INTRACRANIAL EPENDYMONA IN ADULT PATIENTS: LONG-TERM RESULTS OF POSTOPERATIVE IRRADIATION.

Gliński Bogdan, Szpytma Teresa, Pluta Elżbieta

Department of Radiation Therapy, Centre of Oncology Maria Skłodowska – Curie Memorial Institute, Garncarska 11 Street, Kraków, Poland.

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SUMMARY

Twenty-nine adult patients with intracranial ependymoma received postoperative radiotherapy with curative intent between 1978 and 1993. The primary site was located above tentorium in 17 cases and below in 12. In 17 patients the tumours were classified as low-grade. Most patients with high-grade lesions received radiotherapy to the craniospinal axis, low-grade tumours received a more limited treatment. Actuarial survival rates at 5 and 10 years were 59% and 51% in the whole group respectively. Histologically actuarial survival rates at 5 and 10 years were 50% and 41% for high-grade tumours, and 65% and 57% for low-grade lesions respectively. This difference was not statistically significant at 0,05 level.
The primary site was the most common pattern of failure.

INTRODUCTION

Ependymomas are infrequent tumours that account for 2-5% of all neoplasms of the central nervous system, and at least half of them occur in the first two decades of life. They typically project from an ependymal surface, most commonly in the floor of the fourth ventricle or lateral and third ventricles, but can also arise in the cerebellopontine angle, the region of the spinal cord, or from the filum terminale [1]. About two thirds are infratentorial, and about one third supratentorial. Tumours of the posterior fossa predominate in young children and adolescents [2].

Surgery has always been the primary treatment for ependymomas, whose, complete removal due to their location is often impossible without significant morbidity. Consequently, results in a pure surgical series are generally disappointing with survival rates less than 30% after 5 years [3]. Therefore the postoperative radiation therapy plays an important role, and has consistently improved survival [4].
This paper describes a retrospective study of 29 adult patients treated with postoperative irradiation, and discusses therapeutic implications of the findings.

MATERIALS AND METHODS

Patients

Between 1978 and 1993, 29 adult patients with histologically verified primary intracranial ependymoma were referred to the Maria Skłodowska – Curie Memorial Institute Center in Kraków for further treatment after initial surgery. The 18 female and 11 male patients ranged from 17 to 57 years (mean age 38 years). The tumour was supratentorial in 17 (59%) patients and infratentorial in 12 (41%). The most commonly involved side was the fourth ventricle, among supratentorial tumours, cerebral hemispheres being most frequently involved often with association with the third and/or lateral ventricles.

All patients underwent open craniotomy: only for biopsy in 1 (3%) case, for subtotal resection in 24 (83%) cases, and for gross total removal in four (14%) cases. The same pathologist evaluated all surgical specimens according to the criteria of the WHO [5]. By histological subtype, 12 (41%) tumours were of the cellular type, 12 were anaplastic, and 5 (10%) represented mixed a cellular and papillary variant. All tumours were graded on an ascending scale of malignancy from 1 to 4. Grading was based upon the recognition of three features: mitotic figures, endothelial proliferation and necrosis, using the following scale: grade 1 – devoid of mitotic activity, grade 2 – mitotic figures present with no endothelial proliferation or necrosis, grade 3- mitotic figures plus either endothelial proliferation or necrosis or both, and grade 4- basic features similar to those of primitive neuroectodermal tumour but with evidence of ependymal differentiation. Overall, 17 (59%) tumours were low-grade and 12 (41%) were those of high-grade. The distribution of patho-clinical characteristics of 29 patients is given in Table 1.

Table 1. Patients characteristics.

Characteristics	Number of patients
Age (years)	
40 and less	15
More than 40	14
Gender	
Male	11
Female	18
Tumour location	
Supratentorial	17
Infratentorial	12
Surgery	
Biopsy	1
Partial resection	24
Total resection	4
Histology	
Low-grade (1 and 2)	17
High-grade (3 and 4)	12

RADIATION THERAPY

All patients were treated with either a 10 MeV linear accelerator, or with ^{60}Co. The radiotherapy treatment fields are listed in Table 2.

The brain was treated with two opposed lateral fields (for infratentorial tumours the upper cervical region of the spine was included in the radiation field). All spine fields were irradiated with two direct posterior beams with appropriate shifting gaps. Partial brain fields were planned by estimating the tumour volume from radiographic studies. The target volume encompassed a CT scan contrast-enhanced zone plus a margin of 2 cm. In the pre-CT era the tumour volume was based on the neurosurgeon's description of the anatomic area of tumour involvement. Brain doses, calculated at midplane, ranged from 40 to 50 Gy (median 46 Gy), whereas spinal cord doses, calculated at the appropriate cord depth, ranged from 30 to 35 Gy (median 32 Gy). The median doses per fraction for the brain and spinal cord were 180 and 135 cGy, respectively. In a partial brain irradiation the dose to the primary site was 56 to 60 Gy (median, 58 Gy), delivered in 24-30 fractions.

Table 2. Radiation treatment fields by tumour location and grade.

Treatment fields	Supratentorial		Infratentorial	
	Low-grade	High-grade	Low-grade	High-grade
Partial brain	10	2	2	1
Whole brain	2	2	1	1
Craniospinal axis	-	1	2	5

SUPPORTIVE TREATMENT

Systemic anticonvulsants were administered to all patients during irradiation, steroids were given only as symptomatic medication required to control cerebral oedema.

STATISTICAL CONSIDERATION

A minimum follow-up was five years. The length of survival was measured from the day of surgery, survival plots were generated using the Kaplan-Meier product limit method [6], and comparisons were made using the Gehan modification of the Wilcoxon test [7].

RESULTS

TOLERANCE

The treatment was generally well tolerated, only one patient who received craniospinal axis irradiation, had onset of intermittent vomiting which caused a two day break in irradiation.

SURVIVAL

At the time of this analysis, 14 of the 29 patients were known to have died. The overall actuarial survival of 29 patients is presented in Fig. 1. Actuarial survival rates at 5 and 10 years were 59% and 51%, respectively. The probability of survival according to the histological grade is given in Fig. 2.

Actuarial survival rates at 5 and 10 years were 50% and 41% for high-grade, 65% and 57% for low-grade tumours respectively. This difference is not statistically significant (p=0,3283).

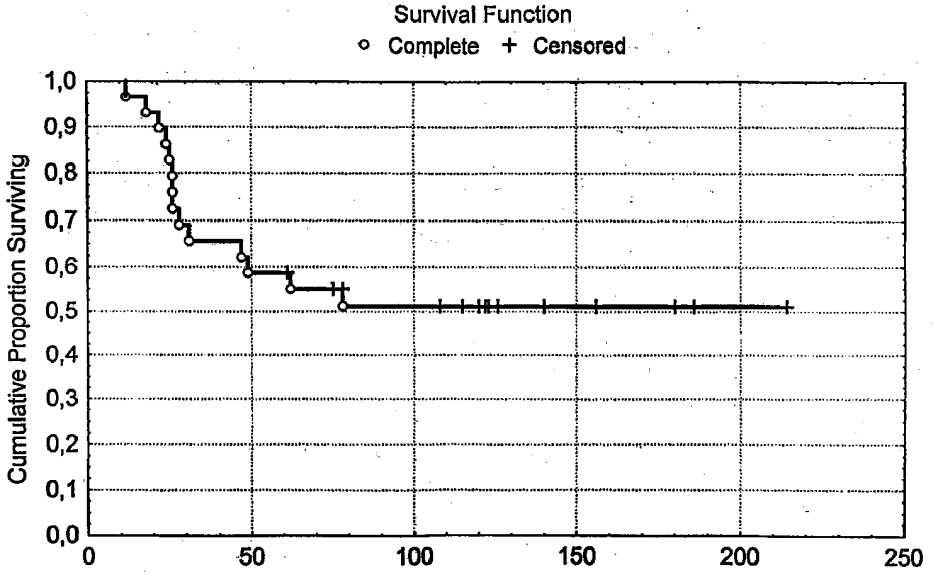

Fig. 1. The actuarial overall survival of 29 adult patients with intracranial ependymomas treated with postoperative irradiation.

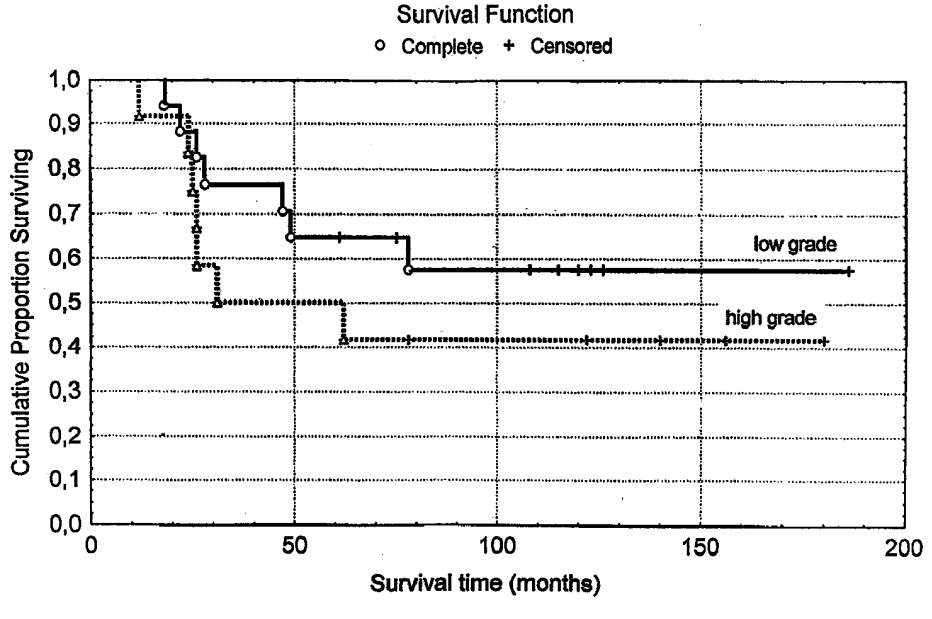

Fig. 2. The actuarial survival of 29 adult patients with intracranial ependymomas treated with postoperative irradiation according to the histological grade.

PATTERNS OF FAILURE

Twelve patients were considered appropriate for the analysis of patterns of failure (for two patients reliable information about the site of recurrence was lacking). Eleven tumours recurred at the primary site, one patient had metastasis to the spine (a high-grade infratentorial tumour treated with whole brain radiotherapy). Patterns of failure of 12 eligible patients are summarised in Table 3.

Table 3. Patterns of failure (12 eligible patients).

No	Grade	Tumour site	Radiation field	Dose (Gy)	Location of failure
1.	1	IF	Partial brain	50	Brain
2.	1	IF	Partial brain	55	Brain
3.	2	ST	Whole brain	50	Brain
4.	2	ST	Partial brain	56	Brain
5.	2	ST	Partial brain	60	Brain
6.	2	ST	Partial brain	60	Brain
7.	3	ST	Partial brain	56	Brain
8.	3	ST	Whole brain	45	Brain
9.	3	IF	Whole brain	45	Spine
10.	4	IF	Craniospinal axis	$35/50^{x}$	Brain
11.	4	IF	Craniospinal axis	$34/50^{x}$	Brain
12.	4	IF	Craniospinal axis	$30/50^{x}$	Brain

IF- infratentorial, ST- Supratentorial, ^{x} - dose at the craniospinal axis/dose at the involved site

DISCUSSION

Intracranial ependymomas of adult patients are relatively infrequent [8,9]. We report the long-term results of a cohort of 29 adult patients with these tumours. The survival rates at 5 and 10 years are shown in Table 4, in which results of other published series are also reported. The results referred to by Show et al. and more recently by Zorlu et al., seem to be very interesting reporting 10-year survival rates of 60% and 57% respectively [9,10]. In the series of 10 adult patients from the New York Medical Center, with a median follow-up of 64 months, seven patients were alive and free of disease, while two died of intercurrent disease without evidence of tumour at 7 and 9 years following treatment. The authors conclude that postoperative radiotherapy is effective in preventing regrowth of intracranial ependymoma following subtotal resection in adults. Treatment fields should cover the initial tumour bed with a 1-2 cm margin to avoid late radiation damage [8].

Table 4. Results of postoperative irradiation of intracranial ependymomas in adult patients.

Author	Number of patients	5-year survival	10-year survival
(West et al., 1985)	13	48%	42%
(Wallner et al., 1986)	12	58%	42%
(Shaw et al., 1987)	15	73%	60%
(Di Marco et al., 1988)	33	48%	38%
(Vanuytsel et al., 1991)	35	57%	48%
(Zorlu et al., 1994)	21	62%	57%
(McLaughlin et al., 1998)	18	51%	46%
Present series	29	59%	41%

It should be noted that in most series reported the principles of radiation treatments varied videly. It is mainly the whole brain irradiation, or partial brain irradiation that was employed, whereas craniospinal axis was used only in fewer cases. Today, the benefit of postoperative irradiation in intracranial ependymomas is well accepted, the main controversy centering on the field size in radiation therapy. For supratentorial low-grade tumours there is general agreement as to the local irradiation or whole brain treatment [11,12]. For infratentorial low-grade lesions a number of treatment policies have been proposed from local fields to craniospinal irradiation [13, 14].

For high-grade tumours craniospinal axis irradiation is considered by most authors as the treatment of choice [15]. The need for whole brain or spinal irradiation is strictly related to the probability of seeding of neoplastic cells, which is difficult to asses, and in this case frequencies range from nil to more than 60% [4, 13]. A review of the clinical literature on ependymoma, published between 1969 and 1989, was made to assess the effect of tumour grade and site, tumour control at the primary site, and extent of irradiation on the incidence of spinal seeding after initial treatment. The pooled data show that the incidence of seeding was 8.4% (7/83) for high grade tumours, and 4.5% (6/132) for low grade tumours. Seeding occurred more frequently in infratentorial tumours than in supratentorial tumours. For high grade tumours, the incidence was 0% (0/26) for supratentorial and 15.7%(6/38) for infratentorial lesions; while for low grade tumours the respective incidences were 2.7% (1/37) and 5.5%(4/73). Spinal seeding was 9.5%(15/157) in the event of failure at the primary site compared to 3.3%(4/122) when local control was achieved. The development of spinal metastases was not influenced by the extent of irradiation. For high grade tumours the incidence was 9.4%(5/53) with spinal irradiation, and 6.7%(2/30) without prophylactic treatment; for low grade tumours the respective values were 9.3%(4/43) and 2.2%(2/89) [16]. Because of rarity of ependymomas, there has been no prospective, randomised trial to test the benefits of extended versus local fields irradiation.

In our study, the dominant pattern of recurrence was the primary site (11/12=92%). This was also the case for patients reported by the Mayo Clinic, Princess Margareth Hospital, University of California, San Francisco and University of Florida College of Medicine [9, 17, 18, 19]. In our study of the recurrences, 83% of all cases occurred within the first three years after treatment initiation, as in that of other authors [4, 18, 19].

In our series, histological grade did not influence survival, none of the differences shown in Fig. 2. having reached statistical significance ($p>0.05$). These differences can be regarded as interesting trends, which may be verified on larger patient populations. The lack of histopathologic correlation to clinical outcome was also described by Ross and Rubinstein [20].

In conclusion, we have found that nearly all patients who die of ependymoma do so because of intracranial treatment failure at the site of the primary tumour. Our current recommendation is to treat all supratentorial and low-grade infratentorial tumours, as well as high-grade supratentorial lesions with partial brain fields. Even though data in the literature remains somewhat controversial, we continue to advocate craniospinal irradiation in patients with infratentorial anaplastic (grade 3,4) ependymoma.

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