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# Fourth Ventricle Ependymomas

## A Study of 20 Cases with Survival Analysis

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## Summary

Twenty patients with fourth ventricle ependymoma were treated surgically at our Neurosurgery Division between January 1976 und December 1990. Ependymoblastomas and mixed gliomas operated on in the same period have not been considered. A statistical analysis of our cases and a review of the largest published series show that favourable prognostic factors are: age over 16, post-operative radiotherapy to the posterior cranial fossa and a good Karnofsky performance status (KPS) after operation. The 5-year survival rate of patients under 16 was 20%, in comparison with 60% of adults ($p = 0.013$). Post-operative radiotherapy to the posterior cranial fossa improved the survival markedly (5-year survival rate 68%, versus 18% without treatment; $p = 0.011$). The differences of survival are also significant according to a multivariate analysis ($p = 0.038$). Patients with a post-operative KPS over 70 had a 5-year survival rate of 61% as against 17% of the group with a worse clinical condition ($p = 0.032$); the multivariate analysis confirmed also that this difference was significant ($p = 0.046$). Pre-operative symptoms and signs, and KPS, histological grade and extent of surgical removal seem to influence the prognosis, even if the differences of survival are not statistically significant. The statistical relevance of postoperative residual tumour on CT or MRI was brought out on multivariate analysis ($p = 0.044$).

*Keywords:* Ependymoma; fourth ventricle tumour; posterior cranial fossa; radiotherapy; surgery.

## Introduction

Ependymoma is a relatively uncommon primary tumour of the central nervous system (2–6% of CNS tumours and about 1–9% of all intracranial tumours), but it is the most common intramedullary spinal cord oncotype (30–60%) of spinal cord gliomas)[1, 19, 21, 33, 34, 43, 48, 51, 53, 55, 60]. 43%–82% of intracranial ependymomas at any age are localized in the posterior cranial foss[6, 10, 13, 21, 23, 29, 55, 61] and most of them (75%–100%) arise from the floor or the roof of fourth ventricle[13, 18, 23, 24, 29, 33, 42, 54]. In childhood, ependymoma is the third most common intracranial tumour[2, 8, 12, 28, 31, 37, 39, 48, 54] and 2/3 of cases are infratentorial[1, 3, 6, 8, 12, 15, 21, 23, 29, 31, 39, 42, 54]. Unlike supratentorial, infratentorial ependymomas generally have a low mitotic index[18, 46, 62], but have a "clinical malignancy" caused by their localization[13, 54].

For posterior fossa ependymomas, and especially for those arising from the fourth ventricle, there are different opinions about methods of treatment and prognostic factors. Reporting on a retrospective series of 20 patients who received surgical treatment in our Neurosurgery Division between 1976 and 1990, we have analyzed the influence on prognosis of several variables, focusing our attention on the degree of surgical removal and on the role of postoperative radiotherapy.

## Clinical Material and Methods

Twenty consecutive patients with histologically verified fourth ventricle ependymomas received surgical treatment in the Neurosurgery Division of our Department between January 1976 and December 1990. Patients with ependymoblastomas and mixed gliomas are excluded.

### *Statistical Analysis*

Even if the number of our patients is small, mainly in relation to the relative rarity of the tumour, a statistical analysis of results has been possible.

Survival curves from the time of surgery were estimated by using the Kaplan-Meier method[26] and survival differences among subgroups were evaluated using the two-tailed log rank test[41]. In order to separate the influence of different variables on survival, we have analyzed the data using covariate analysis techniques with the Cox proportional hazards (PH) regression[9]. The hazard function calculated the risk of dying at each time point among the patients still alive at that time[9]. We performed the stepwise modelling procedures

to generate Cox-single-variable PH models, each containing one of the following covariates: age ($\leqslant 16$ or $> 16$ and $\leqslant 6$ or $> 6$ years); neurological symptoms (intracranial hypertension, cerebellar deficits, cranial nerves deficits); pre-operative Karnofsky performance status (KPS $\leqslant 70$ or $> 70$); extent of surgical removal (macroscopically total or subtotal); postoperative residual tumour on CT or MRI (present or absent); postoperative radiotherapy (done or not done); histological grade (low or high-grade) and postoperative KPS ($\leqslant 70$ or $> 70$). These procedures were followed by the series of multivariate Cox models in which covariates are successively added in decreasing order of the strength of their association with survival. The first analysis (univariate) extimates the association of length of survival with each individual covariate, while the multivariate models extimate the strength of association of survival time with each covariate after correction for the effects of the other variables in the model.

*Clinical Features*

Of the 20 patient 9 were male and 11 female, with an M/F ratio of 0.8. Mean age was about 25 years (median 19), and the range from 3 to 65 years. Nine patients (45%) were under 16 and 5 (25%) under 6 years. The mean age of the males was 18 years (range 3–57) and of the females 26 years (range 3–65); the difference is not statistically significant. The mean duration of the clinical history was 6 months (median 3), and the range from 1 to 24 months. Intracranial hypertension was the first symptom in 12 cases (60%), a deficit of a cranial nerve in 5 (25%) and a cerebellar disturbance in 3 (15%); in the last 8 patients the raised intracranial pressure was the second symptom (40%). At the time of diagnosis 18 patients (90%) complained of symptoms and signs of intracranial hypertension, 18 of cerebellar deficits, 8 of cranial nerves palsy, 8 of nystagmus, 4 of psychic impairment, and 2 of vertigo. One patient had a urinary incontinence.

*Radiological Features*

Pre-operative radiological evaluation consisted of conventional X-rays in all, pneumoencephalography in 2, angiography in 6, cerebral CT scan in 16 and MRI in 3.

Cerebral angiography revealed neovascularity in 2 patients, showed indirect signs of posterior cranial fossa tumour in 3 and was normal in 1.

Cerebral CT scan showed in all cases an inhomogeneous posterior fossa neoplasm, with contrast enhancement in 12, calcifications in 4, cyst in 1. Brain stem involvement was observed in 4 cases and an extension into the cerebellopontine angle in 2.

MRI imaged a posterior fossa tumour, hypo-intense on T1-weighted and inhomogeneously hyperintense on T2 images; the enhancement with Gd-DTPA was irregular in all cases. Neither brain stem invasion nor cerebellopontine angle extension was observed.

The neuroradiological investigations revealed pre-operative hydrocephalus in 15 patients.

*Treatment*

Sixteen patients were operated on in the prone position and four in the sitting position, mainly in relation to the surgeon's experience. All received steroids and antibiotics both pre- and postoperatively.

## Results

*Operation*

A total gross resection of tumour was possible in 7 cases (35%) and a subtotal removal in 13 (65%). After debulking the lesion with CUSA, total tumour excision was achieved with microsurgical technique in 6 of the 15 patients operated on after 1980, that is 40% compared with 20% (1/5 cases) before that date. In 6 cases the tumour invaded the floor of 4th ventricle, in 5 cases it projected caudally into the cervical canal, and in 2 it extended into the cerebellopontine angle. In 11 patients cerebral CT scan (8 cases) or MRI (3 cases) were performed 1 to 3 months after surgery, to check the presence of residual tumour: the findings confirmed the intra-operative surgical evaluation.

Overall operative mortality was 15% (3 patients) but there were no operative deaths since 1980. Of the 3 patients who died postoperatively 1 had pulmonary embolism and 2 had high-grade ependymomas invading the floor of IVth ventricle.

On *pathological examination*, in 13 cases the tumour was considered low-grade and in 7 high-grade, in relation to the presence of necrosis, mitosis, and endothelial proliferation[48].

Ten patients accepted to receive *postoperative radiotherapy* to the posterior cranial fossa; in 3 the tumour removal was total and in 7 subtotal. The dose ranged from 45 to 60 Gy (median 54) and there were no side effects or evidence of cerebral toxicity. None of the patients received postoperative chemotherapy, save for one patient with spinal seeding.

In the postoperative period 5 patients had *CSF shunt for hydrocephalus.*

*Relapses and metastases:* 13 patients (5 with total and 8 with subtotal removal) died because of clinical and radiological recurrence, within the span of 14 to 108 months; 8 of them had received postoperative radiotherapy. The 4 cases with a residual tumour observed after operation on CT or MRI were followed until the clinical recurrence (from 14 to 61 months after operation). In relation to the general condition of patient, to brainstem extension of tumour, to time between surgery and clinical relapse, and to patient's or relatives' decision 5 of the 13 patients had a second operation (and in one case a third operation), combined with radiotherapy in 3; another 3 received radiotherapy only. Another 5 patients refused any treatment and died after few weeks. The patients who underwent reoperation experienced partial regression or clinical sta-

bility for a period ranging from 3 months to 9 years while the patients who received radiotherapy only presented progressive neurological deterioration within 3 months.

Clinical and radiological (MRI) evidence of spinal seeding (D1-level) was observed in one patient, a 29-year old man operated on 12 months previously with subtotal removal of a low-grade IVth ventricle ependymoma. Because of his poor general and neurological condition he was treated by spinal irradiation (35 Gy) and chemotherapy (vincristine and cisplatin) and survived only for an additional 2 months.

Lumbar CSF analysis was performed in the last eight patients of the series and the fluid was negative for cytology in all but the one case with spinal metastasis.

*Survival Analysis*

The median survival time was approximately 4 years (52 months), with 3-year, 5-year, 10-year, and 15-year survival rates of 60%, 41%, 27% and 12%, respectively. Four patients were still living at the last follow-up contact.

Age under 16 at diagnosis was a statistically significant prognostic factor (two-tailed log rank, $p = 0.013$) related to survival (Fig. 1). The 8 patients under 16 years had a poorer prognosis (median survival: 1.8 years; 5-year and 10-year survival rates, 20% and zero, respectively) than the 9 adults (median survival: 9.1 years; 5-years and 10-years survival rates, 60% and 60%, respectively). On comparing survival data of patients under and over 6 years of age at diagnosis there are no statistically significant differences ($p = 0.374$). Moreover, on comparing survival of children under 6 years at diagnosis and of boys over 6 and under 16 years the 5-year survival rates are 50% and 0%, respectively, and the median survival 1.8 and 2.5 years; these differences too are not statistically significant ($p = 0.07$).

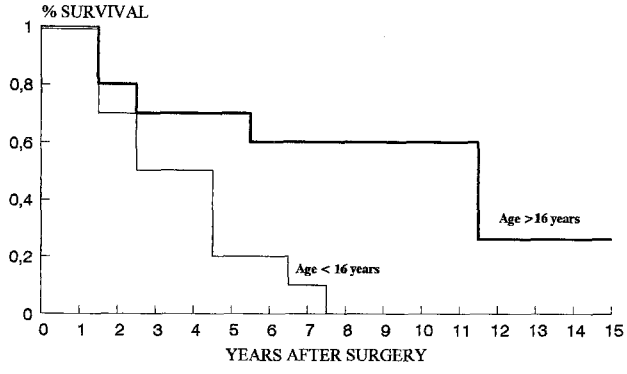


Fig. 1. Survival rates: adults versus children

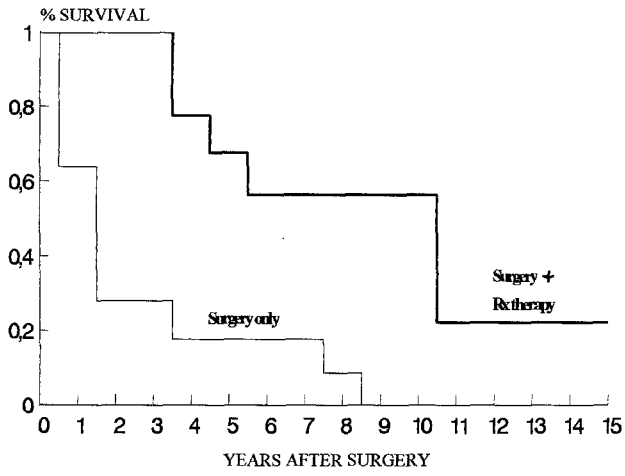


Fig. 2. Survival rates: postoperative radiotherapy (Rx therapy) versus surgery only

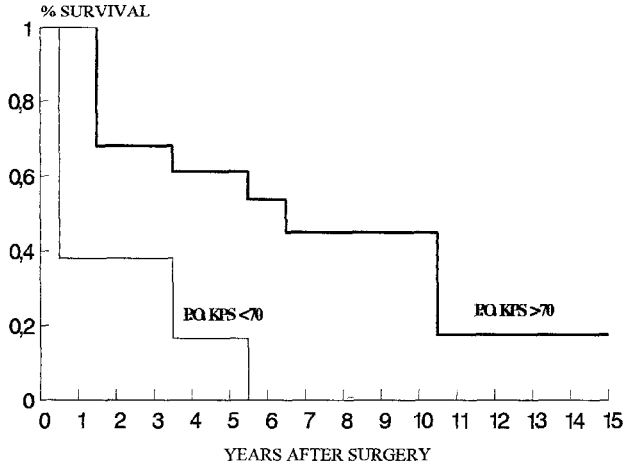


Fig. 3. Survival rates in relation to postoperative KPS

Neither the pre-operative symptoms and signs nor the pre-operative KPS ($\leqslant 70$ or $> 70$) had any significant correlation with survival ($p = 0.850$ and $p = 0.169$, respectively).

The median survival time of the 6 patients undergoing total surgical removal was 8 years and the 5-year and 10-year survival rates were 63% and 50%, respectively. In patients operated on with subtotal removal the median survival was 2.4 years, and the 5-year and 10-year rates were 25% and zero, respectively. These differences were not, however, statistically significant ($p = 0.179$), presumably in relation to the small

number of cases. When the analysis was limited to the 11 cases with radiologically documented extension of resection, the 5-year and 10-year survival rates of the 4 patients with postoperative residual tumour were 20% and zero, respectively, versus 76% and 50% of patients without residual disease. The median survival time was 2 years in the first group and 7 years in the second. These differences were not, however, statistically significant on univariate analysis ($p = 0.136$), mainly in relation to the low number of patients examined.

The 10 patients who received adjuvant radiotherapy after surgery had a significantly better survival curve ($p = 0.011$) than the 7 who did not (Fig. 2). The median survival period of the first group was 9.1 years versus 1.7 for the second. The 5-year and 10-year survival rates in the patients who received radiation were 68% and 56%, respectively; in contrast, the same survival rates in patients not irradiated were 18% and zero.

The 5-year survival rate of the 3 patients who received total surgical excision of tumour and postoperative radiotherapy was 100%; the same survival rate was 25% in the 3 patients with total removal not followed by radiation, 50% in the 2 patients who received subtotal removal and radiation therapy, and 30% in the 9 patients who received subtotal removal only. These differences were not, however, statistically significant ($p = 0.186$), presumably because of the small number of patients in each subgroup.

Postoperative KPS was a statistically significant prognostic variable related to survival ($p = 0.032$). The median survival time of the 6 patients with a postoperative KPS $> 70$ was 8 years versus 1.3 of the subjects with a KPS $\leqslant 70$ (Fig. 3). The 5-year and 10-year survival rates of the first group were 61% and 45%, respectively, versus 16.5% and zero of the second. The relation between extent of tumour resection and postoperative KPS was the following: 3 patients had a good KPS and 8 a poor KPS after subtotal removal, 3 a good KPS and 3 a poor KPS after total removal.

The 5-year and 10-year survival rates of the 12 patients with low-grade ependymoma were 57% and 28%, respectively, versus 20% and 20% of patients operated on for high-grade tumours (anaplastic ependymoma). The median survival times were 6 years and 1.2 year, respectively ($p = 0.264$). On comparing the survival curve of the 16 patients with low-grade ependymomas who received postoperative radiotherapy with the curve of the 6 patients with low-grade tumour treated only by surgery, we observed that the 5-year and 10-year survival rates of the first group were 63% and 50%, respectively, versus 28% and zero of the second group. The respective median survival times were 7.5 years and 2.6 years. However, these differences too were not statistically significant ($p = 0.121$).

Table 1. *Multivariate Analysis of Prognostic Factors for Survival in 17 Patients Operated on for IVth Ventricle Ependymoma*

| Variable | β Coefficient | p Value |
|---|---|---|
| Age at diagnosis ($\leqslant 16/> 16$ years) | −0.87 | 0.260 |
| ($\leqslant 6/> 6$ years) | | 0.990 |
| Symptoms and signs (intracranial hypertension/cerebellar deficits/cranial nerves deficits) | −0.38 | 0.457 |
| Pre-operative KPS ($\leqslant 70/> 70$) | −0.92 | 0.274 |
| Surgical removal (total/subtotal) | −0.77 | 0.363 |
| Postoperative radiotherapy (yes/no) | −1.79 | 0.038 |
| Postoperative KPS ($\leqslant 70/> 70$) | −1.87 | 0.046 |
| Postoperative residual disease (yes/no) | 2.29 | 0.044 |
| Histology (low grade/high grade) | −0.11 | 0.896 |

The multivariate analyses using Cox models confirmed – with the limits already stressed – the prognostic relevance of postoperative radiotherapy ($p = 0.038$) and of good postoperative KPS ($p = 0.046$). Moreover, the same analyses showed the statistical importance of the presence of postoperative residual disease on CT and MRI ($p = 0.044$), not significant on the univariate analysis: this contradiction is presumably in relation to the small number of cases examinated. Table 1 summarizes the results, showing the strength of association between the variables and the survival data.

## Discussion

The prognosis of fourth ventricle ependymomas is generally poor, mainly in relation to the high-risk location and to the consequent technical difficulties in performing a complete excision[4, 13, 21–24, 29, 33, 39, 43, 54]. In fact, even if microsurgical total removal of intracranial masses is the aim of every neurosurgeon, the obstacle to the attainment of this goal during surgery is the frequent tendency of ependymoma to infiltrate the floor of the ventricle and then the brainstem[13, 21, 23, 24, 33, 40, 43, 47, 54]. Therefore, the inability to control local disease, the most important factor related to treatment failure, is strictly connected with the frequent only subtotal resection of tumour. However, in accordance with other authors[18, 21, 33, 42, 50], the extent of surgical removal did not impact on survival time of our patients

in a statistically significant manner (two-tailed log rank: $p = 0.179$; multivariate analysis: $p = 0.363$). Notwithstanding, the 5-year, 10-year, and 15-year survival rates of our patients undergoing complete excision (63%, 50% and 20%, respectively) were clearly better than those having a subtotal removal. Even if the subjective evaluation of the surgeon may be fallacious, the 11 cases who underwent postoperative radiological control of the extent of tumour removal allow one to affirm that the two criteria of evaluation are not discordant. It seems to be important to consider that the subtotal group included most patients with tumours infiltrating the floor of the fourth ventricle and the brainstem.

Considering that a good postoperative KPS influenced positively the prognosis of our patients, it is, however, reasonable to evaluate in each case the possibility of obtaining a massive or complete surgical removal avoiding the risk of a serious impairment of the postoperative neurological condition[33], and then of KPS. These considerations are mainly directed to those patients with ependymomas infiltrating the floor of fourth ventricle.

Even if our experience is limited to few patients, a second operation for relapse of tumour seems to be advisable in patients with a good KPS[33, 37].

According to Ikezaki *et al.*[24] the ependymomas arising from the lateral recess of the fourth ventricle and from the vestibular area would have a lower survival, presumably because of the difficulty of total surgical removal. This analysis was impossible in our series because of the small number of patients in the lateral type subgroup (2 cases).

The usefulness of postoperative radiotherapy for IVth ventricle ependymomas and its efficacy on the long-term prognosis are undoubted, especially with a global dose of more than 4500–5000 cGy[3, 6, 11–13, 15, 16, 18, 27, 29, 33, 35, 38, 42, 44, 50–52, 57, 58]. In our series the statistical differences between treated and untreated patients are highly significant (Fig. 2). Though some authors suggested craniospinal irradiation[3, 16, 49] and others whole-brain radiotherapy with a boost to the posterior fossa[35, 50], the irradiation of posterior cranial fossa alone seems to be the treatment of choice[18, 33, 51, 52, 54, 58], especially for low-grade ependymomas. In fact, in our series the 5-year and the 10-year survival rates of low-grade tumours were 63% and 50%, respectively, in 6 patients treated with posterior fossa irradiation, versus 28% and zero, in 6 untreated, even if these data are not statistically proved ($p = 0.121$). Moreover, it is possible that the hyperfractionation of doses and the use of radiosensitizers may enhance the therapeutic role of postoperative radiotherapy[21].

The role of spinal irradiation should be limited to patients with invasive or high-grade ependymomas, with spinal seeding (about 6% of cases)[21] or with positive CS cytology, and preferably older than 2 years of age[5, 15, 20, 21, 29, 33, 39, 54].

In spite of a wide variety of drugs used, the role of postoperative chemotherapy is still of uncertain value[12, 16, 18, 32, 33, 36, 39, 42, 45, 54, 56] being perhaps useful for very young children with spinal seeding[38], for recurrences, and for high-grade ependymomas[6, 33, 35].

Among several variables studied in our series the analysis of age-related survival factors has revealed that patients less than 16 years of age have a poorer prognosis than older patients ($p = 0.013$), in accordance with other series[1, 12, 16, 21, 23, 25, 29, 33, 39, 44, 54, 59], even if the multivariate analysis does not confirm these data. Furthermore, even though some authors reported a better outlook in children than in adults[6, 30, 50], it is possible to affirm that the younger the patient is, the worse is the prognosis[11, 33, 39, 42]. In fact, even if the data are not statistically significant, our patients under 6 years had a worse median survival (1.8 years) versus older patients (4.7 years), and long-term survival rates (10-year and 15-year) were zero versus 38% and 16%, respectively. In accordance with other authors[10, 14, 33, 47, 52], we agree with the opinion that ependymomas in children arise from more immature and more aggressive cells. Consequently, it is reasonable to consider two types of posterior cranial fossa ependymoma: adult type and children type, with different clinical courses and prognoses[33].

The prognostic importance of CT and/or MRI residual tumour after posterior fossa ependymoma surgery has been demonstrated by other authors[21] and the multivariate analysis of our data seems to confirm the role of this factor in the outlook of fourth ventricle ependymomas ($p = 0.044$). Thus, it is possible that the postoperative images can predict the prognosis of posterior fossa ependymomas better than the operative reports[21], perhaps because of the difficulty fo confirm during surgery exactly the extent of removal.

The doubts still remaining around the prognostic aspects of fourth ventricle ependymomas could be solved only with co-operative group studies, essential to obtain further knowledge for the appropriate multimodal treatment of this uncommon tumour.

## Conclusions

With the continued advance of surgical techniques and of anaesthetic-resuscitation procedures the total removal of fourth ventricle ependymomas has become progressively more feasible, even if it is always proper to evaluate patient by patient the optimal grade of resection, especially when an infiltration of the floor is present. Postoperative radiotherapy at doses over 45 Gy seems to have control over long-terem recurrences and overall survival, independent of the histological grade of tumour. The treatment of choice for recurrences seems to be likewise surgical and radiotherapeutic. Apart from good postoperative KPS and radiotherapy, favourable factors for long-term survival are the age over 16 years at diagnosis and the absence of postoperative residual disease on CT or MRI.

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