Postoperative radiotherapy of spinal and intracranial ependymomas: analysis of prognostic factors

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Abstract

Purpose: Postoperative radiation therapy adds significantly to disease control and survival of patients with ependymoma. However, much controversy exists about the radiation treatment policy. We report the long-term results of a cohort of 56 patients with primary intracranial and spinal ependymomas. Special effort has been taken to define prognostic indicators as a basis for future treatment strategies.

Patients and methods: Between November 1963 and May 1995, 56 patients with histological proven ependymoma were referred to our clinic for further treatment following surgery. Thirty patients had a high grading tumor and 26 had low grade tumors. Seventeen patients had supratentorial tumors and 24 had infratentorial tumors. Fifteen patients suffered from localized spinal tumors.

Results: The mean survival time for all patients was 77 months. Five- and 10-year survival probabilities were 60 and 51%, respectively. The mean progression free survival (PFS) probability for all patients was 67 months with corresponding 5- and 10-year PFS probabilities of 53 and 39%, respectively. On univariate analysis initial performance status, age and tumor grade were significant for survival probability. Concerning PFS radiation dose was significant with improved survival with doses >45 Gy. On multivariate analysis, tumor grade and initial performance status proved to be the only independent prognostic factors.

Conclusions: Tumor grade, age, initial performance status and radiation dose are significant factors for the clinical course of patients and have to be taken into account for the urgently needed prospective trials.

Keywords: Ependymoma; Radiotherapy; Prognostic factors

1. Introduction

Ependymomas are rare tumors derived from ependymal cells in the brain and spinal cord being first described in detail in the 1930s by Baily [1]. Intracranial ependymomas constitute 2–4% of intracranial tumors and 40–60% of spinal tumors [12] in all age groups; in the pediatric age group, the incidence is usually less than 10% of intracranial tumors [11,18]. Postoperative radiotherapy remains a standard treatment in many situations, although much controversy remains about the extent of irradiation. The potential spread of ependymoma through the cerebro-spinal fluid pathways is the biological rationale for extended irradiation fields. The data on the incidence of spinal seeding are conflicting, although in general it seems related to tumor grade and localization [17,29,32]. We report the long-term results of a cohort of 56 patients with primary intracranial and spinal ependymomas treated at the Department of Radiotherapy of the University of Essen. Special effort has been taken to define prognostic indicators as a basis for future treatment strategies.

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2. Materials and methods

2.1. Patients

Between November 1963 and May 1995, 56 patients with histologically proven ependymoma were referred to our clinic for further treatment following surgery. Twenty-nine patients were female and 27 were male. Mean age at diagnosis was 25 years (range 1–70 years). The age distribution is shown in Fig. 1. Grading [16] was available for all patients. Thirty patients had a high grade (HG) (III and IV)

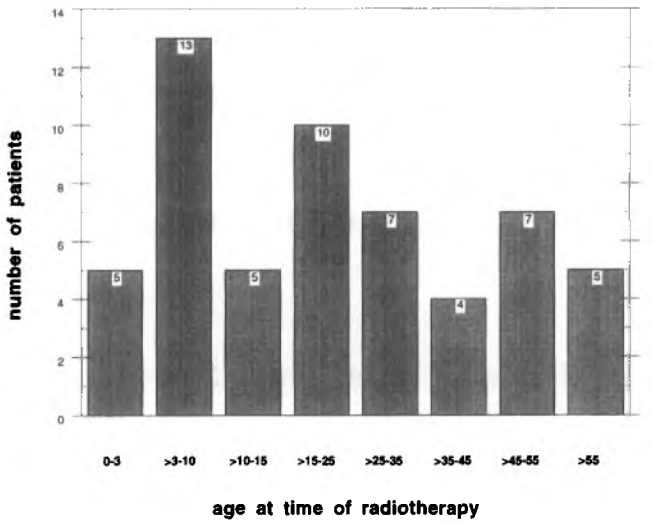

Fig. 1. Age distribution of patients.

tumor and 26 had low grade tumors (LG) (I and II). Seventeen patients had supratentorial tumors and 24 had infratentorial tumors. Six patients with intracranial tumors had proven spinal seeding at the time of radiotherapy. Fifteen patients suffered from localized spinal tumors. Table 1 shows the site of tumors stratified by grading.

2.2. Treatment

The extent of surgery was assessed from the operation notes and histological records prior to radiotherapy. Following attempted resection, five tumors could be removed surgically without microscopically residual tumor (R0, four supratentorial, one infratentorial). Three patients had a microscopic residual tumor, 37 patients had a macroscopic residual tumor and 11 patients had a biopsy (+laminectomy).

Between 1963 and 1995, 17 patients with supratentorial tumors were treated in 11 cases with megavolt equipment (5.7 MeV/10 MeV) and in six cases with cobalt 60 (SSD 80 cm). The dose to the primary tumor plus safety margin was 34.9–50.0 Gy in 18–25 fractions given in 4–6 weeks. Seven patients received a boost dose from 14 to 20 Gy in 7–10 fractions to a total dose of 54–60 Gy. Twelve patients had local treatment alone and five patients received local treatment and whole spine irradiation (34.9–36 Gy). Four patients had chemotherapy, including vincristine and lomustine (CCNU) in varying schedules and doses.

The majority of patients with infratentorial tumor were treated (n = 15) with megavolt equipment (5.7 MeV) while nine cases had cobalt 60 irradiation. The dose to the primary tumor plus safety margin was 34.9–55 Gy in 18–25 fractions given in 4–7 weeks. Seventeen patients received a boost dose of 8–20 Gy to a total dose of 54–60 Gy. Eight patients had local treatment only and 16 patients received both local treatment and whole spine irradiation (34.2–36 Gy). Six patients received chemotherapy including vincristine and lomustine (CCNU).

The patients with the spinal tumor only were treated in four cases with megavolt equipment (5.7/10/15 MeV) and in 11 cases with cobalt 60 irradiation. The dose to the primary tumor plus safety margin was 30–50 Gy. Seven patients received a boost dose of 7.2–20 Gy to a total dose of 55 Gy. Ten patients had local treatment alone and five patients received local treatment and a radiation of the brain. Seven patients received some form of chemotherapy (mainly CCNU) in varying schedules.

2.3. Follow-up and analysis

Most of the patients (>70%) had regular follow-up in our clinic. For the patients we could not see regularly we received the information about the patient's course from several sources. A questionnaire concerning the status of patients was send to the family doctors and last treating specialists.

The date of death was extracted from the mandatory residence register of the communities. Median follow-up from end of radiotherapy was 63 months (range 6–391 months).

Survival and progression-free survival (PFS) were calculated by the actuarial method of Kaplan and Meier [15] from the end of radiotherapy. Two patients who died during radiotherapy were excluded from the survival analysis. Prior to the introduction of CT scanning diagnosis of progression was based on clinical evidence. Later, confirmation of progression was obtained by CT or NMRI, which was available in 77% of patients. The significance level of differences between actuarial survival curves was determined using the log rank test [21]. Independent significance of prognostic variables was tested by a multivariate analysis using the proportional hazard model of Cox [5].

3. Results

3.1. Univariate analysis of survival

The mean survival time for all patients was 77 months (SD 6.8 months) (Fig. 2a). Five- and 10-year survival probabilities were 60 and 51%, respectively. Univariate analysis of survival by gender, performance status, age, site, grade, resection status, radiation dose and technique are displayed in Table 2.

In summary, gender had little impact on the survival probability. Five- and 10-year survival of female patients was 56 and 46% compared to 64 and 58% of male patients,

Table 1

Histology versus site

	Grades I and II (%)	Grades III and IV (%)
Supratentorial	10/17 (59)	7/17 (41)
Infratentorial	7/24 (29)	17/24 (71)
Spinal	9/15 (60)	6/15 (40)

respectively. Tumor grade was a significant factor influencing the prognosis. The 5- and 10-year survival of patients with LG tumors was 73 and 68%, compared to 47 and 33%, respectively, for patients with HG tumors (Fig. 2a). The initial performance status had a significant impact on the survival probability. The 5- and 10-year survival of patients with normal or slight reduced physical activity (WHO status 0 and 1) was 72 and 64% compared to 50 and 42%, for WHO status 2 and 3, respectively (Fig. 2b). The difference in survival of children and adults was statistically significant with better prognosis for older (>16 years) patients (Fig. 2c). Tumor site had no detectable impact on the actuarial survival. Known extent of surgery, radiation dose and extent of radiation fields were insignificant determinants of actuarial survival on univariate analysis.

3.2. *Progression free survival*

The mean PFS probability for all patients was 67 months (SD 6.9 months) with corresponding 5- and 10-year PFS probabilities of 53 and 39%, respectively. Univariate analysis of progression free survival by gender, performance

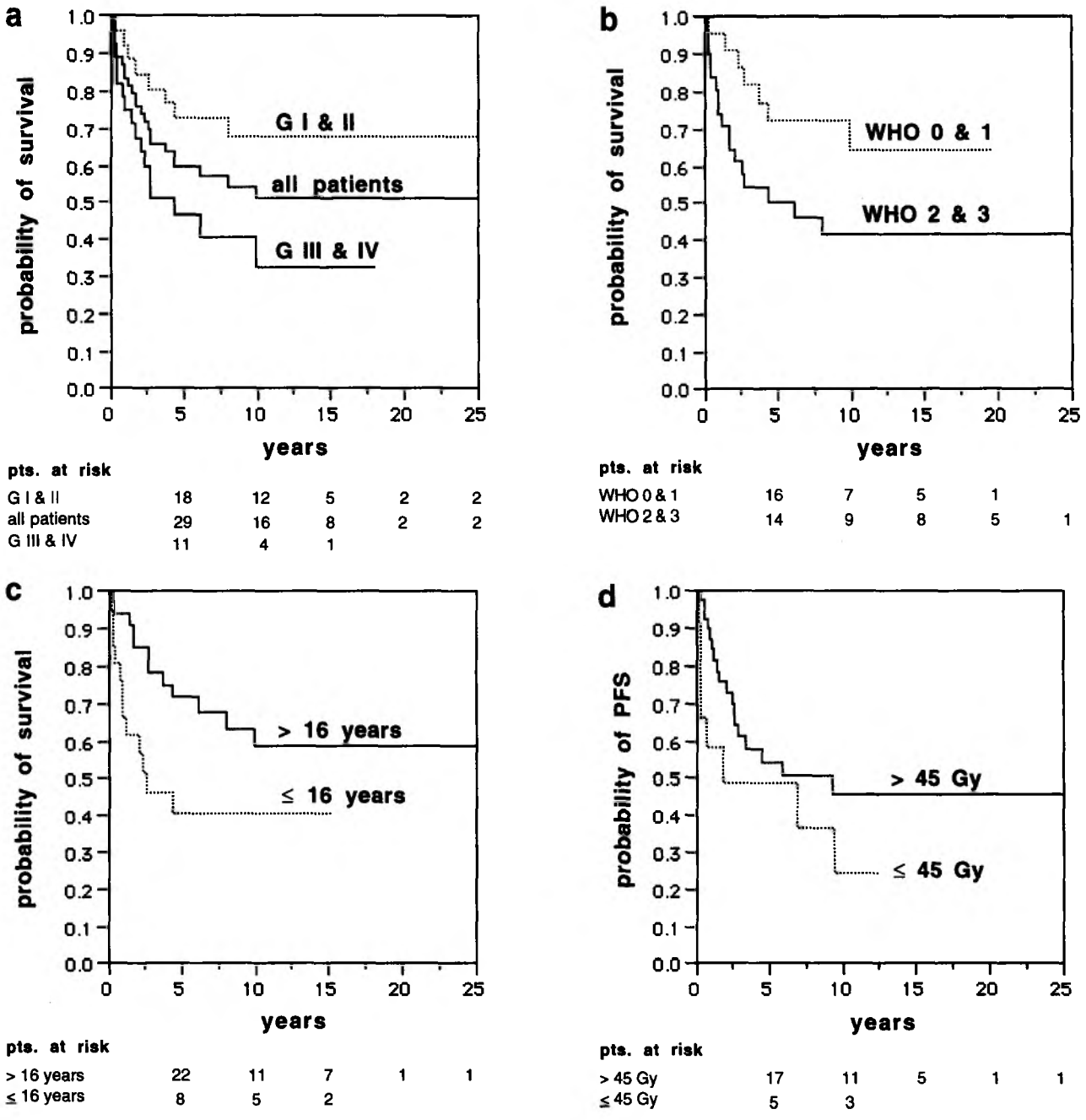

Fig. 2. Actuarial survival curve for all (n = 54) patients stratified by (a) grade, (b) performance status (WHO) and (c) age. (d) Progression free survival curve for all (n = 54) patients stratified by radiation dose.

Table 2
Prognostic factors influencing survival

Factor	Number of patients	Actuarial 5-/10-year survival rate (%)	*P*-value	Progression free 5-/10-year survival rate (%)	*P*-value
Gender					
Female	28	56/46		53/40	
Male	26	64/58	NS	52/39	NS
Performance status					
WHO 0 and 1	23	72/64		63/48	
WHO 2 and 3	31	50/42	0.02	40/33	NS
Age					
≤16 years	21	40/40		38/38	
>16 years	33	72/58	0.03	55/39	NS
Tumor Site					
Supratentorial	17	76/61		74/65	
Infratentorial	22	40/27		45/29	
Spinal	15	62/62	NS	41/24	NS
Tumor grading					
I and II	26	73/68		60/54	
III and IV	28	47/33	0.02	36/18	NS
Extent of resection					
R0	5	80/80		40/40	
R1	3	67/67		67/67	
R2	46	55/50	NS	51/39	NS
Radiation dose					
≤45 Gy	12	48/48		36/24	
>45 Gy	42	63/52	NS	54/45	0.05
Craniospinal irradiation					
Yes	23	48/30		45/30	
No	31	67/63	NS	58/45	NS

NS, not statistically different ($P > 0.05$).

status, age, site, grade, resection status, radiation dose and extent are displayed in Table 2.

The gender of the patients had no impact on the prognosis. Initial performance status was an important prognostic factor with PFS probabilities at 5 and 10 years of 63 and 48% for WHO I and II compared to 40 and 33% for WHO III and IV performance status, respectively. Disease control of young patients (≤16 years) was marginally worse than of adults. Localization of the tumor did influence PFS with better prognosis for supratentorial tumors. Tumor grade had influence on the prognosis with PFS probabilities at 5 and 10 years of 60 and 54% for grade I and II tumors compared to 36 and 18% for grade III and IV tumors, respectively. However, this difference was not statistically significant ($P = 0.1$). The extent of resection was an insignificant determinant of PFS on univariate analysis. There was a significant difference in survival probability between patients treated with doses up to 45 Gy compared to patients having received more than 45 Gy (36 versus 54% 5-year PFS survival, Fig. 2d). The difference in survival probability between patients treated with limited or extensive radiation fields was not significant.

3.3. Multivariate analysis of actuarial survival

On multivariate analysis, tumor grade and initial performance status proved to be the only independent prognostic factors for survival with relative risk values of 2.8 (1.2–7.4 CL) (grades I and II versus III and IV) and 2.8 (1.2–7.2 CL) (WHO performance status values of 0 and 1 versus 2 and 3).

3.4. Multivariate analysis of progression free survival (PFS)

A multivariate analysis showed performance status and tumor grade as independent prognostic indicators for PFS with a relative risk of recurrence of 2.0 (1.1–4.7 CL) for WHO performance status values of 0 and 1 versus 2 and 3. The corresponding risk factors were 2.4 (1.1–5.5 CL) for tumor grades I and II compared to grade III and IV tumors. A further multivariate analysis was inappropriate as subgroups became too small for further stratification.

3.5. Patterns of relapse

Seven of 54 patients (13%) treated developed recurrent tumor after a mean time from irradiation of 34 months (range 12–70 months). Four of these recurrent tumors were observed within the previous irradiation fields. Seven of the 54 patients (13%) developed spinal seeding during follow-up. The incidence of seeding was 17% (5/30 patients) for HG tumors compared to 7.6% (2/26 patients) for LG tumors. The incidence of seeding was smaller for HG supratentorial tumors (2/17 patients, 12%) than

for HG infratentorial tumors (2/7 patients, 28%). For LG tumors the frequency of seeding was dependent on localization; only infratentorial tumors seeded (2/5 patients). Neither of them received a prophylactic irradiation of the craniospinal axes. The HG tumors developed spinal seeding despite irradiation of the craniospinal axes.

3.6. Side effects

Two patients died during the irradiation period. One died due to a large progressive tumor in the brain stem area where an attempt of palliative radiotherapy was performed. One patient died of intercurrent disease (cardiac infarction). These patients were excluded from the further analysis.

During the follow-up period no proven radiation induced myelopathy was observed. No radiation induced (in field) secondary tumor was diagnosed.

3.7. Neurological function

The neurological function of most (n = 33) patients was scored prior to radiotherapy and about 6 months after the end of treatment. From the available patients 9/33 (27%) showed an improvement of initial neurologic deficit(s). Fourteen (42%) patients had virtually unchanged neurologic functions and 10/33 patients (30%) deteriorated. Table 3 summarizes the developments of neurological function stratified by localization of tumors.

4. Discussion

Due to the low incidence of ependymal tumors most published series have few patients, limiting in general the statistical power of the data. The clinician is clearly in a dilemma as no more data are available.

In many situations, postoperative radiation therapy adds significantly to disease control and survival of patients with ependymoma [10,22,23,28,31,35]. However, much controversy exists about the treatment policy. The discrepancies in treatments are based on the lack of generally accepted prognostic factors. An analysis of prognostic indicators contributing to the clinical behavior of this rare tumor might be helpful for the radiation therapist's decision as to which volume has to be treated with what dose.

Table 3

Development of neurologic deficit(s) 6 months after radiotherapy stratified by tumor site

Localization	Neurologic deficit (s)		
	Improved (%)	Unchanged (%)	Deteriorated (%)
Supratentorial	4/12 (33)	6/12 (50)	2/12 (17)
Infratentorial	2/12 (17)	6/12 (50)	4/12 (33)
Spinal	3/9 (42)	2/9 (26)	4/9 (44)

An overview of available data from larger series on survival of both intracranial and spinal ependymoma is summarized in Table 4.

Especially for comparison with older studies, the death of the patient is the most robust endpoint, especially in view of the lack of possibilities to visualize a recurrent tumor before CT or NMRI was broadly available. Our actuarial survival data for intracranial tumors agree well with published data. In the investigation of Vanuytsel et al. [34] on 93 patients with intracranial ependymoma the survival probability of patients at 5 and 10 years was 51 and 42%, respectively, which is comparable to our study where 5- and 10-year actuarial survival probabilities of 58 and 45% were estimated. Virtually identical data were published by Bloom et al. [3] for a pediatric group of patients. Our data for PFS are also in agreement with the data of larger published series [7,11,34].

In our investigation on the subset of 15 spinal ependymomas, 5- and 10-year actuarial survival probabilities of 62% were estimated. The corresponding data for PFS are 41 and 24%. Hulshof et al. [13] published the results of 34 patients with spinal ependymoma. They described no difference in 5-year survival for the patients having received radiotherapy or surgery alone (5-year survival 91%), yet in this investigation, only 3/34 patients had grade II and III tumors, while in our study the majority of patients (11/15) suffered from grade II and III tumors. This reflects the current referral policy of the primary treating neurosurgeons. The data of Garrett and Simpson [7] for spinal tumors also were derived from a favorable patient subset with only 2/41 HG tumors. In a detailed comparative study by site of tumor origin Marks and Adler [22] estimated a 5-year actuarial survival of 57% for spinal cord tumors, which is highly comparable to our patients with spinal tumors, who had a 5-year actuarial survival of 62%. The authors of the study on 61 patients [22] also showed pronounced differences in the prognosis depending on tumor site, with worse prognosis for supratentorial tumors compared to infratentorial and spinal tumors. Our study did not support this finding.

Only few data are available on the neurological status following postoperative radiotherapy. In the present study, sufficient data on the neurological status of 33 patients were available. Approximately 30% of patients showed an improvement of neurological deficits 6 months after radiation therapy. About 42% of patients had a virtually unchanged neurologic function and 30% deteriorated with their neurologic deficits. Hulshof et al. [13] published results on 30 spinal glioma (only few ependymoma), where 47% of patients improved their neurologic function, 43% remained unchanged and 10% deteriorated. In his series, the proportion of LG spinal tumor was favorable with corresponding high PFS data. This might explain the smaller amount of lasting improvements, as a deterioration of neurologic status is usually associated with recurrent tumor, which is more likely in HG tumors.

In summary our analysis of prognostic factors of all

Table 4
Survival of patients with ependymoma

Author	Number of patients	Stratum	5-/10-year actuarial survival	5-/10-year PFS survival
Salazar et al. [30]	51	All intracranial	34	
	17	LG	39	
	34	HG	26	
	18[a]	All intracranial[a]	NS/69[a]	
	NS[a]	LG[a]	NS/75[a]	
	NS[a]	HG[a]	NS/67[a]	
Shaw et al. [31]	33	All intracranial	62/51	
	26	LG	71	
	7	HG	29	
Bloom et al. [3]	51	All intracranial	51/40	
	22	LG	58/47	
	23	HG	39/30	
Vanuytsel et al. [34]	93	All intracranial	51/42	41/38
	41	LG	67/58	
	49	HG	36/30	
	40	Supratentorial	48/40	37/34
	53	Infratentorial	53/43	44/42
Goldwein et al. [11]	45	All intracranial	46	30
	17	Supratentorial	35	15
	28	Infratentorial	50	38
Garret and Simpson [7]	91	Intracranial and spinal	60/54	56/53
	50	All intracranial	43	
	41	Spinal	83	
Marks and Adler [22]	20	Supratentorial	35	
	26	Infratentorial	59	
	7	Spinal	57	
Carrie et al. [4]	28	All intracranial	40/40	40/40
Rousseau et al. [28]	65	All intracranial	63	45
Nazar et al. [24]	35	Infratentorial	45	
Hulshof et al. [13]	34	Spinal	91/91	
Linstadt et al. [20]	21	Spinal	93/93	81/58
Present study	39	All intracranial	58/45	53/48
	17	Supratentorial	76/61	74/65
	22	Infratentorial	40/27	45/29
	15	Spinal	62/62	41/24
	26	LG	73/68	60/54
	28	HG	47/33	36/18

NS, not stated.
[a]A subset with 'appropriate' treatment, based on age, grade, site, dose and treatment volume.

patients indicated that age, grading, initial performance status and radiation dose contribute to the clinical course of patients.

In other studies [2,7,29,31,34] grading was also identified as a prognostic factor. Bloom et al. [3] and Garret and Simpson [7] also clearly showed the impact of functional status at the time of referral for radiotherapy of patients with intracranial tumors.

In a univariate analysis of PFS a dose-response effect was detectable with a significantly improved PFS for patients having received more than 45 Gy. In other series where a larger spectrum of radiation doses was applied a dose response relationship could also be shown [7], especially for intracranial tumors [9]. In addition, Bloom et al. showed a significant correlation between maximum tumor dose and survival in children. A 15-year survival rate of 56% was estimated for patients having received 55 Gy or more compared to 32% for the patients given less than 45 Gy. Other authors could not show a correlation between dose and survival [22,28,34], most probably due to the narrow dose range applied in this series and the relative small amount of recurrent tumors for subsets of patients.

Much controversy exists concerning the extent of radiation fields and especially concerning the adjuvant craniospinal axis irradiation. The biological rationale of extended irradiation fields is the potential risk of spinal fluid spread. Most authors show an incidence of seeding in the range of 0–15% [22,34], which is in agreement with our data, where 17% seeding was diagnosed. Some authors showed an increase of seeding for undifferentiated tumors [17,32,34] while others [6,26,27] could not show a correlation of seeding with grade. However, for high grade tumors most authors prefer craniospinal axis irradiation [8,14,17,19,30] regardless of tumor site.

For low grade tumors the situation is even more complex. Whole brain or localized irradiation is preferred by most authors for supratentorial LG tumors [2,8,1922, 25,30]. For supratentorial LG ependymoma the trend towards entire cranial treatment compared to local irradiation may be based on insufficient imaging and planing procedures in older studies [19].

For infratentorial LG ependymoma some radiotherapists suggest whole brain irradiation with a boost [8,22,30], some suggest localized treatment only [31,33,36], while others tend to irradiate the craniospinal axis [2,7,14,17,25]. In view of an analysis of failure Shaw et al. [31] did not support the use of spinal axis irradiation for low grade infratentorial ependymoma. These data were confirmed by Goldwein et al. [9] who could not demonstrate an advantage of craniospinal irradiation for patients with LG tumors. They therefore suggest treating patients with benign lesions locally.

Based on the observation that there was no difference in survival of patients whose neuroaxis was irradiated from those whose neuroaxis was not irradiated, Marks and Adler [22] favor this irradiation only in selected situations. The authors suggest neuroaxis irradiation for patients with HG ependymoma in the posterior fossa or those with proven spinal metastases. In their view well differentiated tumors seldom seed and may be irradiated with generous local fields. However, as in our study, where also no difference in survival for different extents of radiation fields was observed, a possible bias is the prescription of extended fields with more undifferentiated tumors. In a careful analysis of relapses of 17 children with histologically malignant intracranial ependymomas, the need for prophylactic treatment for children with anaplastic ependymoma could neither be substantiated nor refuted [9]. According to this study the use of local radiation alone should be restricted to carefully designed clinical trials with careful post treatment evaluation of the spine and brain. Patients with supratentorial anaplastic tumors should receive whole brain irradiation with a boost and those with anaplastic infratentorial, documented leptomeningeal spread, or anaplastic tumors impinging on CSF pathways should receive craniospinal irradiation with a local boost. Carrie et al. [4] could not show a benefit of craniospinal irradiation in 37 patients with a majority of HG tumors. These findings are in contrast to the study of Salazar et al. [30] who showed a reduction of local failure after craniospinal irradiation. The comparison was made with a historical group treated from 1959 to 1979 where the standard of pre-treatment and follow-up was insufficient by today's standard.

Based on our experience and review of the literature, we presently prefer local irradiation of localized LG tumors regardless of site. For HG supratentorial tumors local treatment is also preferred, while for infratentorial HG tumors craniospinal axis irradiation is performed. In summary, the limited number of patients precludes definitive statements concerning the extent of radiation fields necessary. Tumor grade, age, initial performance status and radiation dose are significant factors for the clinical course of patients and have to be taken into account for the urgently needed prospective trials.

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