Strahlentherapie
und Onkologie

Review Article

Current and Future Strategies in Radiotherapy of Childhood Low-Grade Glioma of the Brain

Part II: Treatment-Related Late Toxicity

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Background: For more than 60 years, radiation therapy has been an integral part in the management of childhood low-grade glioma. As this tumor carries an excellent long-term prognosis, the risk of late effects is of particular clinical importance and impinges upon radiotherapeutic treatment strategies.
Material and Methods: Studies on the use of radiation therapy in children with low-grade glioma were systematically reviewed for data on radiotherapy-induced side effects on brain parenchyma, endocrine dysfunction, growth retardation, neurocognitive dysfunction, vasculopathy, and secondary neoplasms.
Results: Data on late effects are scarce and heterogeneous. Past reports included only retrospective series from the 1930s to present days, a time during which treatment policies and radiation techniques widely varied and considerably changed in recent years. Often, considerable uncertainty existed regarding pretreatment health status and radiotherapy-related factors (e.g., total dose, dose per fraction, treatment fields). In spite of these shortcomings and often conflicting observations, it appears that especially younger children and children with neurofibromatosis (NF) are at risk of endocrinopathies in terms of growth retardation and developmental abnormalities, as well as neurocognitive dysfunction expressed as problems in the psychosocial environment such as in education and occupation. However, both observations may be attributed to the higher proportion of NF in the very young who frequently develop large tumors spreading along the entire supratentorial midline. The risk of radiation-induced disturbances in visual function is low (no case reported). Young children with NF appear to have an increased risk of vasculopathies. 33 cases of moyamoya disease were found (preferably in the very young), 18 of whom were NF-positive. Other cerebrovascular accidents (24 cases, of whom 14 were NF-positive) and secondary neoplasms (15 cases, of whom only five occurred in field – four were high-grade astrocytomas) are a rare condition. The latter cannot be distinguished from late relapses with malignant transformation. Modern treatment techniques appear to reduce the risk of radiation-induced late effects.
Conclusions: More studies and clear definitions of clinical endpoints such as neurocognitive and endocrinological outcome are needed in order to clarify the impact of radiation therapy on the risk of late sequelae. Presently, the strategy to postpone radiotherapy in the younger children, especially with NF, is justified to reduce the risk of late effects. These information and the contribution of tumor, surgery and chemotherapy will help to define the role of radiation therapy in the future management of childhood low-grade glioma and whether the use of highly sophisticated and expensive treatment techniques is justifiable. The recently initiated prospective study of the APRO (Pediatric Radiooncology Working Party) on documentation of dose prescription to organs at risk and the network of the GPOH to explore late effects as well as the forthcoming prospective SIOP/GPOH (International Society of Pediatric Oncology/German Society of Pediatric Oncology and Hematology) LGG 2003 trial are addressing these issues.

Key Words: Children · Toxicity · Late effects · Radiation therapy · Low-grade glioma

Strahlenther Onkol 2003;179:585–97
DOI 10.1007/s00066-003-8104-0

Aktuelle und zukünftige Strategien bei der Bestrahlung von niedrigmalignen Gliomen des Gehirns im Kindesalter. Teil II: Therapiebedingte Spätfolgen

Hintergrund: Seit mehr als 60 Jahren bildet die Bestrahlung einen integralen Therapiebestandteil bei der Behandlung von niedrigmalignen Gliomen im Kindesalter. Da diese Tumoren eine sehr gute Langzeitprognose besitzen, spielt das Risiko für Therapiefolgen eine besondere klinische Rolle und beeinflusst damit radiotherapeutische Behandlungsstrategien.

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Received: October 16, 2002; accepted: May 6, 2003

Material und Methodik: Studien über die Anwendung von Radiotherapie bei niedrigmalignen Gliomen im Kindesalter wurden systematisch analysiert im Hinblick auf Daten bezüglich strahlentherapieinduzierter Spätfolgen im Hirnparenchym, endokriner Funktion, Wachstum und Entwicklung, neurokognitiver Funktion, Gefäßveränderungen und Zweittumoren.
Ergebnisse: Literaturangaben über Späteffekte sind gering und heterogen. Zurückliegende Berichte schlossen nur retrospektive Serien der 30er Jahre bis heute ein, also eine Zeit, in der sich Behandlungsrichtlinien und Strahlentherapietechniken erheblich unterschieden und sich in jüngster Zeit deutlich änderten. Häufig bestand eine ausgeprägte Unsicherheit hinsichtlich des Gesundheitszustands vor Therapie und strahlentherapiebezogener Faktoren (wie Gesamtdosis, Einzeldosis, Bestrahlungsfelder). Trotz dieser Einschränkungen und häufig widersprüchlicher Beobachtungen scheint es, als wiesen insbesondere jüngere Kinder und Kinder mit Neurofibromatose (NF) ein besonderes Risiko für endokrinologische Störungen in Form von Wachstumsverzögerung und Entwicklungsstörungen ebenso wie für neurokognitive Dysfunktionen, ausgedrückt als Probleme in der psychosozialen Umgebung wie Erziehung, Ausbildung und Beruf, auf. Beide Beobachtungen können jedoch dem höheren Anteil von NF bei sehr jungen Kindern zugeschrieben werden, die häufig große Tumoren entlang der gesamten supratentoriellen Mittellinie entwickeln. Das Risiko für strahlentherapieinduzierte Störungen der Visusfunktion ist gering (kein Literaturbericht hierzu). Jüngere Kinder mit NF scheinen ein erhöhtes Risiko für Gefäßerkrankungen aufzuweisen. 33 Fälle von Moyamoya-Syndrom wurden gefunden (vorzugsweise bei sehr jungen Kindern), von denen 18 das klinische Bild einer NF boten. Andere zerebrovaskuläre Ereignisse (24 Fälle, davon 14 NF-positiv) und Zweittumoren (15 Fälle, von denen fünf innerhalb der Bestrahlungsfelder auftraten – vier waren hochmaligne Astrozytome) sind selten. Letztere sind nicht von späten Rückfällen mit Malignisierung zu unterscheiden. Moderne Bestrahlungstechniken scheinen das Risiko für strahlentherapiebedingte Spätfolgen zu senken.
Schlussfolgerungen: Weitere prospektive Studien und eine klare Definition klinischer Endpunkte wie neurokognitives und endokrinologisches Behandlungsergebnis sind notwendig, um den Einfluss der Strahlentherapie auf das Risiko für Therapiefolgen abzuklären. Derzeit ist die Strategie, die Strahlentherapie bei jüngeren Kindern hinauszuzögern (besonders bei NF), gerechtfertigt, um das Risiko für Therapiefolgen zu reduzieren. Diese Informationen und der Beitrag von Tumor, Operation und Chemotherapie werden dazu dienen, die Rolle der Strahlentherapie in zukünftigen Behandlungsstrategien zu definieren, und klären helfen, ob die Anwendung hochpräziser und aufwendiger Bestrahlungstechniken gerechtfertigt ist. Die kürzlich initiierte prospektive Studie der APRO (Arbeitsgemeinschaft Pädiatrische Radioonkologie) zur Dokumentation von Dosisverschreibungen innerhalb von Risikoorganen und das Kompetenznetzwerk pädiatrische Onkologie der GPOH zur Untersuchung von Spätfolgen befassen sich ebenso wie die in Vorbereitung befindliche SIOP/GPOH- (International Society of Pediatric Oncology/Gesellschaft für Pädiatrische Onkologie und Hämatologie-)LGG-2003-Studie mit diesen Themen.

Schlüsselwörter: Kinder · Nebenwirkungen · Spätfolgen · Strahlentherapie · Niedrigmaligne Gliome

Introduction

Children harboring a low-grade glioma of the supratentorial midline, at hemispheric and cerebellar sites show an excellent prognosis with 10- and 20-year overall survival rates often in excess of 80%. Resection is the treatment of choice, if location and extent of disease permit aggressive surgery, followed by surveillance, radiotherapy or, recently, chemotherapy [24, 36, 67]. Although there is consensus today to employ nonsurgical treatment in progressive disease only, the selection of radiotherapy or chemotherapy is a matter of controversy. Chemotherapy has been investigated in recent years in younger children in order to postpone the necessity of irradiation, because of an increased risk of severe late effects. However, data on late effects in the literature are difficult to interpret, and the impact on the selection of treatment modality with respect to age, prognostic factors and risk factors to develop late effects is largely unknown [39, 59, 70].

The recognition and importance of radiation-induced sequelae have stimulated investigation of alternative treatment approaches, especially the introduction of modern treatment techniques which have the potential to limit the high-dose regions to the tumor itself, thereby reducing the dose to surrounding normal tissue. Today, low-grade glioma are therefore a challenging issue for the radiooncologist, because the use of modern technologies would ideally lead to a decrease in long-term toxicity while maintaining or even improving the overall outcome.

Medline search was performed for publications including case reports and supplements on radiotherapy in the management of childhood low-grade gliomas of the brain between 1956 and 2002. The literature was reviewed with respect to changes in brain parenchyma, endocrine dysfunction, growth retardation, neurocognitive dysfunction, vascular changes, and radiation-induced secondary neoplasms. Conclusions were drawn from the data on future radiotherapeutic treatment strategies.

Effects on Brain Parenchyma

Postradiation changes include a wide spectrum of abnormalities from subclinical changes detectable only by MRI to focal neurologic deficits and intellectual impairment due to brain necrosis or diffuse white matter injury, respectively. It appears, that all changes are likely to result from complex alterations within several functional compartments with at least four contributing factors: damage to vessel structures, deletion of oligodendrocyte progenitor cells and mature oligodendro-

cytes, deletion of neural stem cell population in the hippocampus, cerebellum and cortex, and, finally, generalized alterations of cytokine expression [7]. Reports on morphologic changes of brain parenchyma in childhood low-grade glioma are scarce and inconclusive with respect to clinically manifest disorders.

Necrosis of Brain Parenchyma

Radiation necrosis is a function of total dose and fraction size with threshold doses of approximately 45 Gy in ten fractions, 60 Gy in 35 fractions, and 70 Gy in 60 fractions, respectively [14, 62]. With conventional fractionation schedules of 1.8–2.0 Gy/day, total doses up to 54 Gy, usually applied in low-grade glioma, are well tolerated without the risk of necrosis.

Single high-dose irradiation ("radiosurgery"), however, may cause frank necrosis or sclerosis. In the series of Grabb et al. [28], eleven patients had received fractionated irradiation before stereotactic radiosurgery. At approximately 6 months, the morbidity was 16%, and neurologic symptoms occurred in children with tumors involving the brain stem. While only one child had a persisting neurologic deficit, marginal restriction of upward gaze, without functional significance, three children had imaging evidence of peritumoral edema causing the morbidity. Weprin et al. [73] reported one of seven children who suffered a persistent lower cranial nerve palsy after radiosurgery. One child treated for a malignant glioma died of complications related to radiosurgery.

With fractionated stereotactic convergence therapy, side effects have only been rarely observed. Approximately 20% patients experienced posttreatment peritumoral edema which is usually clinically silent, resolving either spontaneously after 6–11 months or after steroid treatment [27, 66]. There have been only a few documented cases of radiation-induced necrosis. Benk et al. [8] observed two such cases in 14, eight of whom had low-grade glioma.

After fractionated external radiotherapy, changes on MRI can be observed that may lead to the erroneous diagnosis of tumor progression or brain necrosis. In the series of Bakardjiev et al. [4], twelve of 28 patients (43%) developed one or more changes such as increased size or enhancement of the lesion, cyst formation and/or an increase in edema or mass effect on follow-up MRI, sometimes resembling necrotic changes. Fractionated stereotactic radiation therapy had been applied to a total dose of 52.2–60.0 Gy with fractionated doses ranging between 1.8–2.0 Gy. Most of these changes occurred between 9 and 12 months after the start of fractionated stereotactic radiotherapy and resolved or decreased by 15–21 months. All but one patient had normal or stable neurologic examination. It can be concluded that these asymptomatic MRI changes are common in children with low-grade astrocytomas undergoing conventional fractionated radiation therapy. They follow a certain time course with a peak incidence within 1 year after start of irradiation and generally resolve by an interval of 2 years.

Interstitial radiosurgery employs ionizing radiation most commonly produced by Iodine-125. Due to the high local dose, a circumscribed area of radionecrosis is a constant feature which spreads from the center of the implant to the periphery within weeks [41]. The radioactive source may cause temporary increase in capillary permeability leading sometimes to extensive edema accompanied by a reduced regional cerebral blood flow. Increased intracranial pressure may occur, and steroid medication is often necessary to control symptoms. Although twelve out of 331 adult patients developed progressive symptoms of radiation-induced toxicity after radiosurgery in the series of Kreth et al. [41], no toxicity was described in 124 children. The major risk factors associated with interstitial radiosurgery were tumor volume and mode of implantation. Temporary implants posed lesser risk for acute toxicity and late effects than permanent ones.

Diffuse Changes of White Matter on Imaging (Leukoencephalopathy)

Diffuse white matter changes on imaging often labeled as leukoencephalopathy is a well-known phenomenon after whole brain irradiation for childhood leukemia. Although some authors reported conflicting results, it is assumed that the clinical counterpart of diffuse white matter changes is a decline in neurocognitive function, which essentially depends on age at treatment and concomitant application of methotrexate and dose prescription as low as 18–24 Gy [44, 46, 47, 59]. Changes on imaging, however, do not appear to correlate with neurocognitive dysfunction [61]. Diffuse changes of brain parenchyma as detected by imaging in low-grade glioma are a difficult issue and reports are scarce, although large treatment portals encompassing a large volume of normal brain tissue, even whole brain irradiation, with markedly higher doses have been used in past series. Pierce et al. [53] detected mineralization, brain atrophy or white matter degenerations in their series of 47 patients during regular follow-up investigations. Calcifications were seen on CT scans in eight patients as early as 7 months after treatment (range 7–44 months) and were progressive in five. Cerebral atrophy was apparent in five patients as early as 19 months after therapy (range 19 months to 6 years) and was progressive in two. White matter degeneration was recognized as abnormal low density by CT in eight patients. No correlation was found between changes on imaging and neurocognitive dysfunction which occurred in ten of all patients. Tao et al. [69] observed predominantly features of mineralization, white matter degeneration, and atrophy. Again, an increase in severity and frequency over time was observed. New calcifications were detected in eight patients between 7 and 56 months after radiation therapy, progressing in five. Cerebral atrophy was noted in five patients, manifesting 19 months to 6 years after treatment. As in the series of Pierce et al. [53], no clear correlation was found between clinical features, treatment parameters, and changes on imaging.

The technique of imaging appears to be important, to detect structural changes of brain parenchyma. Quantitative MRI is sensitive to subtle changes below the resolution of conventional MRI. The working group of St. Jude Hospital assessed the effect of ionizing radiation to the brain in 29 pediatric patients undergoing fractionated conformal radiotherapy of brain tumors [65]. Mapping showed that white matter exposed to < 20 Gy and gray matter to < 60 Gy do not undergo pathologic changes.

Neurocognitive Dysfunction/Behavioral Changes

The risk of neurocognitive dysfunction and changes in behavior is an important issue in the management of low-grade glioma, as quality of life may be severely compromised [10, 17, 72]. Pollack et al. [54] reported on complications and treatment-related sequelae presumably related to surgery followed by radiotherapy in glioma of the hemispheres. They observed obvious difficulties in 15 children that necessitated removal from regular classes and/or placement in a special education program and, automatically, led to an inability to work outside a sheltered environment. The incidence of cognitive dysfunction was 34% among the children receiving postoperative radiotherapy versus 8.6% in the group undergoing surgery alone, an association that was at significant levels.

The occurrence of neurocognitive abnormalities in chiasmatic glioma is also difficult to analyze. Danoff et al. [17] reported on four of 15 living patients with mental retardation, two of whom were in semicomatose state after radiation therapy. Weiss et al. [72] noted five of 16 patients with mental retardation after radiation, although one had meningitis as a possible causative factor. Deficits before radiotherapy are not unusual. Lloyd [42] reported that 33% of his patients had mental retardation before treatment. Dosoretz et al. [20] and Rodriguez et al. [57] reported two of 20 cases and four of 33 cases, respectively, of severe mental retardation before radiotherapy. By contrast, in the series of Pierce et al. [53], a high incidence of neurocognitive abnormalities was found with 50% of the evaluable children having some form of learning disability after radiation therapy.

It appears that age and the presence of neurofibromatosis (NF) are important risk factors for developing neurocognitive dysfunction [15, 69]. Cappelli et al. [13] noted in a series of 65 patients, 54 being treated with radiotherapy, that 18 were severely intellectually disabled, most of whom underwent radiotherapy at a median age of 4 years.

In the series of Janss et al. [35], the impact of age was analyzed in children who received chemotherapy as first-line treatment and radiotherapy in progressive disease. Seven of 17 children showed behavioral impairment. Of the seven children with abnormal behavior, four were irradiated before age of 5 years. Of the ten who showed normal behavior, six were never irradiated. Ten of these 17 children were receiving special education. Five of the ten children who had received radiotherapy were irradiated before age 5 years. All of the seven children who attended a mainstream school and received a normal education were irradiated after age 4 or not at all. The association between radiation before age 5 years and the need for special education was statistically of borderline significance. The limited number of children in this study, however, does not permit any firm conclusions about the effects of radiation or chemotherapy on intellect. Sutton et al. [67] retrospectively reviewed 33 patients who were conservatively treated with surgery and subsequently received radiotherapy, if ≥ 5 years, or chemotherapy, if < 5 years of age. At a mean follow-up of 10.9 years from diagnosis, 16 of 28 children (57%) were in school or had completed schooling with regular academic achievements. Twelve children (43%) required a special education. Twelve patients in regular school underwent radiotherapy at a mean age of 11 ± 4.5 years, whereas children in special education received radiotherapy at a mean age of 5.7 ± 3.8 years. The impact of additional chemotherapy in children < 5 years of age on the development of neurocognitive dysfunction is unknown and obscures the interpretation of these observations. Additionally, the impact of tumor size and extent of surgery was not assessed, and initial neuropsychologic testing was not performed. Again, treatment techniques and dose prescription were not adequately assessed.

NF alone is associated with significant cognitive morbidity, and the problem appears to be pronounced, if a brain tumor is present. Tao et al. followed 28 children, eleven of whom had a history of learning difficulties requiring special education prior to treatment [69]. Nine of them had NF. During follow-up, 20 patients needed special education. Of these 20 children, eleven had NF, and three children were treated prior to 5 years of age.

Restriction of treatment fields by using conformal techniques might be able to reduce the risk of neurocognitive deficits. Debus et al. [18] observed only two of ten patients with learning problems during follow-up. Both children were NF-positive and had other tumors of the central nervous system (CNS) at sites distant from the radiation fields. This observation was confirmed by Saran et al. [60] who found only two of 14 patients having learning difficulties after conformal fractionated radiotherapy. Correspondingly, Hug et al. [34] reported that no patient in their series, treated with protons, had a drop of > 10% in quality of life assessment on Lansky performance scale.

Neurologic Deficits

Evaluation of long-term neurologic deficits is difficult, due to frequent tumor effects and surgical morbidity. Slavc et al. [63] analyzed 16 children harboring a low-grade glioma with respect to neurologic complications. Six children had tumors at supratentorial sites, and ten children had cerebellar astrocytoma. Five patients received postoperative radiotherapy. In four cases of supratentorial lesions, epilepsy was present, in posterior fossa tumors three cases with ataxia, two with paresis of the facial nerve, one of whom also had hypacusis and an-

other case of isolated hypacusis. However, in all patients evaluation of these deficits was not performed at time of diagnosis or after surgery. Wallner et al. [71] noted, in their series of 21 patients, one child with seizures and one with neurologic deficits at last follow-up, Horwich & Bloom [33] one case with epilepsy and one case with hemiparesis. Forsyth et al. [26] investigated neurologic function in 51 children with supratentorial pilocytic astrocytoma before and after surgery. 42 children underwent aggressive surgery (total or subtotal resection including 15 children with lobectomy). Presurgical assessment revealed moderate deficits in four. Postoperatively, three children had marked and two had severe complications. The observations indicate that morbidity caused by surgery is an important contributing factor for the overall risk to develop late sequelae.

Endocrine Dysfunction

Endocrine dysfunction may arise as a consequence of tumor or surgical and/or radiotherapeutic approach, particularly in glioma of the supratentorial midline (Table 1). It is often combined with a complex dysregulation of hormonal function causing (among other disorders) precocious or delayed puberty combined with growth retardation. Reference to endocrine abnormalities, however, is variable and incomplete in the literature including uncertainties in the interpretation of tumor/treatment interrelationships and lack of initial assessment.

In many series, endocrinological disorders were noted at time of presentation in tumors of the supratentorial midline indicating that tumor growth and infiltration of functionally important areas are a causative factor. Robertson & Brewin [56] reported the highest incidence in the literature with 70% endocrine dysfunction at presentation. Sung [66] observed seven of 43 patients with disorders at presentation; in one case the deficits improved, and no new case occurred. Five patients had precocious puberty before radiotherapy, and no additional case was observed during follow-up, although large treatment portals, even craniospinal irradiation, had been performed in some cases. This was confirmed by Rodriguez et al. [57] in 33 patients. Wong et al. [74] noted only two new cases in 36 patients, but 21 patients had disorders at diagnosis. In the series of Bataini et al. [5] including children and young adults with optic glioma, 21 of 57 patients (37%) had endocrinological disorders at last follow-up, however, in 14 cases deficits were present at time of diagnosis. Additionally, six cases of precocious puberty were noted, but only one of these cases was observed after treatment.

In other series, the incidence of treatment-induced endocrinological disturbances was considerably higher. In the series of Pierce et al. [53], the incidence of endocrine dysfunction was as high as 83% seen during follow-up, with growth hormone deficiency being the most common. 73% of the patients had newly diagnosed deficiencies. Cappelli et al. [13] described 17 out of 29 patients with normal endocrinological function before treatment as compared to three out of 47 after radiotherapy. Grabenbauer et al. [29] performed a detailed endocrinological workup during follow-up investigations and noted only four of 25 cases prior to surgery and radiotherapy. The variation of different endocrinopathies was high, with a preponderance of growth hormone deficiency in ten patients. Other authors could confirm the high incidence of disorders following treatment [11, 23, 69] (Table 1). Age at treatment was found to be a significant factor to develop endocrinopathies in the series of Grabenbauer et al. [29]. Nine of 13 patients aged ≤ 10 years experienced disorders as compared to three of twelve patients > 10 years ($p = 0.008$).

The causative relationship between tumor, radiotherapy and chemotherapy was confusing in the series of Janss et al. [35]. Chemotherapy was given as first-line postoperative nonsurgical treatment in the very young with glioma of the supratentorial midline. An endocrinological evaluation was done in 34 children. 20 children showed various disorders before and after treatment (Table 1). 14 children hat normal endocrine function, seven received radiation therapy, and seven did not. Endocrinological dysfunction in these children did not correlate with diencephalic irradiation. The results of this analysis showed that endocrinopathies, including growth hormone deficiency, diabetes insipidus, precocious puberty, and testosterone deficiency, may be the effect of tumor, surgery and chemotherapy and cannot be attributed solely to the effects of radiation, even at the age < 5 years.

In an identical setting in which chemotherapy was applied as first-line treatment in younger and radiotherapy in older children (working group of Philadelphia [50]), similar observations were made [67]. Sutton et al. [67] assessed growth and endocrine replacement therapy in 28 surviving patients. Replacement therapy was required by 16 patients. Twelve children did not need endocrine replacement. However, the specific cause of endocrinopathy could not be determined from the series, and it is remarkable that two of the four patients who did not receive radiation treatment did require endocrine replacement indicating that tumor, radical surgery, and possibly chemotherapy are important contributing factors. Collet-Solberg et al. [16] illustrated, in their series, the problems in evaluating endorinological disorders as consequences of treatment. They analyzed 68 patients who survived low-grade hypothalamic chiasmatic gliomas. 38 patients in this cohort received radiation therapy as part of treatment, 42 chemotherapy, and 24 underwent partial or subtotal resection of their tumors. Initial endocrinological status was not assessed. Deficiencies were observed after all treatment modalities in a similar manner suggesting that tumor, surgery, radiotherapy, and chemotherapy possess an impact on the risk of developing endocrinological disorders in an comparable way (Table 1).

Restricting the irradiated volume of brain might decrease the risk of endocrinopathies. Debus et al. [18] used conformal radiotherapy in glioma of the visual pathway in ten patients. Four of them had disorders at diagnosis, and no new case was

Rudoltz et al., 1998 Case report [58]	2	2 years, 3 years	Optic glioma	54/45 Gy FD: 1.8 Gy	Lateral opposed fields	Cerebrovascular accidents (both NF-positive)	3 months/10 years
Maruyama et al., 2000 Case report[c] [43]	1	1st RT: 6 months 2nd RT: 4.5 years	Optic glioma	1st RT: 70 Gy 2nd RT: 30 Gy	1st RT: 3-field technique 2nd RT: 3-D conformal	Moyamoya + ruptured aneurysm (NF?)	10.5 years (2nd RT)
Weiss et al., 1987 1961–1984 [72]	14	n.m	Optic glioma	40–56 Gy FD: n.m.[a]	11 pat.: lateral opposed fields[a] 3 pat.: 3-field technique	3 pat. with vascular accidents (NF?)	n.m.
Flickinger et al., 1988 1965–1983 [25]	36	8 years	Glioma of optic nerve and chiasm	38.0–56.86 Gy[a] FD: 1.4–2.0 Gy 52.16 Gy CO–60/30 fractions[a]	17 pat.: lateral opposed fields[a] 19 pat.: CT-assisted plan (mean field size 6 × 6.5 cm) 4-field technique (6 × 7 cm/6 × 8 cm)	1 pat. moyamoya (NF-negative)	2 years
Bataini et al., 1991 1970–1986 [5]	57	n.m.	Chiasmatic glioma	40–60 Gy[a] FD: 1.45–2.15 Gy	n.m.	2 pat. thrombosis of the middle cerebral artery (both NF-positive)	15/45 months
Kestle et al., 1993 1971–1990 [37]	47	1.3–4.5 years	Optic glioma	RT: 28 pat. 4 pat. ≥ 50 Gy 1 pat. 25 Gy	n.m.	Moyamoya 2/23 pat. without NF 3/5 pat. with NF	2–4 years
Pierce et al., 1990 1971–1986 [53]	24	Median 6.5 years (1–24 years)	Optic glioma	45–56.6 Gy FD: 1.8–2.0 Gy[a]	n.m.	2 pat. moyamoya (both NF-positive)	2/7 years
Kovalic et al., 1990 1956–1986 [40]	33	n.m.	Glioma of optic nerve and chiasm	Surgery + RT: 22 pat.[a] RT alone: 11 pat. 37.8–61 Gy FD: 0.8–2.0 Gy	Lateral opposed fields[a] Mean size: 6 × 7cm	2 pat. moyamoya (both NF-positive)	n.m.
Jenkin et al., 1993 1958–1990 [36]	87	n.m.	Optic glioma	RT (a): 38 pat. Surveillance (b): 49 pat. 36–55.12 Gy[a] FD: 1.8–2.0 Gy	n.m.	1 pat. moyamoya (NF?)	n.m.
Forsyth et al., 1993 1960–1984 [26]	51	n.m.	Supratentorial pilocytic astrocytoma	Surgery alone: 12 pat.[a] Surgery + RT: 39 pat. 18.9–61.25 Gy FD: 1.18–2.54 (mean 1.8 Gy)	19 pat.: whole brain[a] 4 pat.: whole brain + boost 26 pat.: partial brain 2 pat.: n.m.	1 pat. atheromatous disease of cerebral blood vessels (NF?)	n.m.
Grill et al., 1999 Since 1980 [30]	69	1.5–8.0 years 9 pat. < 5 years (median: 4.5 years)	Optic pathway glioma	45–80 Gy (mean 54.2 Gy) FD: n.m.	n.m.	13 pat. occlusive vasculopathies (not moyamoya) (11 pat. NF-positive)	6–72 months (mean 36.3 months)
Tao et al., 1997 1971–1993 [69]	29	n.m.	Optic glioma and thalamic glioma	Surgery + RT: 15 pat.[a] RT alone: 14 pat. 50.4–55.8 Gy (mean 54.0 Gy) FD: 1.8–2.0 Gy	17 pat.: 3-field technique[a] 7 pat.: lateral opposed fields 1 pat.: arc rotation 4 pat. 3-D technique	1 pat. moyamoya (NF-positive)	n.m.
Hug et al., 2002 1991–1997 [34]	27	n.m.	All sites	50.4–63.0 CGE[a]	Proton therapy	1 pat. moyamoya (NF-positive)	n.m.

[a]no specific informations for patients with complications;
[b]10 additional cases reviewed for moyamoya in children with low-grade glioma (4 NF-positive, 6 NF-negative);
[c]3 additional cases reviewed for moyamoya after RT (2 NF-positive, 1 NF-negative)

observed after radiotherapy, however at a short follow-up between 12 and 72 months. Saran et al. [60] reported only two new cases with endocrine deficiencies in 14 children treated with fractionated conformal radiotherapy, whereas seven children had disorders before treatment. Hug et al. [34] have seen four cases of disorders out of 27 patients after proton therapy for low-grade glioma.

Radiation-induced growth hormone deficiencies seem to depend on a dose-volume relationship and the corresponding integral dose distribution. Adan et al. [1] investigated growth hormone deficiency caused by cranial irradiation during childhood in cohorts of 18, 24, 30–40, and 45–60 Gy (optic glioma). Growth hormone levels were significantly lower after 18–40 Gy (whole brain irradiation) as compared to 45–60 Gy (limited volume irradiation). Decrease correlated with dose but not with age at treatment. Merchant et al. [45] addressed the question of volume effect in an analysis on growth hormone deficiency in 25 children with primary brain tumors requiring local treatment fields only. Baseline assessment was normal in all patients. Peak growth hormone 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. Growth hormone deficiency was observed in eleven 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. In future, these calculations may allow to predict or reduce the risk of endocrinological disorders.

Growth retardation, however, without influence of irradiation, can be enhanced by chemotherapy as observed in an analysis of long-term survivors of childhood cancer [68]. The addition of vincristine, an agent frequently used in low-grade glioma, was a significant factor affecting growth in 51 children. Ogilvy-Stuart & Shalet [48] noted, in their analysis, that the replacement therapy with growth hormone inadequately prevents radiation-induced growth retardation and that the addition of chemotherapy to cranial irradiation is an important contributing factor for loss in expected stature as compared to radiotherapy alone.

Radiation Vasculopathy

Cerebrovascular accidents after radiotherapy are rare. Radiation-induced alterations of vasculature are complex and suspected to consist in an initial progressive loss of endothelia with subsequent formation of thrombi, which is followed by an abnormal endothelial proliferation with concomitant thickening of basement membranes. The time interval between treatment and onset of symptoms or diagnosis of changes, respectively, varies widely and is reported to range between a few months and > 10 years (Table 1). The typical features are atheromatous changes and the so-called moyamoya syndrome. Moyamoya or puff of smoke is named for its typical angiographic appearance of telangiectatic basilar arterial ves-

Table 1. Vascular changes reported in retrospective series and case studies after radiotherapy in childhood low-grade glioma. CGE: Cobalt Gray Equivalent; CT: computed tomography; FD: fractionated dose; NF: neurofibromatosis; n.m.: not mentioned; RT: radiotherapy.

Tabelle 1. Gefäßveränderungen in retrospektiven Serien und Fallberichten nach Bestrahlung von niedrigmalignen Gliomen im Kindesalter. CGE: Kobalt-Gray-Äquivalent; CT: Computertomographie; FD: fraktionierte Dosis; NF: Neurofibromatose; n.m.: nicht erwähnt; RT: Strahlentherapie.

Author/period	All patients	Age[a] at treatment	Tumor sites	Dose prescription	RT technique	Vascular changes	Interval
Painter et al., 1975 Case report [51]	1	1st RT: 8 months 2nd RT: 3 years	Glioma of optic chiasm	25 Gy in 4 weeks 35 Gy in 4 weeks	Lateral opposed fields Lateral opposed fields	Vascular occlusive disease (NF?)	4.5 years
Hirata et al., 1985 Case report [32]	1	5 years	Optic glioma/ hypothalmic invasion	47 Gy FD: 1.5 Gy	"Local radiotherapy"	Moyamoya + carotid obstruction (NF-positive)	5 years
Okuno et al., 1985 Case report [49]	2	23 months, 2 years	Optic glioma	45/48 Gy	n.m.	Moyamoya[b] (1 pat. NF-positive)	2/4 years
Beyer et al., 1986 Case report [9]	3	5 months, 10 months, 3 years	Optic glioma	55–60 Gy in 5.5–6.5 weeks	1 pat.: whole brain 2 pat.: lateral opposed fields	Moyamoya (1 pat. NF-positive)	13 months to 5 years
Epstein et al., 1992 Case report [22]	3	9 months, 9 years, 17 years	Optic glioma	45–50.4 Gy FD: 1.8–2.0 Gy	1 pat.: whole brain 2 pat.: lateral opposed fields	Vascular malformations (1 pat. NF-positive)	2–11.5 years

Table 2. Impairment of visual function after radiotherapy for pituitary adenoma in adults. Impact of fractionated dose prescription.

Tabelle 2. Beeinträchtigung der Visusfunktion nach Bestrahlung von Hypophysenadenomen im Erwachsenenalter. Abhängigkeit von der Einzeldosis.

Author	Patients n (%)	Fractionated dose (Gy)	Total dose (Gy)
Harris & Levene, 1976 [31]	5/55 (9.1)	2.5	45.0–50.0
Aristizabal et al., 1977 [2]	4/122 (3.3)	2.0–2.5	50.0
Atkinson et al., 1979 [3]	4/23 (17.4)	3.0	42.0–45.0
Becker et al., 2002 [6]	20/1,202 (1.6)	In the majority: 1.8–2.0	42–60 In the majority: 45–55

sels with stenosis, occlusion or narrowing of one or both internal carotid arteries, finally leading to cerebral infarction.

Atheromatous disease affecting cerebral blood vessels was infrequently observed in the literature and, if occurring, often seen in conjunction with NF [5, 26, 51, 58] (Table 1). In the series of Bataini et al. [5], two patients developed thrombosis of the middle cerebral artery 15 and 45 months after radiotherapy. Both patients presented stigmata of NF, and thrombosis could be explained by NF involvement of the cerebral arterial tree as described in classic NF. The highest incidence of occlusive vasculopathies in conjunction with NF was reported by Grill et al. [30]. 13 of 69 patients developed vasculopathy at a median follow-up of 7 years. The contribution of patients with NF was eleven out of 37 patients (30%) as compared to two of 32 (6%) in patients without the presence of NF. Young age might be an additional predisposing factor. The median age at treatment was 4.5 years, and nine of the 13 patients were < 5 years of age. However, it should be considered that the cases were not specifically investigated with respect to other vascular accidents which could be explained also by involvement of the renal artery or by an eventual pheochromocytoma, which is frequently observed in NF patients. Additionally, no data were given with respect to treatment volumes.

Moyamoya syndrome has also been reported in NF patients without irradiation. In one case study, the initial coexistence of moyamoya syndrome in a child with a pilocytic astrocytoma of the brain stem was seen [38]. Okuno et al. [49] found 22 cases with moyamoya syndrome associated with NF without irradiation. In the same analysis, the authors also reported 14 cases of moyamoya in conjunction with radiotherapy. In twelve patients (85.7%) it followed irradiation for low-grade glioma, affecting the visual pathway in nine of these cases (64.3%). Five of the children had NF.

Other authors have also seen this complication in their series in patients with NF [5, 9, 32, 37, 40, 53], only rarely in patients without NF [25] (Table 1). According to the findings of Kestle et al., particularly children with NF appear to have an increased risk of developing moyamoya after radiotherapy [37]. This phenomenon did not occur in any of the 19 children not receiving radiation therapy, while among the 28 children irradiated, five developed moyamoya disease. Of these patients, only two of 23 without NF developed this cerebrovascular alteration, versus three out of five with NF. In total, 32 cases of moyamoya syndrome were found in the literature, 18 with and eleven without NF association, in three cases no information was given (Table 1). Additionally, younger age at time of radiotherapy appears to be associated with an increased risk. The five patients reported by Kestle et al. [37] received radiotherapy between 1.3 and 4.5 years of age. In the report of Okuno et al. [49], the age at treatment was between 5 months and 7 years. Eight of the eleven children were < 3 years of age.

Vascular malformations after radiotherapy are a rare condition. There is only one report comprising three patients after radiotherapy of chiasmatic/hypothalamic low-grade glioma in children [22]. The age at treatment ranged between 9 months and 17 years. In one patient, NF was present. Aneurysms are rare. There was only one case of a ruptured aneurysm observed in conjunction with moyamoya in a child with repeat irradiation to a cumulative dose of 110 Gy [43].

Radiation-Induced Deterioration of Visual Function

The literature is replete with data reporting that radiation therapy is highly effective in preserving and improving visual function. By contrast, surgical management of chiasmatic gliomas carries a risk of serious morbidity, especially the loss of visual function. Bynke et al. [12] reported that two of eight patients, who underwent partial resections, had immediate postoperative complete loss of vision in one eye. Similarly, Wong et al. [74] showed that in nine of twelve patients, who had partial resection, vision deteriorated after surgery. Despite conservative treatment, however, in approximately 10% of cases visual dysfunction deteriorates during the course of disease. This has been generally attributed to progressive disease. A detailed analysis with the attempt to distinguish between potentially radiation-induced deteriorations or progressive disease has not been performed in the literature. In fact, there was no case in which radiation as a causative factor has been suspected. Although comparisons between adults and children and low-grade glioma and pituitary adenoma, respectively, might be misleading, it is well known that irradiation of parts of the visual pathway in pituitary adenoma at dose prescriptions and fractionation schemes, which are similar to those used in childhood low-grade glioma, does not carry a significant risk of late radiation injury. In a total of 1,202 patients undergoing surgery followed by radiotherapy or radiotherapy alone, only 20 cases (1.6%) of radiation-induced late effects were observed (Table 2) [6]. Fractionated doses in excess of 2.0 Gy, however, are associated with an increased risk of late complications [2, 3, 31] (Table 2).

Development of Secondary Tumors

In adults undergoing radiotherapy for pituitary adenoma in similar dose prescriptions, treatment fields and regions exposed to irradiation, the risk of secondary neoplasms is low (0.7%) [6] (Table 3). In children, however, the risk appears to be higher and varies considerably in the literature. Additional risk factors like young age, genetic disorders (i.e., NF), and additional chemotherapy have to be considered.

Five patients developed a secondary malignant tumor, three of whom occurred within the treatment fields, in the series of Jenkin et al. [36] (Table 4). Overall five out of 48 irradiated patients (10%) developed a secondary malignant tumor as compared to no case with a secondary malignant tumor among 49 nonirradiated patients. Patients with NF appear to be at particular risk of secondary neoplasms but not in conjunction with radiotherapy. Danoff et al. [17] observed one case of fibrosarcoma of the temporal lobe outside the treatment portals 5 years after radiotherapy in a patient with NF. Pierce et al. [53] observed two new neoplasms outside the treatment portals in patients with NF. In one case, an astrocytoma grade III developed 6.5 years after treatment. The other patient incurred a cerebellar astrocytoma and subsequently a cervical spinal cord glioma 7 and 8 years after treatment, respectively. Erkal et al. [23] observed, in their series comprising 33 patients, one case of a meningioma which occurred within the treatment field, without giving further details. Tao et al.

Table 3. Long-term side effects after irradiation for pituitary adenoma in adults (review of the literature, Becker et al., 2002 [6]). RT: radiotherapy.
Tabelle 3. Langzeitfolgen nach Bestrahlung von Hypophysenadenomen (Literaturanalyse, Becker et al., 2002 [6]). RT: Strahlentherapie.

Patients (n)	Therapy	Dose (Gy)	Necrosis n (%)	Vascular changes n (%)	Cognitive dysfunction n (%)	Secondary tumor n (%)	Follow-up (years)
1,202	192 RT only 1,010 surgery + RT	42–60	1 (0.08)	17 (1.4)	8 (0.6)	9 (0.7)	Median 4.5–7.5

Table 4. Secondary neoplasms in the management of childhood low-grade glioma. Abbreviations see Table 1.
Tabelle 4. Zweittumoren bei der Behandlung niedrigmaligner Gliome im Kindesalter. Abkürzungen s. Tabelle 1.

Author/period	All patients	Age at treatment	Tumor sites	Secondary malignancy/histology in field	outside field	Interval
Danoff et al., 1982 1956–1977 [17]	18	n.m.	Optic glioma	None	1 fibrosarcoma (NF-positive)	5 years
Sung, 1982 1950–1975 [66]	42	n.m.	Chiasmatic glioma	None	1 malignant schwannoma (Os zygomaticum) (NF-positive)	n.m.
Wallner et al., 1988 1942–1985 [71]	31	n.m.	All sites	None	1 mandibular neurofibrosarcoma (NF-positive)	14.3 years
Jenkin et al., 1993 1958–1990 [36]	87	n.m.	Optic glioma	a) 1 glioblastoma multiformed) b) 1 anaplastic astrocytoma c) 1 cerebellar astrocytoma	1 maligant melanoma cervical regiona e) 1 Morbus Hodgkin (NF n.m.)	25 years b) 1 year c) 9 years d) 13 years e) 24 years
Pierce et al., 1990 1971–1986 [53]	24	n.m.	Optic glioma	None	a) 1 astrocytoma WHO III b) 1 cerebellar astrocytoma c) 1 spinal cord glioma (b, c: same pat.) (both pat. NF-positive)	a) 6.5 years b) 7 years c) 8 years
Tao et al., 1997 1971–1993 [69]	29	n.m.	Optic and thalamic glioma	None	1 medullary astrocytoma (NF-positive)	n.m.
Erkal et al., 1997 1973–1994 [23]	33	3.5 years	Optic and hypothalamic glioma	1 parasagittal meningioma (NF-positive)	None	n.m.
Cappelli et al., 1998 1980–1992 [13]	69	5 years	Optic and hypothalamic glioma	a) 1 glioblastoma (NF-negative)	b) 1 Ewing's sarcoma (NF n.m.)	a) 14 years b) 6.5 years
Total				5 cases (all brain tumors)	10 cases in 9 patients (4 cases with brain tumors)	

[69] noted one case of secondary tumor (medullary astrocytoma) outside the treatment portals in a patient with NF, without giving further details. Cappelli et al. [13] found one case with glioblastoma in field and one case with Ewing's sarcoma out of field 14 and 6.5 years after treatment, respectively.

Secondary malignancies were found in a total of 14 patients (15 cases). Only five cases occurred within the treatment fields, six of whom were high-grade gliomas. In ten cases, secondary neoplasms developed outside the irradiated area, of whom seven were NF-positive (in three cases fibrosarcoma or neurofibrosarcoma).

The combination of chemotherapy and radiotherapy in primary brain tumors appears to carry an increased risk of secondary tumors according to a recent analysis performed by the Pediatric Oncology Group in 198 children < 3 years of age with malignant brain tumors who were treated with prolonged postoperative chemotherapy in an effort to delay irradiation and reduce long-term neurotoxicity [21]. Five children developed secondary malignancies, with a cumulative risk at 8 years of 11.3%. The authors concluded that the potential causative factors for this high rate of secondary malignancies include prolonged use of alkylating agents and etoposide with or without irradiation. Conversely, in adults a potentially increased risk of developing acute myeloid leukemia was discussed after chemotherapy for high-grade glioma, whereas radiation therapy appeared not to confer additional risk [52]. More intensive chemotherapy increases this risk according to the experience of Relling et al. [55]. The incidence of brain tumors among irradiated children having received intensive chemotherapy protocols was 12.8% and significantly exceeded the incidence observed in preceding studies.

Conclusions

Radiation therapy is an integral part in the management of childhood low-grade glioma. As current therapeutic strategies achieve an excellent long-term survival, potential treatment-induced late effects are of increasing concern. Yet, data on the true risk are scarce, and the reports in the literature are often conflicting. As all presently applied treatments carry a risk of late sequelae and the tumor itself often causes severe deficits, the interrelationship between these factors is far from being clear. A major objection when interpreting these findings is the lack of sufficient pretreatment assessment of deficits, the heterogeneity of treatment techniques, and the fact that in many of these analyses the treatment-related parameters including doses to organs at risk were not documented. Additionally, the series of patients who have been investigated spanned decades ranging from the 1930s to the 1990s, from orthovoltage treatment units to highly specialized megavoltage linear accelerators with varying treatment volumes comprising whole brain and partial brain irradiation and varying fractionation schemes.

In fractionated external radiation therapy, the risk of necrosis of brain parenchyma is low and plays only a role in stereotactic radiosurgery and brachytherapy [27, 28, 41, 66]. The lesions, however, are often small and circumscribed and are usually sufficiently treated conservatively without a risk of long-term morbidity. Structural changes of brain parenchyma are rarely reported, mainly because this issue has been disregarded in past and contemporary series. Newer techniques in MRI are able to precisely identify changes with respect to spatial distribution and corresponding integral dose distribution, but their role remain to be clarified [53, 61, 64, 65, 69].

Neurocognitive dysfunction and behavioral changes are of particular importance after radiation therapy in children with low-grade glioma [35, 53, 67, 69]. The affected children frequently require special schooling and and a protected environment. Pre-radiotherapy evaluation, however, was lacking in the majority of studies, even those reported nowadays. Additionally, the effect of visual abnormalities and psychosocial and psychologic trauma of illness and treatment which contribute to potential learning difficulties, has been disregarded in past series. Decline in neurocognitive dysfunction appears to be age-dependent and associated with the presence of NF [67, 69]. However, the potential relationship should be judged with caution, as younger children often present with NF and harbor large tumors frequently extending over the entire supratentorial midline and requiring large treatment portals. Despite these shortcomings, the data reported support the present strategy to postpone radiotherapy in younger children in order to reduce the risk of severe disorders.

Neurologic deficits appear to correlate with tumor and perioperative morbidity and not with radiotherapy, mandating early diagnosis and adequate surgical management [54, 63].

Data on endocrinological disorders are conflicting. There are several possible explanations for this variation in the literature, one probably being a difference in the calculation of the percentage of patients with endocrinopathy. Another possible explanation could be the mode of surgery, because surgically induced hypothalamic dysfunction can occur. Frequent lack of complete endocrine evaluation at diagnosis and follow-up may also account for the differences. Like in neurocognitive dysfunction, the causative relationship between tumor and treatment remains largely unknown. In spite of these uncertainties, it appears that the risk of developing disorders depends on the neighboring integral dose distribution within the pituitary/hypothalamic areas. In future, dose-volume histograms will offer the possibility to reduce or predict the risk of endocrinopathies [45]. Careful endocrine documentation is therefore important on presentation and for years after treatment. This is of particular importance, because most of these children are young and hormone replacement is crucial to their development.

Vasculopathies were reported in varying frequencies, but have been more often reported in recent years, mainly in case reports (Table 1). The majority of children were < 7 years of age at treatment and had NF [30, 49]. Moyamoya syndrome was the most frequently reported vascular change. The

true risk of radiation-induced vascular accidents, however, remains unknown, because children with NF have a genuine high risk of vasculopathies. It is therefore necessary to specifically address the question of radiation-induced changes with respect to NF and accompanying vascular changes, dose to normal brain tissue, and treatment techniques. At present, the risk of vascular accidents should be of minor importance when deciding on the selection of treatment modality in patients without NF. The risk of radiation-induced deterioration of visual function is low (no case reported). This observation is consistent with experiences in adult pituitary adenoma (1.6%).

The risk of secondary cancers is low (15 cases were found). However, only five cases occurred in field (four of them were high-grade glioma). The latter can be explained by malignant transformation [19]. Seven of ten cases of secondary tumors out of field were associated with NF reflecting the typical tendency of patients with NF to develop metachronous malignancies. Although this observation clearly emphasizes the need for prolonged follow-up of long-term survivors, the decision for radiation therapy should not be based on the risk of radiation-induced secondary malignancies.

Adequate pre-radiotherapy investigation must take into consideration all factors that may eventually adversely influence the treatment outcome, while radiation therapy must enable the highest tumor control with as low toxicity as possible. Identification of possible pretreatment and treatment-related factors that may contribute to the occurrence of toxicity and comprehensive and close follow-up over prolonged periods of time must be considered as an imperative of current "state of the art" of radiation therapy in this disease. With the use of sophisticated treatment planning and delivery such as three-dimensional treatment planning and intensity-modulated radiotherapy (IMRT), it is expected that more limited amount of normal brain tissue is exposed to radiation, enabling, thus, increase in the dose to the target while limiting toxicity. Preliminary results from high precision techniques seem to support this expectation [18, 34]. For this subset of patients, however, the risk of endocrine and neurocognitive dysfunction is unclear, mainly due to short follow-ups. New technologies in imaging and the possibility to record the integral dose distribution within the planning target volume and organs at risk open up new approaches in assessing late effects (i.e., endocrinological disorders and changes in brain parenchyma) with respect to dose prescription [45, 64].

Although the experiences are scarce mainly due to small patient numbers and short follow-ups, the addition of chemotherapy might enhance the risk of late effects, such as endocrinological disorders, growth retardation, and neurocognitive dysfunction. Larger series of patients with other CNS tumors or leukemia indicate, that in particular the risk of secondary tumors might be considerably increased.

The recently initiated prospective study of the APRO (Pediatric Radiooncology Working Party) on recording of doses to organs at risk and the forthcoming SIOP/GPOH (International Society of Pediatric Oncology/Greman Society of Pediatric Oncology and Hematology) LGG 2003 study in cooperation with the GPOH network in pediatric oncology is addressing issues like pre- and posttherapeutic assessment of all relevant clinical and psychosocial parameters, treatment according to risk and age groups, the preferable use of modern radiotherapy techniques in conjunction with recording of integral dose to organs at risk (dose-volume histograms).

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