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CLINICAL STUDY

A multi-center retrospective analysis of treatment effects and quality of life in adult patients with cranial ependymomas

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Abstract Long term quality of life data of adult patients harboring intracranial ependymomas have not been reported. The role of adjuvant radiation therapy in Grade II ependymomas is unclear and differs from study to study. We therefore sought to retrospectively analyze outcome and quality of life of adult patients that were operated on intracranial ependymomas at four different surgical centers in two countries. All patients were attempted to be contacted via telephone to assess quality of life (QoL) at the time of the telephone interview. The standard EORTC QoL Questionnaire C30 (EORTC QLQ-C30) and the EORTC QLQ-Brain Cancer Module (QLQ-BN20) were used. 64 adult patients with intracranial ependymomas were included in the study. The only factor that was associated with increased survival was age <55 years ($p < 0.001$). Supratentorial location was correlated with shorter progression free survival than infratentorial location (PFS; $p = 0.048$). In WHO Grade II tumors local irradiation did not lead to increased PFS ($p = 0.888$) or overall survival ($p = 0.801$). Even for incompletely resected Grade II tumors local irradiation did not lead to a benefit in PFS ($p = 0.911$). In a multivariate analysis of QoL, irradiated patients had significantly worse scores in the item "fatigue" ($p = 0.037$) than non-irradiated patients. Here we present QoL data of adult patients with intracranial ependymomas. Our data show that local radiation therapy may have long-term effects on patients' QoL. Since in the incompletely resected Grade II tumors local irradiation did not lead to a benefit in PFS in this retrospective study, prospective randomized studies are necessary. In addition to age, supratentorial tumor location is associated with a worse prognosis in adult ependymoma patients.

Keywords Ependymoma · Radiation therapy · Quality of life

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Introduction

Ependymomas are rare CNS neoplasms. In adults, they constitute only about 2–8 % of primary central nervous system tumors, while they are more frequently found in the pediatric population [1]. Ependymomas may arise anywhere in the central nervous system, but predilection sites are the spinal cord and the posterior fossa. In the spinal cord, the filum terminale and the central canal of the medulla predominate. In the brain, the fourth ventricle is the most common location.

Due to the rarity of this entity, the vast majority of (mostly retrospective) clinical studies on adult patients with cerebral ependymomas are difficult to interpret

because of: (1) combination of patients with spinal and cerebral tumors [2, 3], (2) mixture of adult and pediatric patients [4, 5] and (3) inclusion of patients from different surgical and diagnostic eras (advent of microsurgery and postoperative resection control by MRI) [4, 6–11]. So far, prospective studies have only been reported for pediatric patients [12]. Furthermore, long-term quality of life (QoL) data for adult ependymoma patients have not been reported. Finally, the role of adjuvant radiation therapy in Grade II ependymomas is unclear [2, 13–16].

At the 2010 meeting of the Neurooncology section of the German Society of Neurosurgery (DGNC) a number of participants grouped together to analyze outcome and quality of life of adult patients who were operated on intracranial ependymomas at four different surgical centers in two countries.

Methods

Patient population

At each participating center the respective patient-databases were searched retrospectively to identify adult patients (>18 years) with histologically proven cranial ependymomas. Depending on institution specific databases, patients were treated between 1990 and 2009. In total, the medical records of 64 patients were reviewed and the following parameters were assessed: age; gender; clinical presentation, histological grading, tumor location (supratentorial vs. infratentorial), pre- and postoperative Karnofsky Performance Scale (KPS) scores, extent of resection as determined by early (72 h) postoperative MRI, adjuvant radiation therapy, local recurrence, and spinal seeding. Local recurrence was defined as reappearance or increase of contrast enhancing tumor tissue adjacent to the resection cavity. Extent of resection was dichotomized between "complete" and "incomplete". None of the patients had a simple biopsy.

Health-related QoL evaluations

Patients were actively contacted via telephone to assess QoL at the time of the telephone interview. The standard EORTC quality of life questionnaire C30 (EORTC QLQ-C30) [17] and the EORTC QLQ-Brain Cancer Module (QLQ-BN20) [18] were used. Both tools have robust psychometric properties resulting from rigorous testing and development from their use in several international clinical trials [19, 20]. The EORTC QLQ-C30 is a core measure designed to be supplemented with disease-specific questionnaires. The EORTC QLQ-BN20 was developed specifically for patients with brain cancer.

The EORTC QLQ-C30 measure comprises five functioning scales—physical, role, emotional, cognitive and social; three symptom scales—fatigue, nausea/vomiting and pain; six single item scales—dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial impact; and the overall health/global QoL scale.

The EORTC QLQ-BN20, designed for use with patients undergoing chemotherapy or radiotherapy, includes 20 items (see Table 1) assessing various neurological functions or treatment toxicities.

No reference values are given by the EORTC for the BN 20 addendum. Therefore an Austrian reference population of brain tumor outpatients in routine clinical practice was used [21]. This population consisted of 110 patients with different intracranial tumors, mainly astrocytomas (30 %), oligodendrogliomas (17 %), glioblastomas (17 %) and meningiomas (13 %). WHO Grades in this population were as follows: WHO Grade I: 19 %; WHO Grade II: 34 %; WHO Grade III: 28 % and WHO Grade IV: 20 %. Roughly 65 % had radiotherapy, 57 % had also chemotherapy and 50 % also had surgery.

The items on both measures were scaled and scored as demanded by the EORTC [22].

One might hypothesize that via telephone we might have only got a hold of people who had a better prognosis, i.e.: had a lower WHO Grade, were completely resected, did not have radiation therapy and had no recurrence. To test for this bias we compared the group of patients who responded to that of patients who did not respond.

Statistics

Statistical analyses were performed using commercially available software (SPSS Statistics 19, IBM, Chicago IL). Binomial dichotomized data were compared using Fisher's exact test and categorical data were compared using Chi

Table 1 Items that were assessed in the EORCT BN20 module to specifically address patients with brain tumors

Item	No. of questions in assessment
Future uncertainty	4
Visual disorder	3
Motor dysfunction	3
Communication deficit	3
Headaches	1
Seizures	1
Drowsiness	1
Itchy skin	1
Hair loss	1
Weakness of legs	1
Bladder control	1

squared test. Survival times were analyzed with Kaplan–Meier method. Kaplan–Meier log rank and Cox proportional hazard tests (for multivariate analyses) using the following variables: age, gender, location, extent of first resection and radiation therapy at initial diagnosis were used for overall survival and progression free survival calculations. p values lower than 0.05 were considered statistically significant. Missing data are clearly pointed out in the text and the figures.

All patients gave informed consent prior to the telephone interview. The local ethics committee at the Johann Wolfgang Goethe-University approved this study (approval no. 4/09, project SNO_NCH_02_11) for the German study sites and the local ethics committee at the University of Geneva approved the study for the Swiss study sides (Code: NAC 11-063R/Comité Central d'Ethique/Hôpitaux Universitaires de Genève).

Results

Demographic data

64 adult patients with intracranial ependymoma were included in the study. Mean age at diagnosis was 46 (range 19–73). Male to female ratio was 1.5:1. Median preoperative KPS score was 80 (Table 2).

The majority of patients initially presented with symptoms related to increased intracranial pressure. Table 3 shows the patients' preoperative signs and symptoms. 18 (28.1 %) patients had WHO Grade I, 33 (51.6 %) patients WHO Grade II and 13 (20.3 %) patients WHO Grade III tumors. 42 (65.6 %) tumors were located infratentorially, and 22 (34.4 %) tumors were supratentorially.

Survival

Median follow up was 47 months (range 0–545). During the follow up period 10 (15 %) patients had died. Two patients died for non direct disease related causes: one developed pneumonia, the cause of death of the other patient at the age of 75 years could not be determined. Median overall survival (OS) was 47 months. In univariate analysis OS tended to be correlated with WHO Grade, but due to the large number of censored patients within the follow-up period statistical significance was not reached ($p = 0.144$; Fig. 1). Extent of resection ($p = 0.866$) and pre-operative KPS score >80 ($p = 0.113$) were also not found to be statistically significantly associated with OS according to univariate testing. Following multivariate analyses, the only factor that was statistically significantly

Table 2 Basic demographic data of the study population

Number of patients	64
Mean age at diagnosis (range)	46 (19–73)
Male:female	1.5:1
WHO Grade I	18 (28.1 %)
WHO Grade II	33 (51.1 %)
WHO Grade III	13 (20.3 %)
Median follow up (months)	47 (0–545)
Total mortality during f/u period	10 (15 %)
Response rate to QoL questionnaire	85.1 %

Table 3 Summary of primary symptoms

Primary symptom	No. (%)
Headache ± nausea/vomiting related to increased ICP	22 (34.4)
Cerebellar dysfunction	15 (23.4)
Incidental finding	7 (10.9)
Unspecific decreased cognitive performance	6 (9.4)
Pain	4 (6.3)
Seizure	3 (4.7)
Hemiparesis	2 (3.1)
New visual disturbance	2 (3.1)
Unknown	2 (3.1)
Frontal lobe dysfunction	1 (1.6)
Total	64 (100)

The majority of patients were symptomatic with symptoms related to increased ICP

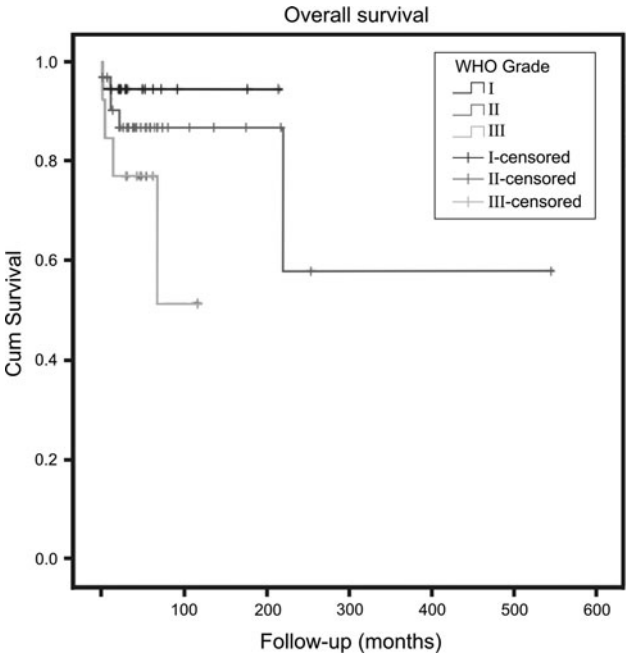

Fig. 1 Overall survival (OS) by WHO Grade. OS of all patients was dependent on WHO Grade. However, due to large number of censored cases within the follow-up period, this correlation failed to meet statistical significance ($p = 0.144$)

associated with increased survival was age <55 years ($p < 0.001$).

Local tumor progression

17 (26 %) patients suffered from local tumor progression (WHO Grade I: 1 (5 %), WHO Grade II: 10 (30.3 %); WHO Grade III: 6 (46.1 %)). Overall median progression-free survival (PFS) was 39 months (range 1–351). In univariate analysis we found a trend for PFS to correlate with WHO Grade. However, this correlation failed to meet statistical significance most likely due to the large number of censored cases ($p = 0.083$; Fig. 2). The occurrence of local tumor progression was significantly associated with decreased OS ($p = 0.008$) (multivariate analysis).

Surgery

60 patients had early postoperative MRI imaging. In 46 (76.6 %) patients a radiologically complete resection could be achieved (WHO Grade I: 17; WHO Grade II: 19; WHO Grade III: 10). Three patients (4.7 %) died in the immediate postoperative period due to complications. Median postoperative KPS was 80. Extent of resection was neither statistically significantly correlated with PFS ($p = 0.166$) nor with OS ($p = 0.866$), albeit a trend towards longer PFS could be seen (Fig. 3, univariate analysis).

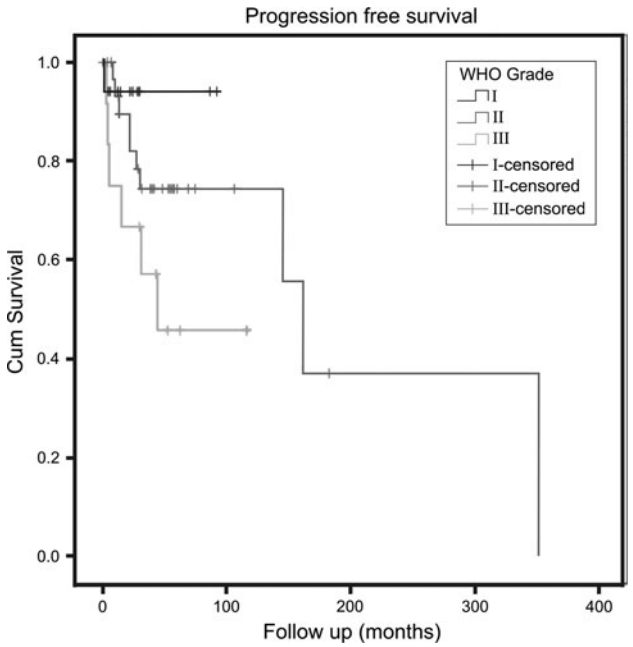

Fig. 2 Progression free survival (PFS) by WHO Grade. PFS correlated with WHO grade, but failed to show statistical significance most likely due to the large number of censored cases ($p = 0.083$, Kaplan–Meier log rank test). The occurrence of a local tumor progression was significantly associated with decreased OS ($p = 0.008$)

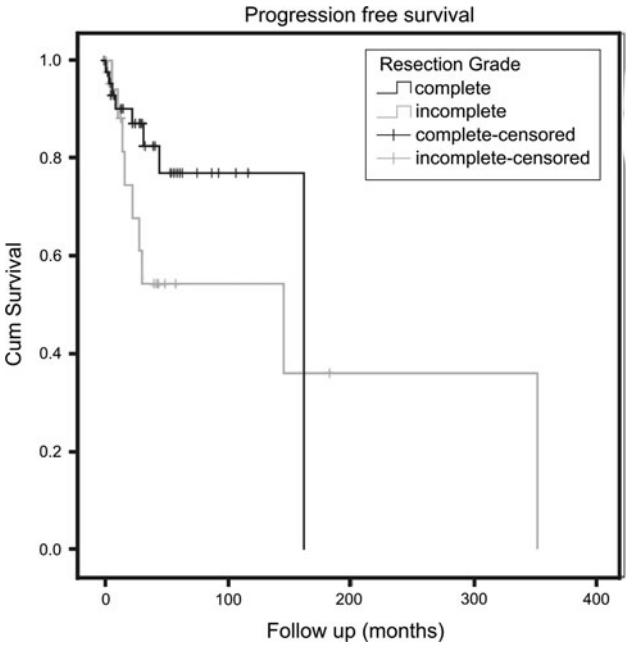

Fig. 3 Progression free survival (PFS) by extent of resection. Extent of resection was not statistically significantly correlated with PFS ($p = 0.166$) albeit a trend towards longer PFS could be seen

Radiation therapy

No patient with WHO Grade I, 11 of 33 patients with WHO Grade II, and 12 of 13 patients with WHO Grade III tumors received postoperative local field irradiation (two patients declined radiation therapy—one with a residual WHO Grade II tumor and one with a Grade III tumor). 8 (73 %) of the patients with WHO Grade II tumors had residual tumor following surgery prior to radiotherapy. In WHO Grade II tumors local irradiation according to univariate analysis did not lead to increased OS ($p = 0.888$) or PFS $p = 0.801$ (Fig. 4) compared to patients who did not receive adjuvant radiotherapy. This finding is not altered when restricting the analysis specifically to patients with incompletely resected Grade II tumors ($p = 0.911$ for PFS, and $p = 0.855$ for OS).

Tumor location correlated with survival

Multivariate Kaplan–Meier log rank and Cox proportional hazard tests using the following variables: age, gender, location, extent of first resection and radiation therapy at initial diagnosis only showed supratentorial location ($p = 0.048$) to be statistically significantly correlated with PFS. In OS location just missed statistical significance ($p = 0.055$), but as evident on the Kaplan–Meier most likely owing to low patient numbers (Fig. 5).

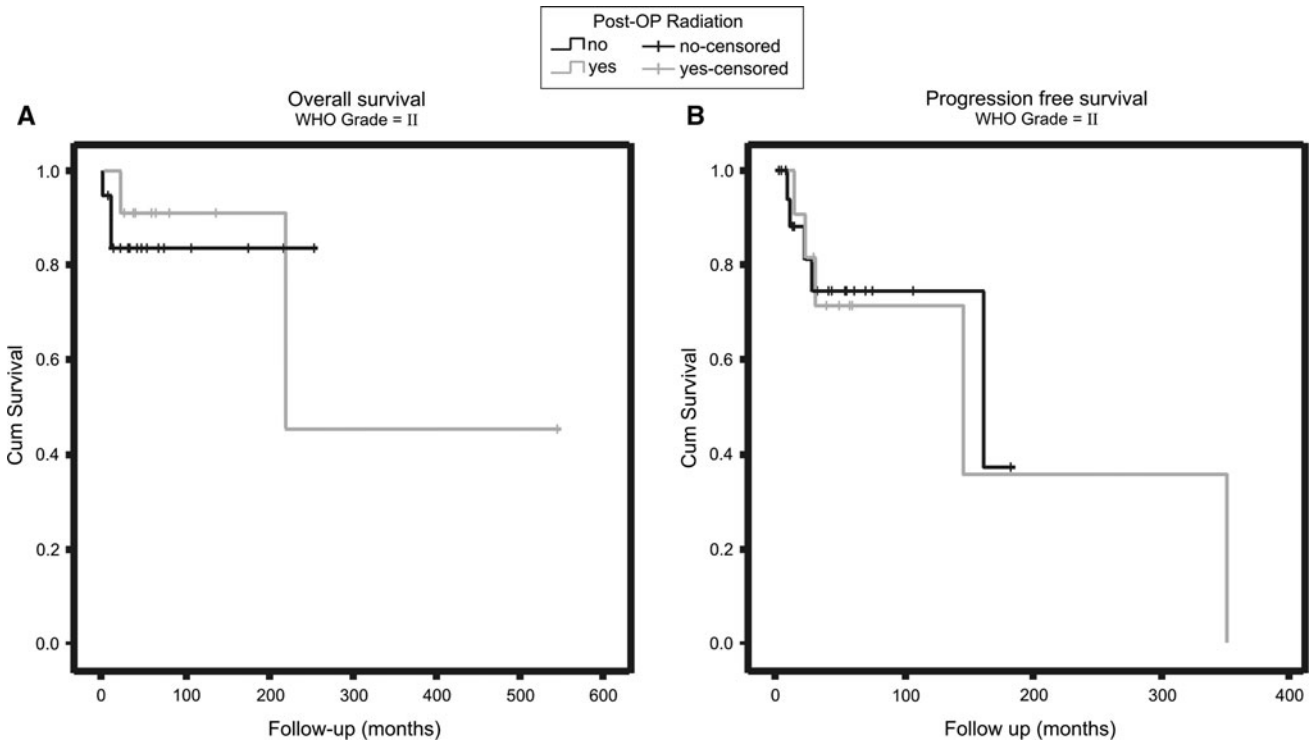

Fig. 4 Overall (**a**) and Progression free (**b**) survival in WHO Grade II tumors with or without adjuvant radiation therapy. In WHO Grade II tumors local field irradiation did not lead to increased OS ($p = 0.888$) or PFS ($p = 0.801$)

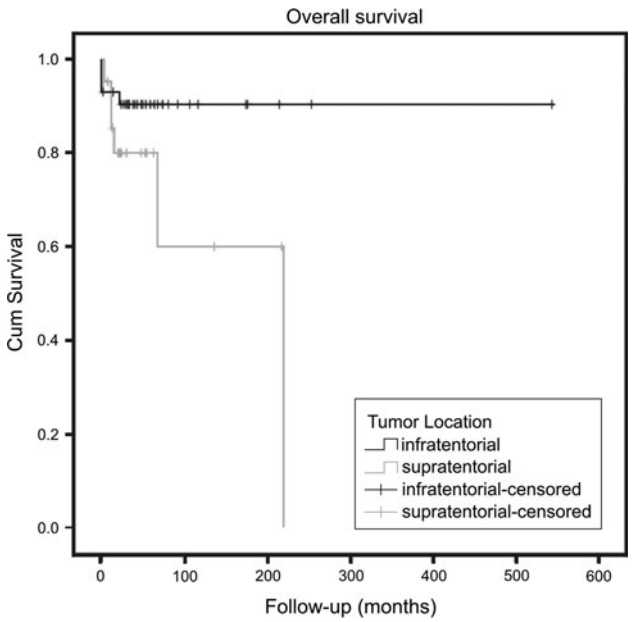

Fig. 5 Overall survival according to tumor location. Patients with an infratentorial tumor had a much better outcome than patients with a supratentorial tumor

Spinal seeding

7 patients (10.9 %) (WHO Grade I: 2; WHO Grade II: 2; WHO Grade III: 3) experienced spinal seeding of their ependymoma. In five of these patients this was heralded by new clinical symptoms. Two spinal metastases were detected through regular MRI screening. In the institution where regular screening is performed three of the three patients with spinal metastases were detected through new clinical symptoms. Notably, there were two patients with WHO Grade I tumors who suffered from spinal metastasis. Spinal metastasis was neither correlated with WHO Grade ($p = 0.266$, Chi Square test) nor with location ($p = 0.571$, Chi Square test) or extent of resection ($p = 0.408$, Chi Square test). The occurrence of spinal seeding was also not associated with decreased OS ($p = 0.284$), even in the WHO Grad II and III subgroup ($p = 0.184$, univariate analysis).

Quality of life

Forty-six patients responded to the EORTC QLQ-C30 + BN20 questionnaire. Overall results are shown in Fig. 6. The QLQ-C30 results, compared to the EORTC Reference values in brain cancer patients, were significantly worse for the ependymoma population in the items "role functioning" ($p = 0.02$, Student's t test), "emotional functioning" ($p = 0.02$), "fatigue" ($p = 0.0006$) and "pain" ($p = 0.02$). General QoL was also slightly worse, but this missed statistical significance ($p = 0.06$). No gender specific difference was found.

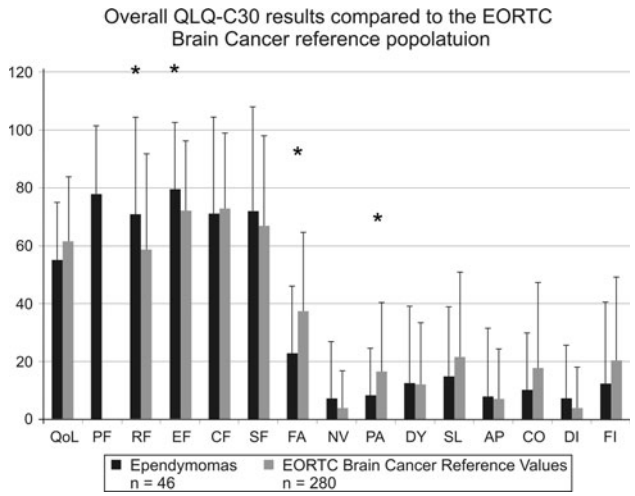

Fig. 6 The QLQ-C30 results of ependymoma patients compared to EORTC Reference values in brain cancer patients. *QoL* Overall QoL, *PF* physical functioning, *RF* role functioning, *EF* emotional functioning, *CF* cognitive functioning, *SF* social functioning, *FA* fatigue, *NV* nausea and vomiting, *PA* pain, *DY* dyspnoea, *SL* insomnia, *AP* appetite loss, *CO* constipation, *DI* diarrhea, *FI* financial difficulties. Values were significantly worse for the ependymoma population in the items "RF" ($p = 0.02$, Student's t test), "EF" ($p = 0.02$), "FA" ($p = 0.0006$) and "PA" ($p = 0.02$) (*Asterisks*). General Quality of Life was also slightly worse, but this missed statistical significance ($p = 0.06$)

In the BN20 addendum, specifically designed for brain cancer patients, ependymoma patients scored significantly worse in the item "motor dysfunction" ($p = 0.04$), but better in items "headache" ($p < 0.001$), "seizures" ($p = 0.004$) and "drowsiness" ($p > 0.001$) (Fig. 7).

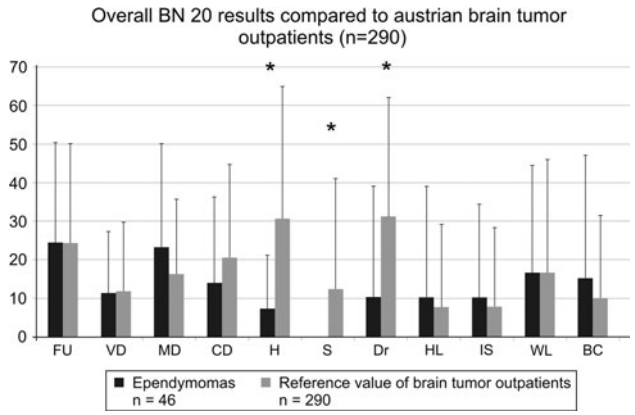

Fig. 7 Results of the BN20 addendum of ependymoma patients compared to the Austrian reference population of brain tumor outpatients in routine clinical practice [21]. *FU* future uncertainty, *VD* visual disorder, *MD* motor dysfunction, *CD* communication deficit, *H* headaches, *S* seizures, *Dr* drowsiness, *HL* hair loss, *IS* itchy skin, *WL* weakness of legs, *BC* bladder control. Ependymoma patients scored significantly worse in the item "MD" ($p = 0.04$), but better in items "H" ($p < 0.001$), "S" ($p = 0.004$) and "Dr" ($p > 0.001$) (*Asterisks*)

As stated above, one might hypothesize that via telephone we might have only got a hold of people who had a better prognosis per se. To test for this bias, we compared the group of patients who responded to the group of patients who did not respond. No statistically significant difference was found between the variables radiation therapy ($p = 1.0$—Fisher's exact test), location ($p = 0.21$—Fisher's exact test), local recurrence ($p = 0.12$—Fisher's exact test) and WHO Grade ($p = 0.093$—Fisher's exact test).

Patients who received adjuvant radiation therapy had significantly lower scores in the items "overall quality of life" ($p = 0.02$, Mann–Whitney U test), "physical functioning" ($p = 0.02$), "role functioning" ($p = 0.04$), "fatigue" ($p = 0.002$), "motor dysfunction" ($p = 0.01$), "communication deficit" ($p = 0.01$), "drowsiness" ($p = 0.04$) and "bladder control" ($p = 0.01$) on univariate analyses compared to patients who did not receive radiation therapy. In a multivariate regression analysis using forward stepwise regression including the items age, gender, location and extent of first resection only the association with item "fatigue" ($p = 0.037$) remained statistically significantly different between irradiated and non-irradiated patients (Fig. 8). Diagnosis of a WHO Grade III tumor did not result in significantly lower scores in all items.

Discussion

We here present one of the largest and most homogeneous retrospective series of adult patients with ependymomas so far and—for the first time in the literature—QoL data of

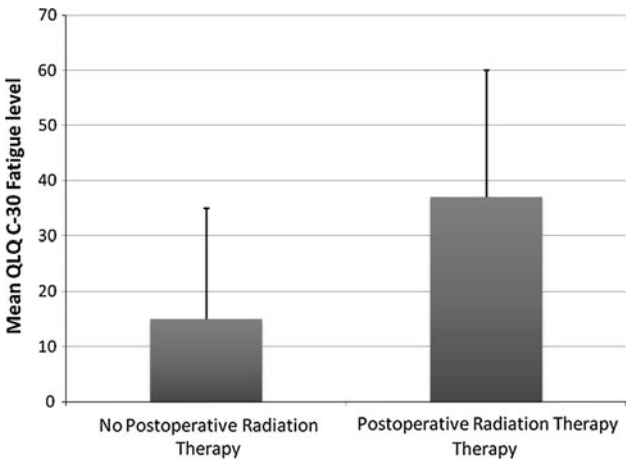

Fig. 8 Mean QLQ-C30 fatigue level of patients who received adjuvant radiation therapy compared to non irradiated patients. Irradiated patients had significantly lower scores in the item "Fatigue" ($p = 0.002$) in a multivariate regression analysis using forward stepwise regression. There were no statistically significant differences in all other items

ependymoma patients. Pooled data from four different institutions in two different countries were analyzed. We excluded pediatric cases and focused on adult patients. This approach is underlined by recent data from Witt and Korshunov et al. [23, 24] who reported distinctly different molecular patterns in adult and pediatric infratentorial ependymomas. Our population is composed similarly compared with other reported series on adult patients: all of them had a slight male predominance, a mean age at diagnosis around 45 years [2, 5, 9, 14] and WHO Grade II tumors were the most prevalent subgroup [2, 6, 14]. Now, there are four major aspects in our series that demand attention:

First, we found that ependymoma patients generally had slightly worse QoL compared to other brain tumor patients. Patients reported lower scores for the items "role functioning", "emotional functioning", "fatigue" and "pain". When compared to an Austrian reference population of heterogeneous brain tumor outpatients, our patients had lower scores in "motor dysfunction" but higher scores for "headache", "seizures" and "drowsiness". One generally has to apply caution to definite conclusions based on the former and especially the latter items, because the reference population for these items is very heterogeneous including astrocytomas (30 %), oligodendrogliomas (17 %), glioblastomas (17 %) and meningiomas (13 %). Furthermore one should consider the possibility of overrepresentation of negative reports in any HRQL survey. Patients who may experience negative consequences of a treatment or disease may exaggerate their feelings if the treatment provider contacts them. Although this bias can occur also in the reference population, the amount of negative impact may lead to false positive results. Nevertheless, these findings underscore that the disease and its treatment have a serious impact on the patients' life. More importantly we found that radiation therapy may have had a significant negative impact on the patients' long term QoL. In a multivariate analysis, irradiated patients complained significantly more "fatigue" than non-irradiated patients. This finding has to be seen in the context of the discussion whether patients with WHO Grade II tumors should be irradiated postoperatively. Recently Caissie et al. [25] and Steinmann et al. [26] reported similar results in patients with brain metastases, although their follow up period was much shorter (1–3 months). Also, radiation therapy in other body regions had similar effects on "fatigue" [27, 28].

Second, the role of radiation therapy in Grade II tumors is still unclear and debated. Reni et al. [7] reported a benefit of postoperative radiation therapy regarding PFS in their WHO Grade II tumors in general. In contrast Metellus et al. [15] found a benefit of radiation therapy only in the subgroup of incompletely resected Grade II tumors. Conversely, our study—similar in size compared to the Reni study but smaller than the Metellus study—suggests that there is no such benefit of radiation therapy.

All clinical studies on ependymomas—including this one—published so far are retrospective and descriptive and cannot control for unknown underlying factors that may have influenced the decision to give radiation in some patients and to refrain from it in others. These factors may have influenced survival as well. Conversely, if radiation had a high impact on patient survival it should be positively associated with survival even if unknown minor cofactors are unbalanced between groups. Thus, the only conclusion that can be drawn from our and the published data is that radiation therapy in WHO Grade II tumors does not have a striking benefit for patient survival. Clearly only randomized trials might help to clarify this issue, but, due to the rarity of the disease, they are difficult to implement. This report may serve as an ignition for a multinational study on radiation therapy in WHO Grade II tumors, the same way the meeting of the Neurooncology section of the German Society of Neurosurgery (DGNC) served to ignite this work.

Third, concerning follow-up scheduling and patient screening, we found that long term clinical follow up is essentially important in all these patients, even in the patients with WHO Grade I tumors. Two patients with WHO Grade I tumors experienced late spinal metastasis. Regular screening with MRI may on the other hand be dispensable, since in the institutions where regular screening was performed all spinal metastases were not detected through regular screening but through imaging prompted by new clinical symptoms. Lastly, in the event of spinal seeding patients should be reassured of the possibly benign nature of this event in the absence of local tumor progression because here spinal seeding was not associated with decreased OS.

Finally, concerning surgical radicality, extent of resection may be important for OS and PFS. As shown before [23], there may be a statistical trend for the association of PFS with the extent of resection although we missed statistical significance. Accordingly, the low progression rate of 34.7 % compared to other published series [2, 14] may reflect the higher number of complete resections that were achieved. One has to keep in mind, however, that we dichotomized between complete and incomplete resections, since none of our patients had a simple biopsy and volumetric data was not available. Any other grading would be arbitrary. Therefore, based on our data, one cannot conclude on differences between i.e. near complete and complete resections. In brain surgery patient functionality is always more important than surgical radicality especially in the context of HRQL. Other variables that were reported to be associated with increased survival in previous larger

series [14] missed statistical significance in our study, as well as in recent studies in size similar to ours [7]. Some of the negative findings may possibly be due to the large number of censored patients in the survival analyses, with only ten events in the follow-up period.

Regarding counseling based on the WHO grading system, our results strengthen the validity of the current classification. Although we missed statistical significance, the Kaplan–Meier graphs on OS and WHO Grade demonstrate the validity of WHO Grades to predict OS and PFS. Still one has to apply caution since Metellus et al. had to re-grade a high number of cases in their central review.

Lastly, it is highly likely that supratentorial location is correlated with a worse prognosis regarding PFS. Although there was no such association shown in one study [2], we found supratentorial location to be statistically significantly correlated with shorter PFS ($p = 0.048$), which corroborates the findings of two other important studies in adults [7, 14].

The multicenter nature of patient data accumulated in this study increased the external validity of the results. Inherent to most observational studies, there are differences in patient characteristics and treatment decisions between the single centers. We dealt with these imbalances through using multivariate analysis, adjusting for relevant co-founders and reporting our data in the most transparent way. We analyzed OS and PFS stratified by a number of variables. We present these analyses in a descriptive way. No definite conclusions can be drawn from these figures, since some variables are inherently related to each other (i.e. nearly all anaplastic tumors received radiation). To address this issue we used Kaplan–Meier log rank and Cox proportional hazard tests using variables such as age, gender, location, extent of first resection and radiation therapy at initial diagnosis. Finally the detailed treatment policy of radiation such as dose, field, and timing could not be assessed, which also might limit the validity of our conclusion.

Conclusion

Our data show that effects of local radiation therapy may have long term effects on patients' QoL. Because in the incompletely resected Grade II tumors local irradiation did not lead to a benefit in PFS in this retrospective study, prospectively randomized studies are necessary. Supratentorial location is associated with a worse prognosis.

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Conflict of interest This study is not funded. The authors report no conflict of interest. Part of the results of this study were presented at the annual meeting of the Section of Neuro-Oncology of the German Association of Neurological Surgeons (DGNC).

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