

## Ependymoma: Outcome and Prognostic Factors

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### ABSTRACT

**Purpose:** This analysis was performed to identify risk factors for overall and relapse-free survival in ependymomas and to provide treatment recommendations.

**Patients and Methods:** Forty-eight ependymoma patients, in the period from April 1994 to May 2002, were evaluated retrospectively. The WHO classification was used for tumor subtyping and grading. Follow-up ranged from 4 to 115 months (mean 29 months).

**Results:** There were 26 males (54%) and 22 females (46%). Age ranged from 2-57 years (mean 22±15). Children constituted 52% of the cases. Ten patients had supratentorial lesions, 18 had infratentorial lesions and 20 had spinal cord lesions. Thirty-seven (77%) and 11 (23%) patients had low and high-grade tumors, respectively. Nine (82%), out of the 11 cases with high-grade pathology were children. Similarly, 73% (8 patients) of those 11 cases were infratentorial. Twenty-five patients had partial resection and 23 had gross total resection. Forty-four patients had postoperative adjuvant external beam radiotherapy. Of all the cases, 19 (40%) experienced treatment failure, 17 at the primary site, one with spinal seedling and the last one outside the primary site. At 10-years, survival rates were 79% (absolute) and 53% (relapse-free). Age and dose of radiotherapy proved to be of statistical significance with *p* values of 0.058 and 0.054, respectively. Grade showed significant difference only when analyzed on bases of radiotherapy treatment volume. Site and extent of surgery failed to be of significant difference. Since CSF examination and the initial tumor size were not documented for 54% and 45% of the patients, respectively, we couldn't evaluate their significance.

**Conclusion:** The primary tumor site is the most common site of failure. Our current recommendation is to treat all supratentorial and low-grade infratentorial tumors with partial brain fields. Craniospinal irradiation is to be reserved for those patients with high-grade infratentorial lesions and those with evidence of craniospinal seedling either radiologically or pathologically. Investigation of biologic markers may provide additional information that allows further refinement of our prognostic ability and enable

identification a cohort of patients at a higher risk for progression.

**Key Words:** Ependymoma - Outcome - Prognostic factors.

### INTRODUCTION

Ependymomas account for about 10% of all intracranial tumors [1]. They arise from ependymal cells forming the lining of the ventricles and central canal of the spinal cord. In the past 3 decades, there has been remarkable improvement of survival, thanks for the advances in neuro-radiological imaging, neuro-surgical techniques, postoperative care and the percision of radiotherapy. However, the results are still relatively poor. This has been attributed to a number of prognostic factors, both patient and treatment related. Age at presentation, the extent of resection, spread beyond the primary site and tumor grade have been identified as important prognostic factors [2]. The influence of histological grade on outcome is among the most controversial of these prognostic factors. Earlier reviews from institutional series indicated a lack of correlation between pathologic features and outcome [3-5]. Recent clinical reports have more consistently identified a correlation between tumor grade and disease control; a large number of series suggest a difference in outcome when comparing patients with differentiated ependymoma to those with anaplastic equivalents [6-10]. Similarly, controversies exist concerning the need for craniospinal, whole brain, or partial brain irradiation [7,11-14] and dose needed [7] as well as influence of tumor size and location [15-16].

The aim of this study was to investigate the

demographic, histopathological, clinical and therapeutic factors that might influence the outcome of ependymoma patient.

### **PATIENTS AND METHODS**

Forty-eight ependymoma patients presented to the radiotherapy department, National Cancer Institute, Cairo University, during the period from April 1994 to May 2002. Those patients were the subject of this study. All of them had their surgical intervention outside NCI. Workup consisted of brain and spine imaging computed tomography (CT) and/or magnetic resonance (MRI).

Factors suggested to influence the prognosis of this type of tumor were classified into three categories; demographic criteria of patients, tumor factors and therapeutic factors.

Demographic Factors included age and sex. Patients in the pediatric group were those aged 18 years or younger.

#### *Tumor factors:*

The site of the tumor was determined radiologically. The lesions were classified either cranial or spinal. Cranial lesions were further subdivided into supra- and infratentorial lesions. Cerebrospinal fluid examination was not routinely done. Similarly, the preoperative maximum size of lesion was not recorded for all patients.

The referred slides of each patient were reviewed and the WHO classification was used for grading [17].

Grade 1 "myxopapillary" characterised by cuboidal to elongated cells radially arranged in a papillary manner around vascularized stromal cores. A mucoid matrix accumulated between tumor cells and blood vessels as well as in microcysts. Mitotic activity was very low or absent.

Grade 2 when the lesion was moderately cellular tissue in which perivascular pseudorosettes and rarely true ependymal rosettes and canals were the key histologic features. Mitosis was rare or absent. Necrosis was not uncommon. Unless it was only very focal and unaccompanied by regions of higher cellularity and mitotic activity, vascular endothelial proliferation was not encountered in this category. Cellular, papillary, clear cell and tanycytic were grade 2 variants.

Grade 3 "anaplastic ependymoma" included only tumors with clearly defined ependymal differentiation in the form of perivascular pseudorosettes. They showed increased cellularity, brisk mitotic activity and variable degrees of cellular pleomorphism with nuclear atypia, often associated with endothelial/pericytic proliferation. The hypercellularity could be diffuse or focal and was often in the form of multiple rather well-circumscribed regions that abutted sharply with those of lower cellularity. Vascular proliferation was found within or just outside of the hypercellular regions. Microscopic or geographic necrosis could be present but necrosis alone was not a robust discriminating feature. The issue that made grading difficult and subjective was that tumors occurred along a spectrum in terms of the amount of markedly cellular tissue that was usually mitotically more active than less cellular components. The lesions did not, therefore, fit neatly into either the well-differentiated or anaplastic categories. For that reason, vascular proliferation is needed for this category, except for a few cases in which the anaplastic appearing histologic qualities were overt, but no vascular proliferation was present.

Grade 4 "ependyoblastoma". In which high cellularity and mitotic activity with poorly differentiated small cells formed either amorphous arrangements or the characteristic rosettes and tubules. In distinction to ependymoma, these rosettes were pseudostratified with frequent juxtaluminous mitosis. Well-developed perivascular rosettes common in ependymomas, were rare.

#### *Therapeutic factors:*

The extent of surgical resection was either gross or partial resection.

Post-operative treatment was either radiotherapy, chemotherapy, or both. Radiotherapy was either localized/whole cranial or spinal, or craniospinal irradiation. The brain was treated with opposed lateral fields; the spine was treated with one or two posterior fields with appropriate gap calculations. All fields were treated daily. If craniospinal-axis irradiation was used, the dose to the brain site was supplemented with opposing lateral and vertex fields, or wedge-pair fields. Partial brain fields were planned by estimating the pre-operative tumor volume from radiographic CT-studies. A minimum 2-cm margin of uninvolved tissue was treated. Localized brain irradiation is determined using computerized 2D/3D

planning system. Megavoltage external-beam radiotherapy was delivered from 36 to 61 Gy (median 51.3 Gy), 2 Gy/fraction, 5 fractions/week to the primary site. Those received the craniospinal irradiation had an average of 30 Gy to the spine, 1.5 Gy/fraction, 5 fractions/week.

#### *Statistical methods:*

The overall survival was calculated from the date of surgery to the date of death from disease or last follow-up. Relapse-free survival (RFS) was calculated from the date of surgery to the date of progression (whether local, distant, or combined as confirmed by CT/MRI of the brain or spine). In case of death before definite sign of progression the relapse-free survival is the same as overall survival. Follow-up ranged from 4 to 115 months, with a mean follow-up of  $29 \pm 25$  months and a median of 21 months. "SPSSwin ver. 9" package was used for statistical analysis. Numerical data were described in terms of means and medians for central tendency and standard deviation and range, minimum and maximum for dispersion. Chi-square test is used to compare qualitative variables. Overall survival and relapse-free survival were determined using the Kaplan-Meier product limit method [18]. Comparison between survivals of different groups was determined using the log-rank test [19]. Probability (*p*-value) of less than 0.05 is considered to be significant.

## RESULTS

This study included 26 male (54%) and 22 female patients (46%). The median age for the study group was 16.5 years with a range of 2-57 years. Mean age ( $\pm$  SD) was  $22 \pm 15$  years. Children constituted 52% (25 cases) (Table 1).

Twenty-eight patients (58.3%) had cranial tumors. Ten had supratentorial and 18 had infratentorial lesions. Fourteen patients (78%) out of the 18 infratentorial lesions were children (18 years old or younger). There were 20 (41.7%) primary spinal cord tumors; four of them had multiple-lesions at different spinal levels. In this series, 23 patients had gross excision and 25 patients had partial resection.

The majority of patients (77%) had low grade lesions; 5 patients myxopapillary (Fig. 1a) and 32 patients grade 2 ependymoma (Fig.1b). Of grade 2 lesions, two cases were of the cellular variant. Eleven patients (23%) had high grade

tumors (9 cases anaplastic and 2 cases ependymoma) (Fig. 1c and d).

Out of the 11 patients with high-grade tumors, 82% (9 patients) were children and 18% (2 patients) were adults. The majority of high-grade cases 73% (8 patients) were infratentorial. Table (1) shows patients' characteristics by site.

No patients with primary cranial lesion had spinal seedling at presentation. Seventeen patients (35.4%) had pretreatment cerebrospinal fluid proved positive for ependymoma, five patients (10.4%) were negative. CSF examination was not performed in more than half of the patients (26 patients = 54.2%). Tumor maximum size was documented pre-operatively in only 31 patients (65%) and it ranged from 3-14 cm. Twenty-three patients had gross excision and 25 patients had partial resection of their tumors.

Radiotherapy was used as adjuvant treatment in 44 patients, 3 of them received chemotherapy in addition. Localized irradiation was delivered in 15 patients (34%), whole cranial or spinal fields for 11 patients (25%) and craniospinal irradiation for 18 patients (41%). Two patients were treated by chemotherapy as the sole adjuvant treatment, one low grade supratentorial and one low grade infratentorial. Table (2) summarizes the post-operative adjuvant treatment for all the patients by site and grade.

Out of the studied 48 patients, 19 (40%) experienced treatment failure. Eight of them showed primary disease progression, nine recurred within the primary site, one with spinal seedling and the remaining one outside the primary site. Of the 19 recurrences, 10 (53%) occurred during the first year post treatment, 17 (88%) during the first 2 years. At 10 years, the overall survival rate was 79% and the relapse-free survival rate was 53%. No deaths were attributed to treatment complications.

The pediatric group has an inferior relapse-free survival (39%) compared to their adult partner (69%) ( $p = 0.0587$ ). On the other hand, there was no significant difference between spinal (55%) and cranial lesions (52%) ( $p = 0.6706$ ). Analyzing the cranial lesions separately, the infratentorial site was superior to the supratentorial with relapse-free survival of 64% and 22%, respectively ( $p = 0.0706$ ) (Fig. 2a and b).

The grade didn't show an independent effect

on survival. Relapse-free survival was 52% for patients with low-grade tumors (myxopapillary and grade 2 ependymoma) as compared to 58% for those with high-grade tumors (anaplastic and ependymblastoma) ( $p = 0.7661$ ). A marginal significant difference was found between the patients with high-grade lesions treated with craniospinal irradiation 86% compared to those treated with localized fields 25% ( $p = 0.099$ ). For the patients with low-grade lesions, the corresponding figures were 64% and 52% ( $p = 0.485$ ) (Fig. 3 a,b and c).

In spite of the higher relapse-free survival of the group treated with gross resection (62%) than those with partial resection (45%), the

difference was not statistically significant ( $p = 0.168$ ).

The other variable, which proved to be significant, was the dose of radiotherapy delivered to the primary site. Those lesions received a dose of 45 Gy or more had a relapse-free survival of 62% compared to 45% for those who received lower doses ( $p = 0.054$ ). Chemotherapy as a treatment modality variable was not valuable for analysis being used in 7 patients only who received different regimens.

Evaluation of CSF examination and tumor size were not feasible as they were not documented in high percentage of patients.

Table (1): Patients' characteristics by site.

	Supratentorial (10) No. (%)	Infratentorial (18) No. (%)	Spinal (20) No. (%)	Total = 48 No. (%)
<i>Gender:</i>				
Male	5 (50)	10 (56)	11 (55)	26 (54)
Female	5 (50)	8 (44)	9 (45)	22 (46)
<i>Age:</i>				
Pediatric	4 (40)	14 (78)	7 (35)	25 (52)
Adult	6 (60)	4 (22)	13 (65)	23 (48)
<i>Grade:</i>				
Low	8 (80)	10 (56)	19 (95)	37 (77)
High	2 (20)	8 (44)	1 (5)	11 (23)
<i>CSF examination:</i>				
Positive	3 (30)	6 (33)	8 (40)	17 (35.4)
Negative	1 (10)	0 (0)	4 (20)	5 (10.4)
Not done	6 (60)	12 (67)	8 (40)	26 (54.2)

Table (2): Post-operative treatment modalities by site and grade (No = 44).

	Radiotherapy				Chemotherapy	
	Craniospinal	Whole cranium/spine	Localized	Total*	Total*	
<i>Supratentorial:</i>						
High grade	3	4	2	9/10	1	1/10
Low grade	1	1	0	2	0	0
	2	3	2	7	1	1#
<i>Infratentorial:</i>						
High grade	11	1	4	16/18	3	3/18
Low grade	6	1	1	8	2	2
	5	0	3	8	1	1#
<i>Spinal:</i>						
High grade	4	6	9	19/20	3	3/20
Low grade	0	0	1	1	0	0
	4	6	8	18	3	3
<b>Total</b>	<b>18 (41%)</b>	<b>11 (25%)</b>	<b>15 (34%)</b>	<b>44/48</b>	<b>7 (14%)</b>	<b>7/48</b>

\* Number treated / overall number by site.

# Received only chemotherapy as adjuvant treatment.

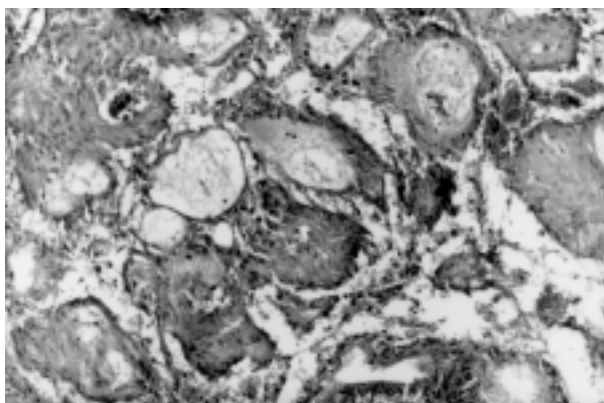


Fig. (1-A): Myxopapillary ependymoma showing arrangement of tumor cells around blood vessels with mucin deposition (H&E 100).



Fig. (1-B): Ependymoma grade 2 with polarized orientation around blood vessels to form pseudorosettes (H&E 100).

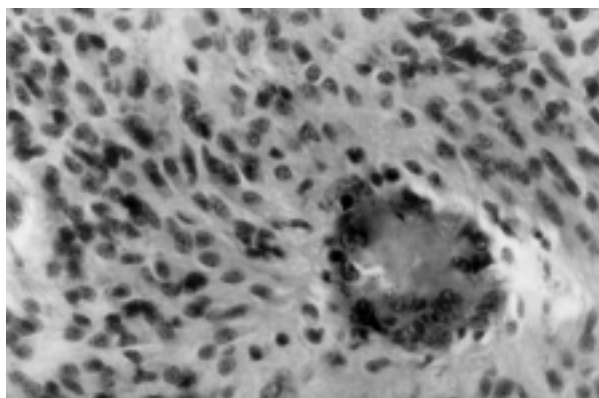


Fig. (1-C): Vascular endothelial proliferation in anaplastic ependymoma (H&E 400).

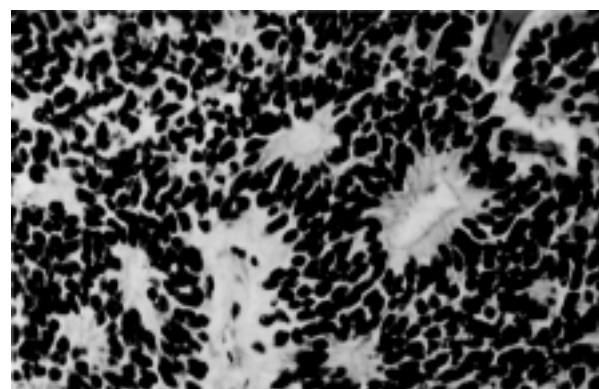


Fig. (1-D): Ependymoblastoma with the characteristic multilayered ependymoblastic rosettes. (H&E 400).

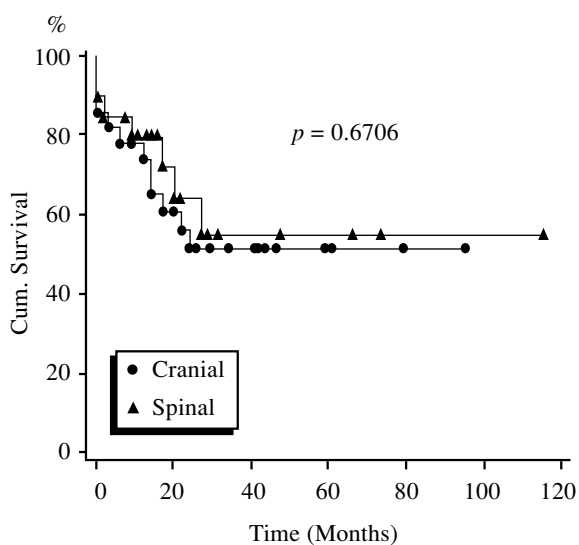


Fig. (2-A): Relapse-free survival according to tumor site: Cranial versus spinal.

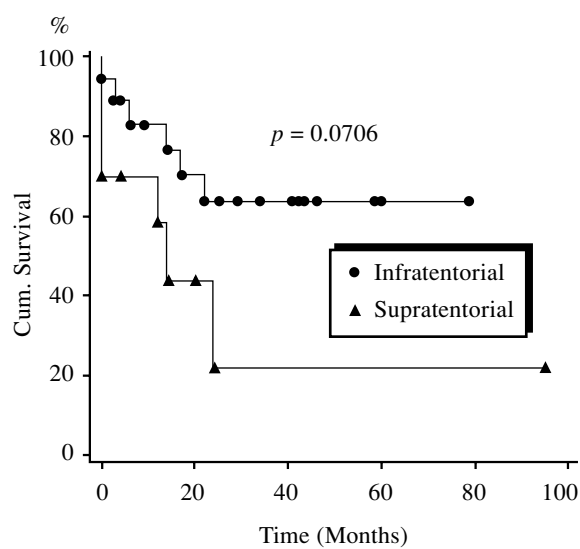


Fig. (2-B): Relapse-free survival for cranial lesions: Supratentorial versus infratentorial.

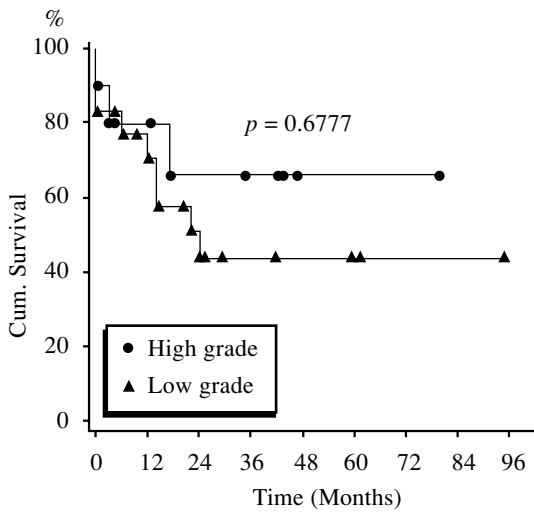


Fig. (3-A): Relapse-free survival according to tumor grade.

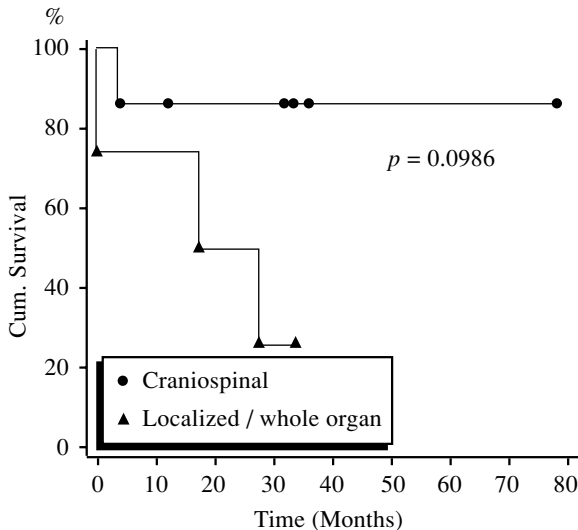


Fig. (3-B): Relapse-free survival according to radiotherapy treatment volume split by grade. 1-High Grade.

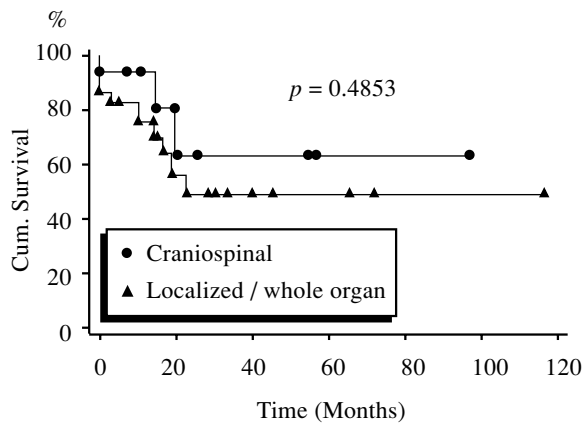


Fig. (3-C): Relapse-free survival according to radiotherapy treatment volume split by grade. 2-Low Grade.

## DISCUSSION

Ependymoma showed many controversies (variations in the pediatric age definition, staging procedures, grading assignment and radiation therapy dose and volume). Consequently, we found contradicting information on the outcome of different treatments for ependymomas that remained with no consensus for the optimal therapy.

In this study, patients within the pediatric age (18 years old or less) had worse prognosis compared to older age ( $p = 0.058$ ). This could be explained by the fact that, in our population, more high-grade lesions were noticed in this age category. Age is the only patient related factor that had been assigned as an independent predictive factor in some reports which were concerned with the pediatric age group [3,20-21]. The studies, which evaluated all age groups, did not show this trend [1,6,22].

In the current series, the disease free survival was almost the same for both spinal and intracranial lesions with a trend for better survival for the infratentorial tumors compared to that of the supratentorial ones ( $p = 0.071$ ). In accordance, McLaughlin et al. [7] showed a significant higher survival rate for the infratentorial lesions. This was contradictory to Foreman et al. [2] who observed a survival advantage in patients with supratentorial ependymomas compared to infratentorial lesions. Other investigators could not have any significant effect [4,5,8-10,22-27]. In some reports, spinal lesions showed a better outcome compared to intracranial ones [7,10]. On the other hand, there was a controversy concerning the impact of the tumor site (for the intracranial lesions) on survival. Survival differences according to tumor site may be explained by differences in the ability to resect tumor according to its site. The review of pathologic aspects of ependymomas by Fokes and Earle [28] showed that most supratentorial tumors exhibit infiltrative growth into the brain parenchyma compared to infratentorial tumors, which grow exophytically, often filling the ventricle. This makes surgical resection easier for infratentorial than for supratentorial tumors. In addition, supratentorial tumors tend to be only partially encapsulated and lobulated, whereas infratentorial tumors are usually entirely encapsulated. In the present series, the rate of gross

total resection was similar for supratentorial and infratentorial tumors. However, because of the infiltrative growth of supratentorial tumors, there could be residual parenchymal disease not easily apparent to either the surgeon, or radiologist.

Although tumor grade was not an independent predictive factor, high-grade ependymomas had a more favorable outcome when treated with craniospinal field. However, this was statistically insignificant ( $p = 0.098$ ). Meanwhile, treatment volume didn't influence the clinical outcome with low-grade lesions ( $p = 0.485$ ). The controversies concerning grade were the most prominent in the literature. McLaughlin et al. and others [3-5,7] reported upon the lack of histopathologic correlation to clinical outcome. They found no correlation between grade and survival time in a study on 298 cases, survival of patients with the anaplastic variant recognized by classic histological criteria did not markedly differ from those with low-grade ependymoma [26]. In a similar manner, Pollack et al. [23], in a single institution study included 40 patients, found no effect of tumor grade on outcome. A multi-institutional study conducted with 11 institutions contributing 83 patients demonstrated a significant difference in event-free survival and overall survival on the basis of tumor grade. Patients with grade 3 histologic features fared worse than those with grade 2 histologic features [29]. In a series of 31 patients, 12 with classic and 19 with anaplastic ependymoma, the 5 and 10 year progression-free survivals were 60% and 48% for ependymoma grade II, 55% and 26% for anaplastic tumors respectively [30]. Another study of intracranial ependymoma that excluded localization-linked operative mortality found a median progression-free survival of 7.5 years for grade II tumors, but only 1.5 years for anaplastic variants [31]. A possible explanation for this disagreement between different publications could be the ambiguity in grade assignment and the unresolved problem related to the definition of reliable histopathologic indicators of anaplasia [8]. Some authors graded these tumors based primarily on cellularity and mitoses, others used grading system that depends on mitotic activity and endothelial proliferation. Also because one of the criteria for high grade lesions is high cellularity, and most ependymomas are cellular, high grade tumors may be over-diagnosed. Determination of biologic markers, such as proliferation index, as an adjunct to tumor grade may

provide additional information that allows further refinement of the prognostic capabilities.

Initial CSF examination, as well as follow up neuraxis radiological assessment, was not routinely performed in the past decades. In the present study, 54% of the patients did not undergo an initial cytological analysis of the CSF, that made it difficult to assess its prognostic significance.

In the present series, gross resection was associated with improved disease free survival, but not enough to be of statistical significance ( $p = 0.168$ ). Some authors considered the complete resection as the most significant predictor of outcome [13,20,32,33]. However, other studies failed to show an advantage for complete resection [5,21].

Since postoperative irradiation started to be used, the survival rate has improved from 20% to 60% [3,9,11,28]. Most of the reports which studied radiotherapy in ependymoma, were retrospective studies, limiting their values to have a solid conclusion for the optimum radiotherapy. The only prospective study for ependymoma was the multi-center German trials HIT 88/89 and Hit 91 [27]. Even from this study, we could not get a clear idea for the optimum radiation therapy because: a) the randomization were designed for chemotherapy and not for radiotherapy protocols, b) the trials included only anaplastic ependymoma and medulloblastoma, c) only intracranial lesions are included and d) only children between 3-18 years old were eligible for the study.

Some authors presented a significant survival advantages with craniospinal irradiation for high-grade tumors preventing seedling [5,11,14]. Others didn't accept craniospinal irradiation as a treatment modality, even for anaplastic ependymomas, because of its toxicity. However, because some authors have reported that spinal seedling occurs only in infratentorial ependymomas, a third group of authors have prescribed craniospinal irradiation only for disseminated and high-grade infratentorial tumors [7,9,12,27]. Unfortunately, in our study, the treatment field design was markedly heterogeneous within the patient population for site and grade, Table (2). In addition, the small number of patients (48 patients), makes stratification of the patients by site, grade

and treatment volume of no analytical value. Nevertheless, we noticed a more favorable result for the patients with high-grade pathology when treated by craniospinal irradiation than when treated by localized/whole organ fields  $p = 0.098$ . Treatment volume did not affect the disease free survival for those with low-grade lesions. These results agreed with that of Vanuytsel et al., Salazar et al. and Wallner et al. [5,11,14].

There was a general agreement that relapse within the primary site, is the main pattern of treatment failure, justifying the dose intensification for the primary site. The studies which showed a dose response indicated that doses greater than 45 Gy have to be delivered to the primary site [12,13]. Merchant et al. [13], who studied exclusively anaplastic ependymomas, found that by increasing the dose to the primary site, the outcome was positively influenced. Some other reports could not be able to demonstrate such a dose-response relationship for survival [7,9,10,27]. In these studies, the majority of the children were treated with a small dose range (42-56 Gy) to the primary site. In the present study, a dose level more than 45Gy had a superior disease free survival,  $p = 0.054$ .

Chemotherapy was proposed as a possible treatment modality to improve survival for anaplastic ependymoma [7,10,11]. However, other randomized trials which enrolled chemotherapy as a primary adjuvant treatment, have failed to show a survival advantage for chemotherapy [27]. The SIOP (Société Internationale Oncologie Pédiatrique) and the Children's Cancer Study Group trials [3,34-35], didn't show a chemotherapy positive effect. Taking in consideration that many patients with low-grade ependymomas were enrolled in these studies, that might influence the results.

Our current recommendation is to treat all supratentorial and low-grade infratentorial tumors with partial brain fields. Craniospinal irradiation is to be reserved for those patients with high-grade infratentorial lesions and those with evidence of craniospinal seeding either radiologically or pathologically. However, prospective multidisplianry trials, should be carried on to conclude a definite treatment strategy for those patients. Using conformal radiotherapy, the dose to the primary site may be escalated with the hope of increasing tumor control.

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