deficits ($n=1$). One patient received local radiotherapy for cervical LGG and later developed oligoastrocytoma grade III of the temporal lobe as second malignancy. He was treated by neuroaxis irradiation followed by chemotherapy and developed severe combined late effects (seizures, complete anterior pituitary insufficiency, renal insufficiency, leukoencephalomalacia with mental retardation).

Radiotherapy and radiotherapy-related late effects

Twenty-nine out of 87 patients (33.3%) were treated by radiotherapy (Table 1). Fourteen of these 29 patients underwent surgery before radiotherapy; 5 patients received additional chemotherapy and 9 both surgery and chemotherapy. Eight patients with cerebellar or cerebral hemispheric tumors were irradiated, only one of them after 1990.

Twelve of the irradiated patients died, most of them (9/12; 75%) had brain stem gliomas. Of the 17 long-term survivors who received radiotherapy all had at least one chronic medical problem. Fifteen patients (88%) developed endocrine dysfunctions (GH-deficiency: $n=10$; anterior pituitary insufficiency: $n=3$; hypothyroidism: $n=4$, amenorrhoea: $n=4$; total of numbers in brackets does not equal 17, since some patients had more than one of the endocrine dysfunctions listed). Eleven patients (65%) developed neurologic late effects (seizures: $n=4$, hemiparesis/cranial nerve palsies: $n=7$, extrapyramidal symptoms: $n=1$). Ocular and auditory late effects were found in 6 and 4 irradiated patients, respectively.

Late effects in patients who underwent surgery only

Fourty-six patients underwent surgery only (cerebellar tumors: $n=25$, cerebral hemispheric tumors: $n=16$; tumors of other locations: $n=5$). Three of them died. Of the 43 long-term survivors who underwent surgery 19 (44%) had at least one chronic medical problem (corresponding number in irradiated patients: 100%). No endocrine late effects were observed in these patients. Late effects in patients who underwent surgery only included neurologic late effects ($n=15$), visual impairment ($n=4$) and hearing loss ($n=2$), respectively.

Telephone survey

Thirty of 69 long-term survivors (43.5%) were >20 years old at the time of the last contact. The majority of these patients, particularly those with completely resected cerebellar or cerebral hemispheric tumors had finished their regular visits at our department and were followed by adult specialists (e.g. neurologists) or general practitioners. Some of them made their follow-up appointments irregularly and independently of follow-up programs and some of them declined to be regularly followed. The telephone survey included a total of 23 patients with cerebellar ($n=12$) or cerebral hemispheric LGG ($n=11$). Thirteen of these

patients underwent follow-up neuroimaging at regular intervals, whereas 10 patients did not. None of these patients developed disease recurrence or progression of residual tumors. Only one patient underwent partial resection of a cerebellar LGG with brain stem involvement at the age of 23 years. None received additional non-surgical therapies. Nineteen patients declared that they were able to lead normal or fairly normal lives, although some of them had chronic medical problems requiring on-going medical care (e.g. seizures) (Table 3). Three patients, however, were severely disabled and one patient had severe neurobehavioral problems. Seventeen patients were employed, attended school or had completed school. Of the remaining six patients no information concerning employment was available in 2; one patient was unemployed, two worked in a special job for handicapped people and one was unemployable due to severe disabilities.

Discussion

The incidence and spectrum of late effects after treatment of childhood CNS tumors has been extensively described since the late seventies [22–26]. It is well known that a high number of long-term survivors of brain tumors have permanent endocrine dysfunctions, neurologic deficits and neuropsychologic impairment following surgery, radiotherapy and/or chemotherapy. Earlier reports on late effects, however, included patients with different subtypes of brain tumors irrespective of histology, grading and location of the tumor. Fewer studies have in particular addressed questions concerning late effects in long-term survivors of LGG [4,27–33]. Not surprisingly, endocrine dysfunctions occurred more frequently in patients who received radiotherapy for LGG than in non-irradiated patients [4]. However, incidence rates of endocrine deficiencies ranging from 10% to 100% have been reported among patients with LGG depending on tumor location and treatment [4,27–30,33]. The likelihood to develop GH-deficiency following cranial irradiation for LGG approaches almost 100% [27]. A number of studies, however, have demonstrated that patients may also present with endocrine deficiencies at diagnosis [29,30,33]. In addition to radiotherapy younger age at diagnosis seems to be a risk factor associated with a higher incidence of endocrine dysfunctions [30]. In our study group endocrine deficiencies were observed in 15/17 (88%) of long-term survivors who received radiotherapy. Five of 45 long-term survivors with cerebellar (1/25) or cerebral hemispheric LGG (4/20) developed endocrine deficiencies. All of them received cranial irradiation. Corresponding figures for patients with mesencephalic/tectal tumors, brainstem gliomas and LGG of other locations were 1/5, 2/3, and 1/4 (all four patients were irradiated), respectively. In contrast endocrine dysfunctions were observed in eight of 12 survivors (66%) with hypothalamic/chiasmatic tumors. Six of them underwent cranial irradiation and five have or had to receive hormone replacement therapy. However, endocrine dysfunctions were also documented in two patients with hypothalamic/chiasmatic tumors (anterior pituitary insufficiency and GH-deficiency) who never had been irradiated confirming previous observations that the tumor itself or surgical procedures may cause endocrine deficiencies [28–30,33]. In eight long-term survivors with hypothalamic/chiasmatic LGG body weight was ≥97th percentile indicating that obesity seems to be closely related to the complex endocrine dysfunctions in these patients.

Focal neurological deficits and seizures are well known treatment-related complications in patients with hemispheric LGG [4,34]. The incidence of postoperative epileptic seizures during follow-up is reported to range between 15% [4] and 70% [34] in patients treated for supratentorial gliomas. In our population 7 of 20 long-tem survivors (35%) developed seizures as a late effect during the follow-up period, but motor deficits were observed in only 2 patients. Ataxia is the most commonly observed neurological deficit after treatment for cerebellar LGG [5]. Five of our patients with cerebellar LGG had mild and two patients severe ataxia. As a surgical complication three patients with cerebellar LGG had motor deficits and two other patients developed unilateral deafness postoperatively.

Reports on neuropsychological and cognitive abilities in patients treated for LGG yielded conflicting results. Whereas some authors found a negative correlation between radiotherapy and intellectual outcomes in these patients [4,29,31], others did not [32,33]. In the study by Taphoorn et al. which included only adult patients with LGG treated with or without radiotherapy no differences in cognitive and affective functions between irradiated and non-irradiated patients were observed [32]. The authors, therefore, concluded that radiotherapy had no negative impact on the neuropsychological status of their study patients possibly due to the fact that patients received focal radiotherapy only. Similar results have recently been presented for children [33]. Interestingly, mean intelligence quotients (IQ) were already compromised at diagnosis in this study. There was no evidence that IQ changed during the study period in irradiated as well as in non-irradiated patients [33]. In addition Beebe

Table 3. Chronic medical problems in patients who declared to lead normal lives in the telephone survey ($n = 19$)

Category	No. of patients affected
Endocrine	
GH-hormone deficiency	1
Neurology	
Seizures	4
Ataxia	3
Motor deficits (mono-hemiparesis, cranial nerve palsies)	1
Visual deficits	
Visual impairment	1
Hearing impairment	
Deafness (in one or both ears)	1
Others (including alopecia, obesity, shunts, secondary malignancies)	3

et al. recently reported that children with cerebellar LGG who underwent surgery only showed poorer (subnormal) cognitive and adaptive abilities compared to true average indices [35].

Though quality of life testing was not done in our study patients, the majority of patients contacted by telephone survey rated their health as good or fairly good, even if they had chronic medical problems necessitating continuous medical care (e.g. seizures). Most of these patients were also employed, attended school or had completed school at the time the interview was conducted.

In 1984 Li et al. reported that about 10% of patients with astrocytoma showed severe disabilities after treatment [24]. Comparably seven of 69 long-term survivors (10.1%) in our study showed severe disabilities including ataxia, seizures, paresis, mental retardation, multiple endocrine deficits, and auditory or visual loss. These patients had to attend special classes for handicapped people or were unemployable due to their disabilities. Only three of these seven patients were treated by surgery, radio- *and* chemotherapy. Two underwent surgery only indicating that the tumor itself and/or surgery caused these functional deficits. The remaining two patients received surgery/radiotherapy and surgery/chemotherapy, respectively. Of note, all severely disabled patients in our study were treated between 1983 and 1995 indicating a less aggressive treatment approach in children with LGG thereafter. When we tried to quantify late sequela in these patients, it was often difficult to separate the effect of the tumor from the effect of the treatment. The increasing experience with LGG patients during the study period might also have contributed to the lower incidence of severe treatment-related sequela after 1995.

In conclusion, long-term prognosis of patients with LGG is excellent except for those located in the brain stem. This study clearly shows that a considerable number of patients with LGG require a life-long follow-up. The care of severely disabled brain tumor survivors remains a major challenge for parents, clinicians, practitioners, and care givers. The spectrum of tumor- and treatment-related side effects will be prospectively evaluated in ongoing cooperative multicenter trials (SIOP LGG 2004). However, as long-term survival is excellent, future trials should primarily focus on avoiding late sequela.

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