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Ependymoma in Adults: Surgery, Reoperation and Radiotherapy for Survival

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Abstract Purpose: to retrospectively determine the long-term outcome of adult intracranial ependymoma patients treated with surgery, reoperation, and postoperative radiation therapy. Material and Methods: 61 patients were treated at our institution between 1980 and 2004. Forty patients had World Health Organization (WHO) Grade II ependymoma, and 21 patients had Grade III ependymoma. The median age was 34 years. The majority of patients were female (59%), and 35 had gross total resections (60%). Eighteen patients were reoperated, 15 only once but 2 twice and one six times. Survival times following reoperation was mostly short but some of them reached more than 5 or 10 years. Postoperative radiation therapy was delivered to 31 patients postoperative (55.4%) and to 5 after reoperation, a median total dose of 54 Gy. Results: The median follow-up of surviving patients was 10.6 years. The 5-year and 10-year diseasefree survival rates for all patients were 50% and 32.9% respectively. The 5-year and 10-year overall survival rates for all patients were 57.1% and 39.4%, respectively. A statistically significant effect on prognosis was observed with WHO tumour grade as well as with MIB-1 labelling index. Subtotal resection predicted a worse overall survival, but this failed to reach statistical significance. No statistically significant effect on prognosis was observed with tumour location and radiation therapy. Conclusion: In our experience the use of radiotherapy in adult, intracranial WHO Grade II ependymoma patients had no significant effect on prognosis. Radical surgery and eventual reoperation seems to be more favorable.

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Introduction

By various estimates ependymomas account for 2% to 9% of all intracranial tumours, and may occur in any region of the central nervous system at all ages. The incidence of ependymomas in Europe is around 2 per million [1]. Early authors separeted ependymomas into various grading systems, [2–4] the current World Health Organisation (WHO) classification [5] reflects a four tired system similar to the one used in astrocytomas. Schiffer et al. [6] concluded that histological criteria used for astrocytic or oligodendroglial tumours were not applicable and emphasized that necroses, endothel proliferation are not indicative for malignancy. In the recently published "Multicentric French Study" by Metellus et al. [7] adult ependymomas were first classified as WHO grade II or grade III , and subsequently according to the "Marseille neograding system" where necrosis, microvascular proliferation and mitotic count were assesed as objective anaplastic features. An ependymoma was considered low grade if 0 or 1 of the criteria and high grade if 2 or 3 criteria were present. Significant difference was found between E II and E III ependymomas according to the "Marseille neograding system" only.

Histological anaplasia in ependymomas does not always show a clinically similar malignant behaviour: some patients with "anaplastic" histology documented long survival [8–11].There are contradictory reports regarding the prognostic significance of radiotherapy or extent of surgery. Despite this controversy, WHO grade II as well as grade III tumor's surgery is often followed by external

beam radiation therapy. Recently, location and radical excision seem to be also important prognostic factors [12–14]. For postoperative patient management, histological grading should be only of importance [15–17].

In the WHO classification of nervous system tumors [5], "brisk mitotic activity" is defined as the key factor for the distinction of low and high-grade ependymoma. Ki- 67 antigen in theory allows quantification of the tumour cell proliferation in small samples where none or rare mitoses are found. Such quantitative data may be helpful for prediction of patients' outcome, [18–21] but the prognostic significance has not been firmly estabilished [22–24]. Using this added tool for histologic diagnosis, our purpose was to retrospectively determine the long-term outcome of adult intracranial ependymoma patients treated with surgery and in several cases postoperative radiation therapy.

Methods and Materials

Tumours previously classified as ependymomas or anaplastic ependymomas were repeatedly reviewed prior to knowledge of survival data. The results reflect the use of the WHO criteria [5]. Ependymoblastomas, subependymomas and spinal or myxopapillary ependymomas were not included into the study. Histological slides were available for review in 79 cases. Of these, 18 cases were determined to be nonependymal tumors (primitive neuroectodermal tumour, medulloblastoma, astrocytoma, central neurocytoma of the lateral ventricles) and were excluded from further analysis. Thus, a total of 61 intracranial ependymoma patients were included. All clinical and neuropathological data were reviewed, and all surviving patients were called in for control MRI. There were 31 posterior fossa tumours and 30 supratentorial, out of them 9 intraventricular neoplasms. All patients' survival data were known at the time of the preparation of the manuscript. Five patients (8,03%) died within two months postoperatively.

The median age was 32 years with supratentorial and 42.5 years with infratentorial tumours (range 16 to 69 years). Median follow-up of all surviving patients was 10.6 years (range 5 to 316 months). Thirty-one (55.4%) out of 56 patients who recovered after surgery received postoperative radiotherapy. Local irradiation using 6–9 MV photon beams have been delivered up to a median total dose of 54 Gy (range: 50 to 60 Gy) with conventional fractionation (2 Gy/day, five fractions/week). Whole brain irradiation of 30 Gy was followed by a boost of 20 or 30 Gy to the primary site with a margin of 2 cm. Boost field arrangement were defined by CT based planning using 2 or 3 fields. Spinal irradiation was applied only in three cases, with a dose of 30 Gy.

Statistics An outcome analysis was performed to identify those factors that were predictive for overall and progression free survival (PFS). Both univariate and multivariate statistical analyses were performed to assess the prognostic value of age, gender, location, extent of surgery, histology and adjuvant therapies.

MIB-1 (Ki-67) immunostaining was also performed to see correlation of traditional hematoxilin-eosin based grading with grading based solely on MIB-1 proliferation activity. Immunohistochemistry for cell proliferation used monoclonal primary antibodies MIB -1 (Anti Ki-67, 1:50: DAKO, Glostrup, Denmark) on routinely processed praffin embedded tissue sections. The fraction of immunolabelled tumour cell nuclei was expressed as a percentage.

Overall survival and PFS were primary endpoints of the analysis. They were measured from time of surgery up to death or last contact. Univariate analysis was performed using log-rank test [25] for each parameter to asses the strength of association with the outcome. Multivariate analysis was done using the Cox proportional hazards survival model [26]; the variables were selected by forward stepwise inclusion. Statistical relationships were considered significant below the level of 0.05.

Results

Among 30 supratentorial tumours 21 were in the hemispherial white matter but 9 were intraventricular: seven filled in one or both lateral ventricle and two were located in the third ventricle. All of the 31 infratentorial tumours were in the fourth ventricle but 3 extended laterally between the cranial nerves (pontocerebellar) and two reached downwards to the height of the second cervical segment, and another three were partly inside the brain stem. Spinal seeding occurred after surgery in three cases.

Presenting symptoms varied according to the location of the tumour. Patients with intraventricular ependymomas as well as with posterior fossa tumours complained mostly about headache, atactic gait, vertigo, vomitus, actally visual dirturbances. Among the hemispherial tumours epilepsy was frequent , headache or visual disturbance occurred besides local neurological deficit as paresis or aphasy.

Neurological signs depended on location of the tumour: hemisyndromes dominated, six patients had normal neurological examination. Ataxia and nystagmus , in several cases blurred vision occurred with both locations. Twenty-one patients had papilledema. Duration of symptoms before diagnosis was relatively short, in most cases within 12 months.

All but one patients' tumour were diagnosed by CT and/or MRI, in one case vertebral angiography only has been performed. This showed a moderately vascularized tumor.

On CT or MR images the primary lesion was hypodense in 6 cases, 4 demonstrated a large cyst and 2 showed mixed density. The rest of them showed hyperdensity, in most cases with more or less contrast enhancement. Intensive calcification was seen in four patients. A ring-like, marked enhancement appeared in one supratentorial tumour.

All patients have been operated on. According to the operation-protocol of 36 tumours removal was gross-total and subtotal in 25 cases. Unfortunately, systemic, postoperative or late control MRI was not at our disposal in all cases. Immediate or within 3 months control investigation was performed with 11 patients, 3 out of them showed subtotal removal. Twenty-one long survivors were called for repeated MRI control and all of them verified the total excision. Among the infratentorial tumours two arose from the inferior medullary velum and could be totally removed but those of extending pontocerebellar or originating from the floor of the fourth ventricle and attached strongly to the parenchyma a thin sheet of tumour nearly always must be left behind. These cases were regarded as subtotal excision, too. Ventriculo-peritoneal shunting was performed postoperatively in four patients, but two had received it a second or third time also.

Median survival values after total removal was 110 months month and after subtotal excision 78 months. In univariate analysis the difference was significant (p=0.01246) but not in the multivariate (p=0.07146) comparison.

Ependymomas are relative well circumscribed tumors and recurrences are mostly local, repeated surgery is often possible or even mandatory. Although, often grossly adherent to normal brain, both Grade II and Grade III ependymomas show rather expansive growth than infiltrative borders, like those of other glial tumors, such as the diffuse astrocytomas and oligodendrogliomas. Therefore, it is reasonable that some patients after gross-total resection might be longer survivors. A favourable outcome and longer survival could be more frequently observed among the infratentorial ependymomas (median values: 101 and 58, respectively) but this difference appaered only in univatrate analysis (p=0.04329) but not in the Cox regression test (0.10054).

Overall 19 recurrencies occurred during the follow-up period (Table 1). Fifteen local recurrencies were reoperated once, 2 for a second time, and one patient six times altogether reaching 132 months survival time (the recurrent tumour appeared each time on the same location).

The median survival time up to reoperation was 53 and 23 months with E II or E III tumours (range 9 to 136 and 2 to 88 months, respectively). Histology of E II recurrencies turned to Grade III in 6 cases, the rest did not change. Neither the malignant transformation nor the unchanged grading did not influence survival time following reoperation. Classification and grading of ependymomas followed the WHO system [5] which histologically described grade II and grade III ependymomas. Grade II ependymomas were qualified with typical features of ependymoma: mitoses are rare or absent, nuclear morphology is monomorphic. Grade III tumours showed brisk mitotic activity, eventually endothelial proliferation and necrosis. As a rule, high grades were markedly cellular and often showed nucleolar prominence.

Although distribution of E II and E III tumors was uneven—there were 38 survivors of E II and 18 of E III ependymomas—but in survival time of the two groups a significant diference was found (Fig. 1, p=0.02048).

Tissue culture of intracranial ependymomas was successful in 24 cases. The tumour tissue was explanted and treated immediately after surgery according to routine methods. A benign (E II) or a malignant form (E III) could be distinguished in tissue cultures also [27]. The morphology of the tissue cultures mostly corresponded to the histological grading but 7 cases. Three out of them displayed a higher grade of the tumour which was consistent with the worse outcome.

MIB-1 (Ki-67) immunostaining was also performed to see correlation of traditional hematoxilin-eosin based grading with grading based solely on MIB-1 proliferation activity. The fraction of immunolabelled tumour cell nuclei was expressed as a percentage. Patients were separated into low and high index groups using the median proliferation rate as cutoff point (5.0). The difference was significant (0.0007) between the low and high level of percentage of labelled nuclei, correlated with the clinicopathological data (Fig. 2).

Out of 56 survivors 31 (55.4%) received RT postoperatively and 5 following reoperation. Seventeen of E II ependymomas were irradiated but more than the half of them (21) were not.

Fourteen of E III tumours (77.8%), received postoperative radiotherapy and 1 after reoperation but 5 patients did not. Two patients got combined therapy, RT with BCNU, and one patient received BCNU chemotherapy alone.

Comparison of irradiated and not irradiated E II ependymomas did not show a statistically significant difference (p=0.45154). We found significant difference following radiotherapy (p=0.01323) between E II and E III tumors (median values: 111 and 58, respectively).

Discussion

The histologic features required for the diagnosis of anaplastic ependymoma remain, to some degree, controversial. In some studies, anaplasia had prognostic significance [10, 11, 15, 28] while other studies have not shown significant differences in outcome for patients with epen-

Table 1 Main characteristics of reoperated ependymomas

Age	Sex	Local.	Extent of surgery	Histol.	Tissue culture	MIB-1	2. Histol.	Radioth	Survival (mos)
Supratentorial									
46	m	III ventr.	total	E 2	E 2	6%	E 3	50 Gy	58 R
28	m	right pariet.	total	E 3	E 2	7.5%	E 3	50 Gy	**88**+35
22	m	left front.	total	E 2	E 2	6%	E 3	60 Gy	**17**+17
33	f	right pariet	total	E 2	E 3	5%	E 3	60 Gy	**29**+6 R[a]
30	m	left parietal.	total	E 3	E 3	10%	E 3	50 Gy	**16**+3
21	f	left temp.	total	E 3	E 2	25%	E 3	54+30 Gy	**9**+5+4
19	f	left temp.	total	E 3	E 3	8%		60 Gy	2+**36**
25	f	right temp.	subt	E 2	E 2	7%		54 Gy	9+**11**
64	m	right temp.	total	E 3	E 2	25%	E 3	60 Gy	25 R
50	f	right pariet.	total	E 2	E 3	9,80%	E 3	50 Gy	12+**24**[b]
Infratentorial									
25	f	PCB	total	E 2	E 3	5.3%		60 Gy	22+**48**[b]
26	f	IV. ventr.	total	E 2	E 2	3.2%	E2	50 Gy	80+**124**
44	f	IV. ventr.	subtotal	E 2	E 2	8,4%	E 2	50 Gy	**46**+24
17	f	IV. ventr.	total	E 3		10,1%		60 Gy	**56**+56
57	m	IV. ventr.	total	E 2		5%	E 2	50 Gy	**53**+25
38	f	IV. ventr.	total	E 2		0.8%	E 3	60 Gy	**61**+11+38
44	f	IV. ventr.	total	E 3	E 3	30%	E 3	60 Gy	**43**+11
52	f	right cereb.	total	E 2	E 2	5%	E 2	50 Gy	**109** R

Remarks: f = female; m = man; bold numbers = irradiations period; PCB = pontocerebella

[a] Reopeations:+29+37+25+10+25+12 mos

[b] alive

dymoma or anaplastic ependymoma [16, 29–31]. Most of these latter studies, however, did note a trend for worse outcome in anaplastic ependymomas. A comprehensive study of 298 cases, found that high number of mitoses (>20/ ten high power field) were prognostically significant only in supratentorial ependymomas [15]. Several studies have analyzed specific anaplastic features as possible prognostic indicators, these too, have failed to clarify the issue [6, 10, 28, 33]. What is apparent from these studies is that specific features such as mitoses, necrosis and endothelial proliferation do not have the same well-defined relationship to prognosis as do the same features in astrocytomas [6]. Nazar et al. [34] stratified infratentorial ependymomas into three groups based on mitoses, necrosis and dense cellularity and showed mitotic index to be the most important factor.

To highlight the various outcome in anaplastic ependymomas, Ross and Rubinstein [17] studied 15 cases of anaplastic ependymomas and found a 58% 5 year survival. They concluded that histologic criteria do not predict

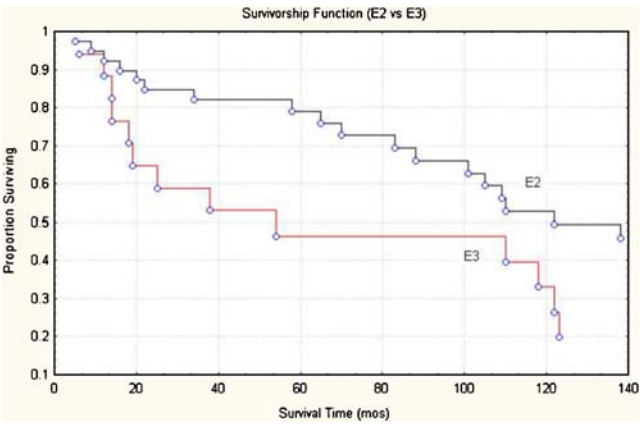

Fig. 1 Kaplan-Meier survival curve for histological groups P = 0.02048

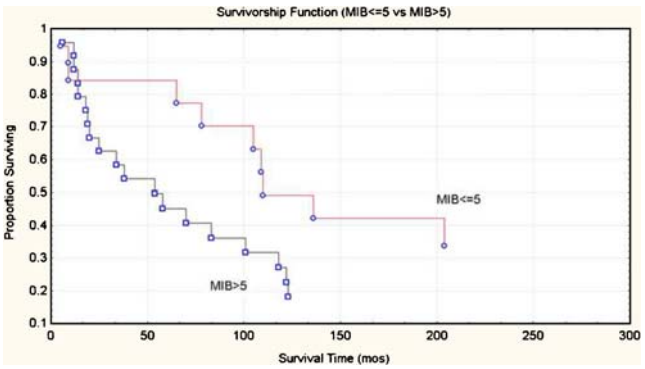

Fig. 2 Kaplan-Meier survival curve for MIB-1 subgroups P = 0.0007

malignant behavior. Although, in our material we found a significant difference in survival of E II and E III ependymomas but this was only a modest one.

Schröder et al. [35] and several authors also [17–20] investigated the growth fraction by labelling cell nuclei by the monoclonal antibody Ki-67 and found that survival times of patients with E III ependymomas was shorter. In our study we observed a significant difference between low and high percentage of labelled nuclei which correlated with histological grading of ependymomas (E II and E III) and prognosis—with a few individual exceptions in both groups.

Schulz et al. [36] in 1968 stated that ependymomas and ependymoblastomas are probably the most radiosensitive of gliomata. This was later confirmed by Leibel and Sheline [37]. Opinions about the role of radiotherapy of ependymomas partly changed during the last two decades: several authors observed a beneficial effect [9, 38–43]. Moreover others [11, 28, 29, 31] observed a poorer prognosis of irradiated ependymomas, irrespective from grading. In our earlier study [8] we dealt with supratentorial ependymomas only, and did not find a significant influence of radiotherapy on survival time, but it was suggested that in some cases the prolongation of survival may have been due to irradiation. In our present study a significant difference was found between E II and E III ependymomas after radiotherapy but not between irradiated and not treated E II tumours. The beneficial effect of RT must be carefully interpreted because our patients were not randomized, the number of cases is low and survival time were sometimes extremly different.

The importance of location was discussed by several authors [7, 12, 13, 32, 44–48, 54]. Spinal ependymomas are showing the longest survival times with very low rate of recurrences [6, 9, 32, 41, 48]. Survival time of children was generally much shorter than that of adults [12, 48, 51]. The posterior fossa tumours seemed to have a longer survival and better prognosis [28, 29, 46]. We also observed a longer, but not a significant difference for infratentorial ependymomas. In agreement with several authors [12, 33, 49–53] radical surgery was the most important prognostic factor. Total exstirpation resulted in a longer, but not significantly different survival.

Following resection, most intracranial ependymomas were treated with local radiation; the use of whole brain or cranio-spinal radiation in three cases with verified spinal seedings, remained ineffective.

We experienced survivals after multiple reoperation from 3 to 124 months. Recurrences were always irradiated, if they did not receive postoperative radiotherapy. In three other cases BCNU therapy was administered without noticable benefit. High dose chemotherapy to date should not be recommended (1) Application of newer therapies, like intraoperative radiotherapy [43] should only introduce after adaequat follow-up achieved. Additionally, postoperative MRI control, continued post-treatment surveillance is justified because early detection of recurrent disease might lead to early reoperation or to more effective salvage therapies.

Conclusions

Although the published results vary widely, the data presented here are in line with many reports. Despite improvement in diagnosis, surgical and other treatment methods, survival of ependymoma patients did not extend during the last two decades, indicating the need for more effective treatments. One of the key issues for a more exact evaluation seems to be the grading of ependymomas where—unfortunately—subjectivity is an important factor further on. In our experience, the use of radiotherapy in adult ependymoma patients has moderate effect on prognosis. In agreement with some earlier authors we think that a progressive, multicentric randomized trial would be necessary to clear the many contradictory results.

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