

**Original
Article**

**EPENDYMOMA: PROGNOSTIC FACTORS AND SURVIVAL SINGLE
INSTITUTION EXPERIENCE (NEMROCK)**

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ABSTRACT

Background: Ependymoma is a rare disease accounting for 5-10% of brain tumors. Different prognostic factors including type of surgery, tumor histopathologic type, site, age, metastasis and stage, affect the survival with a wide variation ranging from 10-87%.

Patients and Methods: This clinical study is based on 30 patients diagnosed with intra-cranial ependymoma treated at NEMROCK between 1998-2004 with a median follow up period of 8.5 years. The patient's age ranged between 2 and 56 years with a median of 16.5 years (SD 16.48). Radiation therapy given was either craniospinal irradiation including; Whole brain irradiation 36 Gy in 18 fractions, whole spine irradiation 24Gy in 12 fractions and boost to post fossa 18 Gy in 10 fractions or wide field irradiation with safety margin 2-3 cm of normal tissue all around the tumor to a total dose of 54 Gy in 27 fractions. Data of the patients was studied as regards different prognostic factors in correlation to progression free and overall survival as well as treatment related events.

Results: The 5 year overall survival and event free survival were 61.4% and 40.9%, respectively. The median event free survival was 39.047 months (95% CI of 29.058-49.036). The OS for supratentorial site (81%) was superior to that of infratentorial site (56%) and the difference was statistically significant (p 0.0489). The OS was affected significantly by sex, grade and radiotherapy (p 0.017, 0.010, 0.027, respectively) in favor of male sex, Grade I and wide field radiotherapy. Pattern of relapse was only local recurrence.

Conclusion: Despite the rarity of ependymoma and low number of patients, this retrospective study may add weight to the findings of others that suggest the importance of total surgical excision as well as the use of radiation therapy in the management of this group of patients.

Key Words: Ependymoma, prognostic factors, survival

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INTRODUCTION

Ependymomas are relatively uncommon, accounting for 5-10% of brain tumors. It occurs in the pediatric age group; however, it is seen in adults at any age¹.

They arise from the ependymal lining of the ventricular system. They can occur at any site within the ventricular system or within the spinal canal. Intracranial ependymomas present as intraventricular masses with frequent extension into the subarachnoid space, while spinal ependymomas present as intradural extramedullary masses arising from the central canal or exophytic masses at the conus and cauda equine. Forty percent of ependymomas are supratentorial, while 60% are infratentorial in location. The posterior fossa ependymoma arises most often in children (mean age, 6 years), while the supratentorial ependymoma generally manifests in an older age group (mean age, 18-24 years².

The WHO grading system recognizes three tumor types: subependymoma and myxopapillary ependymoma (grade I tumor), low grade ependymoma, with cellular, papillary and clear cell variants (grade II tumors) and anaplastic ependymoma (grade III tumors)³.

Treatment of patients with ependymoma depends upon neurosurgical intervention to facilitate definitive diagnosis and decrease tumor burden⁴. Treatment for all grades and types includes maximum surgical resection. For myxopapillary ependymoma, complete removal while maintaining capsule integrity may be curative. Some grade II ependymomas may be observed carefully after imaging confirms complete resection, but grade III tumors require adjuvant radiation treatment. Radiation commonly is given to the region of tumor, except in cases in which there is dissemination evident by imaging or positive cerebrospinal fluid³.

Children younger than 3 years are particularly susceptible to the adverse effect of radiation on brain development⁵. Debilitating effects on growth and neurologic development have frequently been observed, especially in younger children⁶. For this reason, chemotherapy or conformal radiation approaches that minimize damage to normal brain tissue are under evaluation for infants and children with ependymoma⁷. Long-term management of these patients is complex and requires a multidisciplinary approach.

In older children and adults, radiotherapy is the standard treatment following resection for most patients with WHO grade II ependymoma. The evidence for the benefit of post-operative radiotherapy compared with surgery alone has been demonstrated in several series. The 5 year progression free survival (PFS) was 51-70% versus 13%⁸.

Second-look surgery should be considered in patients with residual local tumor because patients who have complete resections have better disease control. The traditional post surgical treatment for children aged 3 years and older has been radiation therapy consisting of 54 Gy to 55.8 Gy to the tumor bed. It is not necessary to treat the entire CNS (whole brain and spine) because these tumors usually recur at the local site⁹. In subtotally resected patients, treatment with radiation therapy results in 30-50% median PFS at 5 years^{7,10} although the outcome of patients with residual tumor within the spinal canal may be better¹¹. There is no evidence that adjuvant chemotherapy, including high-dose chemotherapy with stem cell rescue, is of any benefit¹².

Treatment fields should cover the initial tumor bed with a 1- to 2-cm margin to avoid causing long-term radiation damage¹³. For tumors in the posterior fossa, the recommended dose is 5400 cGy. Craniospinal-axis fields are used only when spinal seeding is radiologically or pathologically evident. Doses of approximately 36 Gy to the entire neuraxis (i.e., the whole brain and spine) should also be administered, but may be modulated depending on the age of the patient. Boosts between 41.4 Gy and 50.4 Gy to bulk areas of spinal disease should be administered, with doses depending on the age of the patient and the location of the tumor¹⁴.

Recurrence is not uncommon in both benign and malignant childhood brain tumors and may develop many years after initial treatment. For ependymoma, delays beyond 10 to 15 years have been reported¹⁰.

Disease generally recurs at the primary tumor site, even in children with malignant ependymomas¹⁵.

Predictors of long-term survival included an estimate of the extent of resection made at surgery (total compared with less than total, $P=0.0001$) and the amount of residual tumor on postoperative imaging as verified by centralized radiologic review. Other factors, including tumor histopathologic type, site, metastasis and tumor stage, patient age, race, gender and chemotherapy treatment regimen were not found to be significantly correlated with long-term survival¹⁶.

The aim of our study is to evaluate different prognostic groups in patients with ependymoma, based on clinical characteristics such as patient's age, tumor site, histology, surgical resection, use of radiation therapy in relation to different survival parameters.

PATIENTS AND METHODS

The current study is a retrospective analysis of patients diagnosed with ependymoma at Kasr El Aini Center of Clinical oncology NEMROCK from January 1998 till January 2004, with a median follow up of 8.5 years.

Patients were studied as regards age, sex, tumor factors included site whether supra or infratentorial, size, histopathologic type according to WHO classification and CSF seedling. Therapeutic factors included extent of surgical resection, residual tumor, adjuvant treatment whether chemotherapy and, or radiotherapy or both and its impact on treatment outcome.

Correlation between the previously mentioned factors and progression free and overall survival as well as treatment related events was done.

Treatment:

Children below 3 years of age received chemotherapy, in the form of 6 cycles of cisplatin/vepsid. Assessment was done every 3 months for all patients by MRI brain or craniospinal and CSF according to the patient initial condition whether there was CSF dissemination or not.

Patients above 3 years of age received either localized field irradiation or craniospinal irradiation if they had positive CSF cytology or seedling MRI.

Craniospinal irradiation included Whole brain irradiation 36 Gy in 18 fractions, Whole spine

irradiation 24Gy in 12 fractions and boost to post fossa 18 Gy in 10 fractions. Patients who received wide field irradiation had a safety margin 2-3Cm of normal tissue all around the tumor to a total dose of 54 Gy in 27 fractions.

Statistical methods:

Data were statistically described in terms of mean +/- standard deviation (+/- SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples when not normally distributed. For comparing categorical data, Chi square (X²) test was performed. Exact test was used instead when the expected frequency is less than 5. Univariate and multivariate analysis models were used to test for the preferential effect of the independent variables on overall survival, disease free survival and final outcome. Survival analysis was done for the different outcome measures using Kaplan Maier statistics with the corresponding survival graphs. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 13 for Microsoft Windows.

RESULTS

This clinical study is based on 30 patients diagnosed with intra-cranial ependymoma treated at Kasr el Aini center of oncology (NEMROCK) between 1998-2004 with a median follow up period of 8.5 years.

The patient's age ranged between 2 and 56 years with a mean of 16.5 years (SD 16.48). The study included eighteen children with age below 18 years and twelve adult patients (age more than or equal to eighteen).

The most frequent site of tumor was infratentorial (17 patients, 56.7%) and represented the dominant site in pediatric patients (age < 18 years old) 77.8% (14 out of 18 pediatric patients). The majority of adult tumors (9 out of the 12 adult patients) 75% had a supratentorial location.

Six patients (20%) had low grade ependymoma grade I, three of which were adults and the other three were ≤ 6 years. Twenty four patients (80%) had grade II ependymoma.

Complete surgical resection associated with no gross residual tumor evidence on post operative CT or MRI images was achieved in 40% of patients (12 patients). Supratentorial tumors had a greater chance of complete surgical resection 61.5% (8 patients out of 13) as compared to infratentorial 23.5% (4 patients out of 17) (p 0.013). The baseline characteristics of study population are shown in Table (1).

All patients received post-operative radiotherapy. Only 8 children (29.6%) out of the irradiated patients received craniospinal irradiation. The spinal subarachnoid space received doses between 18-24 Gy in 1.8-2 Gy per fraction, while the radiation dose to the primary site was 54 Gy.

Five children with age less than or equal to 3 years (18.5%) received adjuvant chemotherapy before irradiation with the intent of local tumor control and avoidance of radiation induced sequelae in the young children. The Radiotherapy given for the patients is presented in Table (2).

The 5 children treated with adjuvant chemotherapy achieved partial remission more than 85%. The median interval from surgery to radiation treatment was 8 months for patients treated with chemotherapy compared with 1.4 months for those who did not receive chemotherapy. The response to treatment for patients treated by irradiation according to the site of primary tumor is shown in Table (3).

More than half of our patients suffered from early radiation related complications mainly headache, nausea and vomiting, but the majority of these complications was successfully corrected by steroids and medical treatment. However, late sequelae were more evident in 50% of our pediatric patients in the form of leukoencephalopathy which was evident in follow up MRI.

The overall survival (OS) for all patients at 5 years was 61.4%. The mean OS was 41 months (95% CI 32.891-50.110). The OS of all patients and according to site is presented in Figures (1,3). The event free survival (EFS) for all patients at 5 years was 40.9%. The mean EFS was 39.047 months (95% CI of 29.058-49.036). The event free survival of all patients is presented in Figure (2).

The relation between Patient characteristics and 5 year EFS and OS is shown in Table 4. The OS for supratentorial site (81%) was superior to that of

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infratentorial site (56%) and the difference was statistically significant (p 0.0489). The median EFS for supratentorial ependymoma was 42 months (CI 1.750-82.250) versus 29 months (CI 14.972-43.028) for the infratentorial with a wide range.

The OS was affected significantly by sex, grade and radiotherapy (p 0.017, 0.010, 0.027, respectively) in favor of male sex, Grade I and wide field radiotherapy.

CSF cytology was positive in 5 patients, 3 males and 2 females. All patients had infratentorial site and their age ranged from 2 to 6 years. All of the five patients received craniospinal irradiation.

Pattern of relapse was only local recurrence. Thirteen patients (43%) relapsed at a median of 29 months (14-43 months) after the start of treatment. Eleven of these patients had local recurrence at the primary tumor, while two patients had also CSF dissemination.

Table 1: Baseline characteristics of 30 patients with Ependymoma presented to NEMROCK from 1998-2004.

	No. of patients No (%) 30 (100%)	Supratent. No. (%) 13 (43.3%)	Infratent. No. (%) 17 (56.7%)	Age		
				≤3yrs No (%) 5 (16.7%)	>3-17yrs No (%) 13 (43.3%)	≥18yrs No (%) 12 (40%)
Sex						
Male	16 (53.3%)	5 (31.3%)	11 (68.7%)	2 (40%)	7 (53.8%)	6 (50%)
Female	14(46.7%)	8 (57.1%)	6 (42.9%)	3 (60%)	6 (46.2%)	6 (50%)
Surgery						
Complete	12 (40%)	8 (66.7%)	4 (33.3%)	0	8 (61.5%)	4 (33.3%)
Incomplet	18 (60%)	5 (27.8%)	13 (72.2%)	5(100%)	5 (38.5%)	8 (66.7%)
Pathology						
Grade I	6 (20%)	5 (83.3%)	1 (16.7%)	1(20%)	2 (15.4%)	3 (25%)
Grade II	24 (80%)	8 (33.3%)	16 (66.7%)	4 (80%)	11 (84.6%)	9 (75%)
Radioth. Alone	25 (83.3%)	13 (52%)	12 (48%)	0	13 (100%)	12(100%)
Both chemo-radioth.	5 (16.7%)	--	5 (100%)	5(100%)	0	0

Table 2: Radiotherapy used for the 30 cases of Ependymoma (NEMROCK 1998-2004).

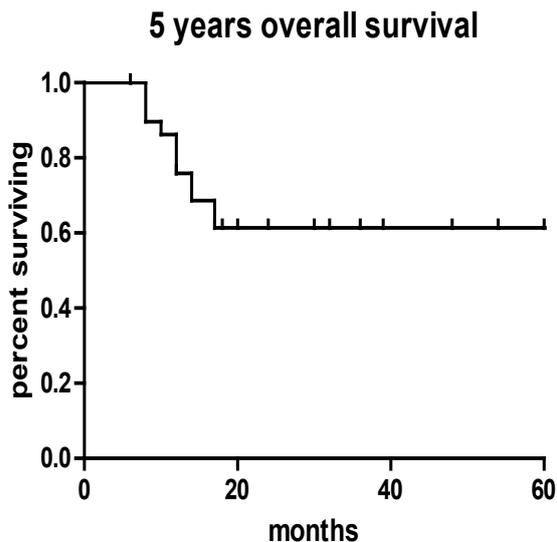
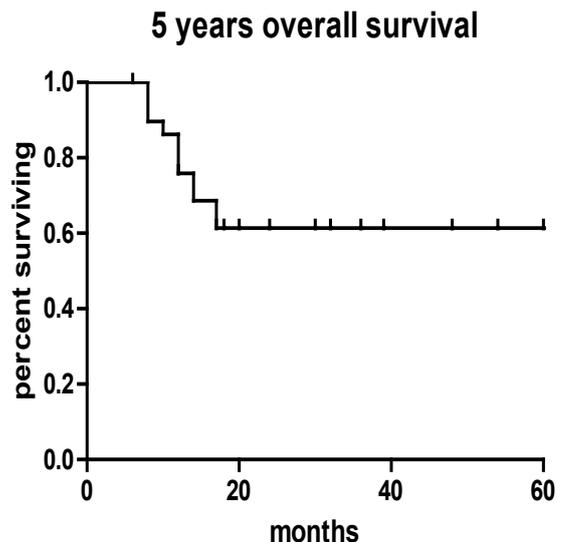
Site and type of ependymoma	No. of patients 30	Localized field No. (%) 22 (73.3%)	Cranio-spinal field No. (%) 8 (26.7%)
Infratentorial (17)			
Grade I	1	1 (5.9%)	
Grade II	16	8 (47.1%)	8 (47.1%)
Supratentorial (13)			
Grade I	5	5 (38.5%)	
Grade II	8	8 (61.5%)	0

Table 3: Response according to site of primary tumor of 30 patients with Ependymoma treated by irradiation at NEMROCK 1998-2004.

Radiotherapy response	Infratentorial No. (%)	Supratentorial No. (%)	Total No. (%)	P value
Complete remission	2 (6.7%)	4 (13.3%)	6 (20%)	0.755
Partial remission	7 (23.3%)	3 (10%)	8 (33.3%)	0.598
Stationary disease	4 (13.3%)	5 (16.7%)	9 (30%)	0.598
Disease progression	4 (13.3%)	1 (3.4%)	5 (16.7%)	0.454
Outcome at 3 years				
Alive	8 (47%)	11 (84.6%)	19 (63.3%)	0.387
Dead	9 (53%)	2 (15.4%)	11 (36.7%)	0.063

Table 4: Relation between Patient characteristics and event free survival in 30 patients treated at NEMROCK 1998-2004

		Total n=30		5 year EFS (%)	P value 5 year EFS	P value 5 year OS
		N0	%			
Age	<3yrs	5	(16.7%)	20%	0.042	0.053
	>3-17yrs	13	(43.3%)	53.8%		
	≥18yrs	12	(40%)	33.3%		
Sex	Male	16	(53.3%)	50%	0.005	0.017
	Female	14	(46.7%)	28.6%		
Site	Supra	13	(43.3%)	66.8%	0.46	0.093
	Infra	17	(56.7)	47.2%		
Surgery	Excision	12	(40%)	58.33%	0.889	0.845
	Biopsy	18	(60%)	55.4%		
Grade	I	6	(20%)	83.3%	0.005	0.010
	II	24	(80%)	29.2%		
Radioth.	CSI	8	(26.7%)	41.9%	0.029	0.027
	Wide F	22	(73.3%)	68.7%		

**Figure 1:** Five years overall survival of 30 patients with ependymoma treated in NEMROCK 1998-2004.**Figure 2:** Five years event free survival of 30 patients with ependymoma treated in NEMROCK 1998-2004.

DISCUSSION

Ependymoma is a rare disease accounting for 5-10% of brain tumors. More than 50% of the cases are usually younger than 11 years¹. Due to their rarity and the lack of awareness of their biological characteristics, ependymoma have escaped attempts of large cooperative prospective trials.

We approached this cohort of patients wondering whether different prognostic groups exist, based on clinical characteristics such as patient's age, tumor site, histology, tumor resection, use of radiation

therapy and Chemotherapy in relation to different survival parameters.

The 5 year overall survival for all patients was 61.4% and this was inferior to Van Veelen-Vincent et al 2002 who reported a 5 year overall survival of 68% (16). This may be due incomplete excision of the majority of the patients (60%) in our study, as well as the small sample size among our patients.

A gross-total resection seems to be the most important prognostic factor in the treatment of ependymoma¹⁷. A complete resection was obtained

in 40% of our patients. Surgery did not affect significantly the survival in our study (p 0.889 and 0.845 for the EFS and OS, respectively). However this may be attributed to the fact that the number of completely resected tumors was relatively small in this study as compared to other studies.

Cognitive and focal neurological deficits may have a great impact on long term survivors of brain tumors. Memory loss, apathy, concentration difficulties and personality changes may have a profound effect¹⁸. Surgery may also contribute to cognitive deficits. Radiation therapy is known to cause early somnolence syndrome, but may also cause late sequelae in particular delayed leukoencephalopathy with cognitive dysfunction and radiation necrosis¹⁹. Radiation therapy may also induce endocrine dysfunction and seizures which may have a great impact on the quality of life in long term survivors of brain tumors. However chemotherapy may also induce late sequelae such as lymphoma, leukemia as well as lung fibrosis, infertility, renal impairment and signs of neurotoxicity of peripheral nervous system²⁰.

More than half of our patients suffered from early radiation related complications mainly headache, nausea and vomiting, but the majority of these complications was successfully corrected by steroids and medical treatment. Late sequelae was evident in 50% of our patients had leukoencephalopathy in follow up MRI. Further concern about quality-of-life is needed especially in long-term survivors, to get a clear insight into the effects of various treatment modalities.

Different prognostic factors affect the survival with a wide variation ranging from 10-87%. In our study, the 5 year overall survival was affected by the site of the disease accounting for 81% in supratentorial ependymoma versus 56% in infratentorial ependymoma at 5 years the difference was statistically significant (p 0.0489). The event free survival at 5 years in supra and infratentorial sites were 66.8% and 47.2%, respectively (p 0.46). This was mainly due to better gross total resection in the supratentorial group. These results were close to the results of other investigators (Kawabata et al.²¹).

As regards pathology, the 5 year overall survival was affected significantly by grade in favor of grade I (0.010). This is in coincidence with Kawabata et al 2005 and Lucio Palma 2006, who found that Tumor pathology and grade affected markedly the survival in favor of low grade^{21,17}.

As regards age in our study, the best 5 years overall survival was seen in patients >3 years-17 years (P 0.053). Younger age has been shown to be a negative prognostic factor in only half of the reported series which was reviewed by Van Veelen-Vincent MC et al.¹⁶. This lack of conformity might, in part, be caused by the considerable variation in cut-off age between different studies. It is often assumed that the absence or delay of radiotherapy in the younger age group causes the difference in outcome, but other factors might also be important. Nazar, et al.²² and Perilongo, et al.²³ reported an association of younger age with malignant lesions, infratentorial location and subtotally resected lesions. On the other hand, Lyons and Kelly²⁴ and Pollack, et al.¹⁰ found that younger age was a negative prognostic factor regardless of histological findings, extent of resection and radiotherapy.

Male patients had a better 5 years overall survival 33.3% compared to females 26.7% which was statistically significant (p 0.017). This is in contrary to Kawabata et al 2005, where male patients had 5 years OS of 77%, while female patients had 5 years OS of 88% (p 0.2376).

Patients receiving craniospinal irradiation fared the worse with 5 year overall survival compared with those receiving wide field radiotherapy (p 0.027). These results may be due to some of the patients below 3 years had positive CSF and received chemotherapy followed by craniospinal irradiation when they were more than 3 years. Patients receiving radiotherapy had a lower survival than other studies⁷ this may be attributed to the fact that only 40% of the patients had complete resection in our study.

Local recurrence was the only site of relapse in our study regardless of the treatment modality used. This was also reported in many other studies where the prominent pattern of relapse was local, even after gross total resection and postoperative radiotherapy^{11,21}.

However this retrospective study was limited by the relatively small number of patients and the lack of genetic and molecular studies that could have an impact on optimization of treatment modalities.

CONCLUSION

Despite the rarity of ependymoma and low number of patients, this retrospective study may add weight to the findings of others that suggest the

importance of total surgical excision as well as the use of radiation therapy in the management of this group of patients. However prognostic factors change with time as better treatment modalities are devised and more accurate imaging and histopathological techniques evolve. These considerations call attention to the need for carefully designed treatment lines that would improve local control and minimize treatment related sequelae in long term survivors. It might be possible to enhance the benefit for radiotherapy by dose escalation with conventionally fractionated conformal radiotherapy.

It is evident that due to the rarity of this neoplasm, no single institution would be able to reach meaningful data in a reasonable time frame. This consideration call attention for the importance of cooperative clinical data gathered from different institutions and its importance on improving control of this rare but potentially devastating CNS tumor.

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