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Treatment of ependymomas. Clinical and non-clinical factors influencing prognosis: a review

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Abstract
We review the epidemiological and clinical features of ependymomas as described in published series as well as the effect on outcome of various treatment strategies.

Key words: *brain tumours, ependymomas, prognosis.*

Introduction

Ependymomas are tumours which arise from the ependymal cells. These cells line the ventricles of the central nervous system, the central canal of the medulla, and the filum terminale. They were described for the first time by Virchow in 1863. Muthmann & Sauerbeck (1903) related ependymomas to the ependyma as the tissue of origin by demonstration of blepharoplasts in these tumours.[1] According to Sageman *et al.*[2] the first case of seeding of an ependymoma was reported by Spiller in 1907.

Initially, tumours of the ependymoma group included ependymomas, subependymomas and ependymoblastomas. Subependymomas are unusual tumours that were characterized as a distinct entity by Scheinker in 1945.[3] Subependymomas seldom give rise to symptoms during life, but are usually an incidental finding at autopsy. Bailey & Cushing set the ependymomas and the ependymoblastomas apart as two different groups. Nowadays, ependymoblastomas are considered as embryonal tumours.[4,5] However, some authors consider ependymoblastomas as a variant of the malignant ependymoma and include these tumours in their series of ependymomas.[6–9]

Ependymomas comprise 2–8% of all primary central nervous system tumours.[10–12] Ependymomas are considered to be relatively benign tumours that respond rather well to irradiation.[11,13–17] Conventional treatment of patients with a suspected ependymoma includes surgery to resect as much as possible and to obtain the histological diagnosis. After surgery some patients will receive radiotherapy. However, controversy prevails about the influence of clinical parameters and histological features on the survival of a patient with an ependymoma. The roles that total versus partial tumour resection, tumour localization, prophylactic neuraxis irradiation and the use of chemotherapy play in the prognosis of the individual patient are controversial. Other points of discussion are the histological grading of these tumours and the frequency with which metastases may arise.

In this report we review the available data concerning ependymomas and discuss the prevailing controversies.

Data acquisition and analysis

We analysed clinical and non-clinical factors on the basis of data retrieved from selected published series which were collected from the CD-ROM Medline 1970–1995. Data include epidemiological, clinical, biological and prognostic factors. Many publications report results on ill defined groups of patients. We decided to include only reports on well-defined groups of patients with central nervous system ependymomas, intracranial ependymomas and intraspinal ependymomas. Other data on subgroups, for instance children, will be discussed when appropriate. Data were obtained from tables, figures and text of the reviewed articles. Percentages given in

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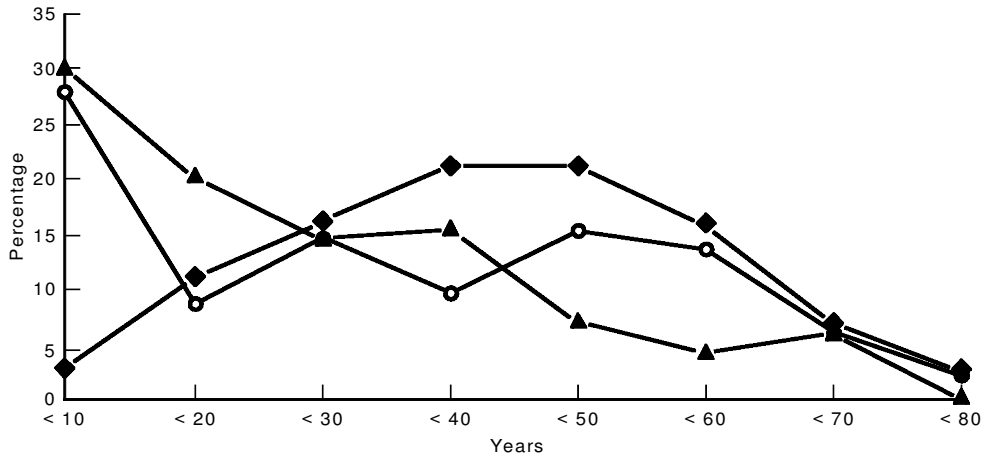

FIG. 1. Age-distribution of ependymomas. ○ series describing ependymomas of all sites: Mørk,[16] Schröder.[50] ▲ series describing Intracranial ependymomas :Ernestus,[46] Di Marco,[63] Wallner,[72] Chin.[9] ◆ series describing spinal ependymomas: Whitaker,[40] Di Marco,[38] McCormick,[39] Ferrante.[81]

the articles were recalculated and expressed in numbers in order to form a large database. However, owing to the retrospective and heterogeneous character of the reviewed published series and the lack of statistical data (in particular the standard error), no statistical analysis could be performed.

Epidemiology

Age

Presentation can take place at any age. Mørk[16] found in their series that there was a bipolar age distribution. The first peak was situated between 0 and 10 years, and the second peak between 40 and 50 years. Others found that the mean age varies between 22 years[10,18] and 25 years.[19] The prevailing opinion is that intracranial ependymomas mainly occur in young children and spinal ependymomas in older people.[9,20] Figure 1 shows the age-distribution as we found it by reviewing the literature.

Compared with adults, both better[11] and worse[12,18,19,21–24] prognoses for children have been reported in the literature. However, Shaw *et al.*[7] found that there was no difference in prognosis between these groups of patients. Amongst children, a worse prognosis has been reported for the very young (< 4 years).[12,16,25] One inference from these results could be that intracranial ependymomas and spinal ependymomas might be considered as two biologically different groups of tumours, each with their own aetiology, age distribution, prognostic factors and treatment.

Sex

The distribution of ependymomas in female and male patients varies between 40–57% and 43–60%, respectively (mean 48.1%, 51.9%). Data concerning the sex-distribution among patients with an ependymoma are presented in Table I. According to many authors the sex of the patient is probably not a significant prognostic factor.[7,26–28] However, several authors found in their series that, compared with male patients, the survival for female patients is worse.[20,25] This is in contrast to Vanuytsel[29] who found a 15-year survival of 19% for male ($n = 38$) patients and 40% ($n = 55$) for female patients with intracranial localization, disregarding the age at presentation.

Race

Goldwein *et al.*[30] found in their series that Caucasian children fared significantly better than non-Caucasian (5-year survival 43 and 14%, respectively). Although they agree that this finding is a sensitive matter, they suggest that this racial variation has not been studied by others and that this might explain some of the differences in outcome that have been reported in the literature.[30–32]

Clinical features

Localization

Ependymomas are found in the entire central nervous system. Generally, they are divided into intracranial and spinal ependymomas. The intracranially located ependymomas are subdivided into supratentorial and infratentorial ependymomas. Ependymomas arising from peripheral, cranial or spinal nerves have been described also.[33,34] Other ectopic ependymomas are found mostly in the sacrococcygeal region.[34,35]

Despite the fact that malignant ependymomas occur more frequently supratentorially[6,7,9,16,25,27,30,36,37] a better prognosis has been observed as compared with those located below the tentorium.[16,22] However, reverse statements regarding prognosis and tumour localization are also

TABLE I. Sex distribution of ependymomas

	n	Variation % female	Mean % female	Variation % male	Mean % male
A	758	40–57	48.1	43–60	51.9
B	286	37–59	50.6	41–63	49.4
C	240	37.5–52	43.3	48–62.5	56.7
D	312	18–65	41.4	35–82	58.6

Abbreviations

A. Data obtained from series describing central nervous system ependymomas of all sites including supra-, infratentorial and spinal ependymomas in both adults and children.[2,4,10,19,21,43,44,47,65]

B. Data obtained from series describing intracranial ependymomas, including supra- and infratentorial ependymomas in both adults and children.[7,9,15,23,27,29,63,72]

C. Data obtained from series describing intracranial ependymomas in children only, including supra- and infratentorial ependymomas.[25,26,28,30,36,73]

D. Data obtained from series describing spinal ependymomas in both adults and children.[38–40,41,43,67,74,79–82]

reported in the literature.[27,29,30,38] Data from the literature concerning tumour localization of ependyremomas are presented in Table II. We found that intracranial ependymomas in children are mostly situated infratentorially (Table II).

Neurology

At presentation, the clinical symptoms of a patient harbouring an ependymoma are non-specific. Symptoms can be, for instance, headache, vomiting and nausea, dizziness, weakness of an extremity and decreased vision. Neurological signs that may occur are papilloedema (mostly bilateral), nystagmus, ataxia, paresis, cranial nerve palsies and abnormal myotatic reflexes. Nazar[12] found in his series that children under the age of 2 years present with different symptoms from older children. Children < 2 years are only lethargic, while elder children may present with headache, or present with ataxia, sixth nerve palsy, nystagmus or brain-stem signs.

The correlation between symptoms, signs and survival is not clear. For instance, some authors state that the presence or duration of a symptom does not have any influence on the survival time.[10,16,23] However, several authors found that some neurological signs and symptoms do have a predictive value. Rawlings[22] concluded that symptoms associated with increased intracranial pressure significantly worsen the prognosis. McCormick[39] found that the pattern and progression of neurological deficits are related to the tumour localization in spinal cord ependymomas. Whitaker[40] found that postoperative progression of neurological signs and symptoms is a significant prognostic factor.

Epstein *et al.*[41] states that pre-operative neurological deterioration as a result of increased tumour volume in spinal ependymomas will complicate surgery and probably results in a less radical resection of the tumour. They also found that the first symptom in the great majority of spinal ependymoma was segmental dysaesthesias. They explain this sensory phenomenon by the fact that the tumour originates in the region of the central canal expanding symmetrically and circumferentially, thus compressing the crossing spinothalamic segmental fibres.

TABLE II. Localization of ependymomas

	Location	*n*	Variation %	Mean %
A	Supratent.	226	11–49	24.8
	Infratent.	360	17–69	39.4
	Spinal.	327	5–52	35.8
B	Supratent.	184	17–75	41.7
	Infratent.	223	25–83	58.3
C	Supratent.	104	21–47	32.1
	Infratent.	220	53–79	67.9

Abbreviations

A. Data obtained from series describing central nervous system ependymomas of all sites including supra-, infratentorial and spinal ependymomas in both adults and children.[2,9,10,16,18,19,22,43,44,47,50]

B. Data obtained from series describing intracranial ependymomas, including supra- and infratentorial ependymomas in both adults and children[7,9,11,15,20,23,27,29,46,63]

C. Data obtained from series describing intracranial ependymomas in children only, including supra- and infratentorial ependymomas.[25,28,30,36,68,69,73]

Biological features

Type and grade of the tumour

In the past, many grading systems have been published.[12,16,18,19,42] Nowadays, ependymomas should histopathologically be graded according to a two-tiered scheme, namely low- and high-graded ependymomas.[5] Moreover, ependymomas can also be classified as cellular, papillary, myxopapillary, clear cell and anaplastic (malignant) ependymoma.[5]

However, Schiffer *et al.*[43] conclude that the histological criteria employed to diagnose anaplasia in gliomas are not useful in recognizing anaplasia in ependymomas. The variation and the lack of uniformity in grading systems make it difficult to compare the results of published data.

Much controversy prevails about the significance of tumour grading for the survival of the patient. Several authors found in their series that the grade of the tumour had a significant prognostic value for the survival of the patient.[9,12,27,29,40,44–46] According to many other authors, there is a lack of correlation between malignancy grade of the tumour and postoperative survival.[6,10,16,18,23,47] In order to predict the clinical course of ependymomas, Reyes-Mugica *et al.*[48] analysed in children the DNA profile of ependymomas by DNA flow cytometry, and concluded that there is no correlation between histology, DNA index and outcome. Also in children Figarella-Branger *et al.*[26] found that infratentorial tumours expressing large amounts of GFAP statistically have a better prognosis and that increased vimentin expression combined with a decreased GFAP immunoreactivity is correlated with anaplasia and worse prognosis. They also identified, in agreement with other authors[12,49,50] three histological criteria which are indicative of bad prognosis, i.e. high mitotic index, a large amount of necrosis and severe loss of differentiation. However, Schiffer *et al.*[49] reported that some histological factors such as cell density and number of mitoses has a limited prognostic value not leading automatically to a shorter survival. Also other histological features suggestive for malignancy seem to be of limited value in predicting the biological and clinical course of ependymomas.[24] Maybe, the effects of different treatment strategies (i.e. surgery alone or with radiotherapy) give rise to these seemingly inconsistent findings.

Another way to indicate the malignancy of the tumour is the Ki-67 labelling index. Schröder *et al.*[50] found in their series that this parameter is related to the grade of malignancy. Schiffer *et al.*[51] found that the number of PCNA (proliferating cell nuclear antigen)-positive nuclei is correlated with cell density and mitotic index, but that only very intensely positive nuclei show a significant correlation with survival.

Summarizing, besides obvious variations in treatment protocols, the lack of consensus regarding classification systems, nomenclature and grading criteria explains the conflicting data concerning tumour grade and prognosis.

Genetic changes

Bijlsma *et al.*[52] concluded that genetic changes that commonly occur in other glial-cell derived tumours are uncommon in both benign and anaplastic ependymomas. Combining data from the literature with their own, they conclude that the only exception is an allelic loss of chromosome 22.[52] Cytogenetic evidence for a chromosome 22 tumour suppressor gene in ependymoma was found by Wereemowicz *et al.*[53] Nijssen *et al.*[54] reported a family with anaplastic ependymomas. They found evidence of loss of chromosome 22 in tumour cells, which was also found by Savard *et al.*,[55] Rogatto *et al.*,[56] and Ransom *et al.*[57] Slavc *et al.*[58] concluded that a locus distinct from the locus of the NF2-gene on chromosome 22 might be responsible for tumour genesis. Genetically, ependymomas may be considered as belonging to the group of low-grade gliomas.[52]

Metastasis

Although ependymomas may spread throughout the entire CNS, such behaviour generally has been reported only in conjunction with high grade tumours or with infratentorially situated ependymomas.[59] However, there is much variation over the incidence of metastasis between various authors. Out of 971 primary intracranial ependymomas reported in the literature (1949–1984), according to Ernestus and Wilcke the total rate of spinal metastases amounts to 11.1%.[60] Reviewing published series concerning ependymomas in the entire central nervous system we found a composite rate of metastasis of 6.5% (10/153). Among published series concerning intracranial ependymomas we found a composite rate of 9.7% (36/372) and in spinal ependymomas 3.7% (5/134). However, frequencies from nil[10] to over 60%[2] have been reported in other articles. Data from the literature concerning the seeding of ependymomas are presented in Table III. The frequency of clinical seeding differs from the frequency with which metastasis is found at autopsy.[44] The frequency of extraneural metastasis is estimated as 6.2%.[61,62]

Recurrence

Tumour recurrence is the predominant pattern of failure in ependymomas.[21–24,59,63,64] The time to recurrence and the total recurrence rate are the strongest indicators of malignancy of the tumour.[65] However, predicting the chance of recurrence of an extirpated ependymoma on the basis of a histopathological grading system is controversial, if not impossible.[23] However, Asai *et al.*[65] reporting that the bromodeoxyuridine labelling index (BudR LI) reflects the proliferative potential of individual ependymomas, states that this index can be used to predict recurrences. The recurrence rate of tumours with $LI > 1\%$ was significantly higher than in tumours with $LI < 1\%$. Ross *et al.*[66] found in their series of myxopapillary ependymomas that nucleolar organising region (NOR) staining could also be useful in determining the risk of recurrence. The BudR-labelling index and NOR-staining may be

TABLE III. Frequency of seeding in the central nervous system

	Author	Year	Period*	Ependymomas *n*	Spin. Metast. *n*	%
A	Garrett	1983	1958–1980	91	5	5.5
	Rawlings	1988	Not given	62	5	8.1
				153	10	6.5**
B	Di Marco	1988	1969–1983	33	4	12.1
	Kim	1977	1955–1972	32	7	21.9
	Ernestus	1989	1951–1985	126	4	3.2
	Salazar	1983	1959–1983	51	12	23.5
	Vanuytsel	1992	1952–1988	88	7	8.0
	Wallner	1986	1959–1981	20	1	5.0
	Ikezaki	1993	1963–1991	22	1	4.5
				372	36	9.7**
C	Goldwein < 21 years	1990	1970–1980	51	7	13.7
	Pierre-Kahn	1983	1969–1979	47	7	14.9
	Rousseau < 16 years	1994	1975–1989	80	13	16.3
				178	27	15.2**
D	Wen	1990	1960–1984	20	1	5.0
	Di Marco	1988	1967–1983	11	2	18.2
	McCormick	1990	1976–1988	23	1	4.3
	Shaw	1986	1963–1983	22	1	4.5
	Whitaker	1991	1950–1987	58	0	0.0
				134	5	3.7**

Abbreviations

A. Data obtained from series describing central nervous system ependymomas of all sites including supra-, infratentorial and spinal ependymomas in both adults and children.

B. Data obtained from series describing intracranial ependymomas, including supra- and infratentorial ependymomas in both adults and children.

C. Data obtained from series describing intracranial ependymomas in children only, including supra- and infratentorial ependymomas.

D. Data obtained from series describing spinal ependymomas in both adults and children.

*Period in which the data were collected.

**Composite percentages.

useful tools in deciding if a patient should receive adjuvant radiation or chemotherapy or if an expectant treatment is preferable. Data from literature concerning the frequency of recurrence are shown in Table IV. Combining Tables III and IV we could not demonstrate a correlation between the number of recurrences and the number of metastases due to the relatively small numbers of patients and incomplete data.

Therapeutic strategies

Surgery

The neurosurgeon strives for a gross total resection of the tumour. However, a complete resection of the tumour is often difficult to accomplish and may endanger the patient's life, especially if the tumour has infiltrated the surrounding brain tissue. After surgery the surgeon assesses the degree of extirpation. The degree of extirpation varies from a gross total resection, through subtotal removal, to just a (stereotactic) biopsy.

Often the description of the extent of extirpation is based on the surgeon's personal view, which is sometimes substantiated by postoperative neuro-imaging (CT, MRI). Healey *et al.*[23] reported, that in 32% of their cases the extent of surgical resection according to the neurosurgeon's operative note did not agree with the extent of surgery according to postoperative neuro-imaging. This may partly explain authors' variations in percentages of gross total and subtotal resections or biopsies. Furthermore, Wen *et al.*[67] differentiate for spinal ependymomas between '*en bloc*' and 'piecemeal' performing of the resection. This might influence the survival of patients with a total resection of a spinal ependymoma. Figures published in the literature regarding the extent of tumour resection are collected in Table V.

The true extent of resection, as confirmed with postoperative MRI, should be correlated with survival, to use it as a prognostic factor. Some authors report a better prognosis in a group of patients with a total resection of an intracranial ependymoma[7,12,20,24,27,29,68] or a spinal cord ependymoma.[16,22,39,40,45] Sutton *et al.*[69] even found that the extent of surgical resection is a major determinant of final outcome in ependymomas. They suggest that this could be explained by the fact that the feasibility of a total tumour resection is a reflection of the tumour's biology, which makes the tumour also less

TABLE IV. Frequency of recurrences* in the central nervous system

	Author	Public. Year	Period**	Ependymomas *n*	Recurrence *n*	%
A	Garrett	1983	1958–1980	91	36	39.6
	Rawlings	1988	not given	62	18	29.0
	Ross	1989	1967–1986	15	6	40.0
				168	60	35.7***
B	Di Marco	1988	1969–1983	33	17	51.5
	Ernestus	1989	1951–1985	77	35	45.5
	Salazar	1983	1959–1983	51	33	64.7
	Chin	1982	1962–1974	16	2	12.5
	Wallner	1986	1959–1981	19	7	36.8
	Shaw	1987	1963–1983	33	12	36.4
	Kovalic	1993	1950–1988	31	16	51.6
	Healey	1991	1970–1989	33	15	45.5
				293	137	46.8***
C	Goldwein < 21 years	1990	1970–1980	51	30	58.8
	Pierre-Kahn	1983	1969–1979	47	14	29.8
	Chiu < 15 years	1992	1955–1986	25	12	48.0
	Rousseau < 16 years	1994	1975–1989	80	34	42.5
				203	90	44.3***
D	Wen	1990	1960–1984	20	7	35.0
	Di Marco	1988	1967–1983	11	7	63.6
	McCormick	1990	1976–1988	23	1	4.3
	Shaw	1986	1963–1983	22	7	31.8
	Schweitzer	1992	1955–1992	15	2	13.3
	Waldron	1993	1958–1987	59	11	18.6
	Ferrante	1992	1951–1990	45	8	17.8
	Ross	1993	1975–1991	14	2	14.3
	Whitaker	1991	1950–1987	58	13	22.4
				267	58	21.7***

Abbreviations

A. Data obtained from series describing central nervous system ependymomas of all sites including supra-, infratentorial and spinal ependymomas in both adults and children.

B. Data obtained from series describing intracranial ependymomas, including supra- and infratentorial ependymomas in both adults and children.

C. Data obtained from series describing intracranial ependymomas in children only, including supra- and infratentorial ependymomas.

D. Data obtained from series describing spinal ependymomas in both adults and children.

*Recurrence is defined as first relapse of the tumour after primary treatment time to recurrence is not given.

**Period in which data were collected.

***Composite percentages.

likely to recur. Epstein *et al.*[41] noted that in spinal ependymoma treatment surgery is more hazardous and will be less radical if the tumour, as a result of its increased volume, has involved the surrounding neural tissue. Ikezaki *et al.*[70] described a correlation between micro-anatomical localization of posterior fossa ependymomas and the feasibility of tumour extirpation. This can be an important prognostic factor and may partly explain the differences in degree of tumour extirpation which we found in the literature (Table V). By contrast, some authors do not find any significant difference in prognosis between patients with a total or subtotal resection.[11,16,64]

Radiotherapy

Although radiotherapy is generally accepted as part of the treatment for ependymomas, the results of surgical treatment alone versus surgery plus radiotherapy have been little published. Only Salazar *et al.*[11] discussed a partly prospective investigation on the results of treating 51 patients with an ependymoma, based on their own suggested guidelines.[11,44] They concluded that their recommendations have improved the survival of these patients.

General goals of radiotherapy are to prevent subarachnoid seeding by eradicating tumour cells within the CSF and to prevent recurrence of the tumour by eradicating the postoperative tumour rest and possible metastases. Radiotherapeutic strategies are based on the age of the patient at diagnosis, the localization and histopathological grade of the tumour and the status of the subarachnoid space together with the CSF. The best response of ependymomas to radiotherapy is achieved in young

TABLE V. Extent of tumour resection

	n	Resect.	Variation %	Mean %*
A	97	Total	6–73	23.4
	306	Partial	27–87	73.9
	11	Biopsy	1–6	2.7
B	98	Total	12–45	31.3
	207	Partial	54–84	66.1
	8	Biopsy	0–6	2.6
C	54	Total	20–47.5	27.9
	130	Partial	47.5–77	67.4
D	182	Total	18–100	51.9
	143	Partial	0–73	40.9
	27	Biopsy	0–19	7.7

Abbreviations

A. Data obtained from series describing central nervous system ependymomas of all sites including supra-, infratentorial and spinal ependymomas in both adults and children.[16,20–22,44,47,65]

B. Data obtained from series describing intracranial ependymomas, including supra- and infratentorial ependymomas in both adults and children.[7,23,27,29,46,59,63]

C. Data obtained from series describing intracranial ependymomas in children only, including supra- and infratentorial ependymomas.[9,26,28,36,68,69,73]

D. Data obtained from series describing spinal ependymomas in both adults and children.[38–41,43,64,66,67,74,81–82]

children[6] and low-grade tumours seem to be the most radiosensitive.[9,71] Various radiation treatment guidelines and recommendations have been put forward (Table VI).

The two most important factors in radiotherapy treatment are the total fractionated dose on the primary tumour site and the extent of treatment fields, eventually including the spinal axis. The total irradiation dose on the tumour is determined by the age of a young patient, the localization, grade and extent of the tumour.[44] Most investigators feel that irradiation of the primary site with at least 45 Gy improves survival.[6,7,11,16,20,21,24,28,36,44,46,59,60,63,72–74] Although the most common cause of failure is recurrence at the primary locus, increasing the total tumour dose is prohibited by an unacceptable increase in longterm complications.[71,75] Moreover, Wallner *et al.* concluded that a dose-response effect above 45 Gy has not been shown.[72]

Extending irradiation fields beyond the primary locus is probably the most discussed theme in ependymoma treatment. According to many authors the extension of fields should be dependent on tumour site and grade.[44]

In the past many different treatments have been used. Intracranial and spinal low and high grade ependymomas have been treated with local, whole brain and craniospinal irradiation (Table VI).

Nowadays, for supratentorially situated low-grade tumours most authors agree on confined fields or whole brain irradiation. For infratentorially-situated low grade ependymomas a number of treatment policies have been advocated. They include craniospinal irradiation, irradiation of the whole brain with cervical field extension and local high dose irradiation with local fields. For spinal low grade ependymomas most authors agree that in case of a total resection no further treatment is required, whereas in case of a subtotal resection or a biopsy, local or total spine irradiation should be given. However, both series concerning spinal ependymomas in which all patients received radiotherapy and series in which none of the patients received radiotherapy have been published (Table VII).

Both for supratentorially- and infratentorially-situated high grade ependymomas, with a few exceptions, all authors agree on craniospinal irradiation with a boost on the primary tumour as treatment of choice. For high grade spinal ependymomas most authors agree on craniospinal irradiation, but no irradiation, local and total spine irradiation have also been suggested. Various treatment recommendations are collected in Table VI. Unfortunately, the publications selected for this review allow no conclusions as to the final therapeutic benefits for the various irradiation strategies. Differences in reported frequencies of metastasis and discrepancies in metastases found at autopsy and those that are clinically detectable, make it impossible to determine the possible effect of radiotherapy and the best volume to be irradiated. As to metastatic spreading, Vanuytsel[29] considered that

TABLE VI. Irradiation treatment recommendations in ependymoma

Localization tumour	Extent of field	
Low-grade ependymomas		
Supratentorial	Local	27,28*,29,30*,36*,83
	WB	11
	CSI	—
Infratentorial	Local	7,27,28*,29,30*,36*†,72,83
	WB	11
	CSI	15,21
Spinal	No Irr	39§,40§,66§,67§,79§
	Local	15,38,41
	WB	—
	CSI	—
High-grade ependymomas		
Supratentorial	Local	27,28*
	WB	29‡,30*‡,36*†,73‡
	CSI	11,15,44,72
Infratentorial	Local	28*,36*†
	WB	29,83
	CSI	7,11,15,30*,44,73*
Spinal	Local	15,21,66,67,41
	WS	—
	CSI	38,74,79

Abbreviations

WB, whole brain irradiation; WS, whole spine irradiation; CSI, craniospinal irradiation.

*Recommendations for intracranial ependymomas in children.

†Local plus whole spine irradiation.

‡In case of positive seeding; CSI.

§In case of a subtotal resection of the tumour, local irradiation is recommended.

TABLE VII. Radiotherapy in intracranial and spinal ependymomas

Author	Year	Number *n*	No radioth. *n*	Local radioth. *n*	Whole brain radioth. *n*	Craniospinal radioth. *n*
Intracranial						
Salazar	1975	28	1	0	17	10
Garrett	1983	50	0	12	0	38
Wallner	1986	19/7*/12†	0	16/5*/11†	3/2*/1†	0
Shaw	1987	33	0	0	16	17
Di Marco	1988	33/13*/20†	0	19/9*/10†	7/4*/3†	7/–*/7†
Vanuytsel	1992	88	0	25‡	3	60
Kovalic	1993	31	1	17	5	8
Pierre-Kahn§	1983	47	12	11	17	7
Goldwein§	1991	17	1	5	0	11
Chiu§	1992	25	6	0	12	7
Rousseau§	1994	80	15	28	12	25
	Total	451	36	133	92	190
%			8%	30%	20%	42%
Spinal						
Shaw	1986	22	0	17	5	0
Di Marco	1988	11	4	6	1	0
McCormick	1990	23	23	0	0	0
Whitaker	1991	58	15	0	25	18
Wen	1991	20	7	0	13	0
Schweitzer	1992	13	5	0	8	0
Epstein	1993	38	38	0	0	0
Waldron	1993	59	0	41	0	18
	Total	244	92	64	52	36
%			38%	26%	21%	15%

Abbreviations
‡Five patients received local irradiation and spinal irradiation.
§Radiotherapy for intracranial ependymomas in children.
*Supratentorial ependymomas.
†Infratentorial ependymomas.

prophylactic spinal irradiation did not influence the incidence of spinal seeding and Rousseau *et al.*[28] concluded that improvement of the treatment ratio will be achieved by increasing the local tumour dose of irradiation and not by trying to prevent meningeal relapses with craniospinal radiotherapy.

Brachytherapy

Voges *et al.*[76] discussed the role that brachytherapy may play in treatment of ependymomas. They suggested that this therapy can be useful in relatively large low-grade supratentorial ependymomas which allow partial tumour resection only, but are clearly outlined on scanning images.

Chemotherapy

Chemotherapy may be used in two situations in ependymoma treatment. First, chemotherapy can be used adjunctive to surgery and radiotherapy. This combination is mainly used as a last resort therapy with tumour recurrence.[17] Trials of chemotherapy during or after postoperative radiotherapy and surgery with carmustin, adriamycin, methotrexate, lomustin, vincristine, procarbazine, cisplatin, ACNU, β-interferon, VCR and carbo-platinum have been of little efficacy.[8,9,29,30,45,69] Secondly, chemotherapy with cyclophosphamid, vincristin, cisplatin and etoposide appears to be an effective primary postoperative treatment in the very young children with an ependymoma who otherwise would need craniospinal irradiation, as adjuvant treatment in order to delay the irradiation.[77,78] The reason is that irradiation of the developing young brain in the long term affects the intellect, the endocrine and the psychosocial functions.[71,75] Therefore, irradiation generally is not given to patients under the age of 2 years.

A wide variety of agents have been used in an attempt to control the tumour including also MCNU, nitrogen-mustard, dianhydrogalactitol, carmustin, triazinate.[8,9,12,17,23–25,28–30,36,40,45,69,77,78] However, information regarding the effect of chemotherapy has often been casual owing to the small numbers of patients.

TABLE VIII. Overall survival in ependymoma, with subgroups and composite figures and percentages

		Total number of patients	Number of patients who survived 5 years	5 years survival	Total number of patients	Number of patients who survived 10 years	10-years survival
A	Intracranial ependymomas in adults + children from series which describe ependymomas of all sites[10,16,20–23,44,65]	230	90	39%	119	25	21%
B	Supratentorial ependymomas in adults + children from series which describe intracranial ependymomas[29,63,15,27*]	89	40	45%	78	30	38%
	Infratentorial ependymomas in adults + children from series which describe intracranial ependymomas	151	77	51%	130	59	45%
	Composite figures & percentages	470	207	44%	327	114	35%
C	Supratentorial ependymomas in children from series which describe intracranial ependymomas in childhood[25,28,30]	44	20	45%	not given	not given	not given
	Infratentorial ependymomas in children from series which describe intracranial ependymomas in childhood[25,28,29]	112	59	53%	not given	not given	not given
	Composite figures & percentages	156	79	51%	not given	not given	not given
D	Spinal ependymomas in adults + children from series which describe ependymomas of all sites[10,16,20–22,44,65]	170	136	80%	91	60	66%
E	Spinal ependymomas in adults + children from series which describe spinal ependymomas[38,67,74,79,81**,40,64]	204	167	82%	249**	190**	76%
	Composite figures & percentages	374	303	81%	340	250	74%
F	Low-grade ependymomas in adults + children from series which describe intracranial ependymomas[15,16,24,27*,29,46,63,7]	273	148	54%	166	74	45%
G	Low-grade ependymomas in children from series which describe intracranial ependymomas[25,28,69*]	141	77	55%	34	7	21%
	Composite figures & percentages	414	225	54%	200	81	41%
H	High-grade ependymomas in adults + children from series which describe intracranial ependymomas[15,16,24,27,46,63,7]	227	69	30%	154	29	19%
I	High-grade ependymomas in children from series which describe intracranial ependymomas[25,28,69*]	73	29	40%	10	3	30%
	Composite figures & percentages	300	98	33%	164	32	20%
J	Gross total resection of ependymomas in adults + children from series which describe intracranial ependymomas[24,29]	21	15	71%	21	13	62%
K	Gross total resection of ependymomas in children from series which describe intracranial ependymomas[25,28,69*]	53	40	75%	91	31	34%
	Composite figures & percentages	74	55	74%	112	44	39%
L	Partial resection of ependymomas in adults + children from series which describe intracranial ependymomas[24,29]	66	30	45%	66	24	36%
M	Partial resection of ependymomas in children from series which describe intracranial ependymomas[25,28,69]	10	8	80%	34	3	9%
	Composite figures & percentages	76	28	50%	100	27	27%

Abbreviations

* Only the progression free survival is given.

**One article (75) documented only results of 10-year survival.

TABLE IX. Proposal staging profile

Anamnesis	Birth-trauma, severe head injury, familial brain tumours
Age	At diagnosis
Sex	F:M
Race	Caucasian:non-Caucasian
Neurological status	Preoperatively
	Duration of symptoms and signs
Localization tumour	CT pre- and postoperatively (interval)
	MRI total neuraxis (interval)
	Myelography (interval)
Prim. surgery	Diameter
	Invasiveness of tumour
	Extent of extirpation: biopsy, partial or gross total extirpation
	Cytology CSF (interval)
Neurological status	Postoperative (interval)
Pathology	Grading according to WHO
	GFAP, vimentin expression, Ki-67 LI, BudR-LI,
(Genetic analysis)	
Chemotherapy	Doses and scheme of medication
Radiotherapy	Doses: frequency, fraction and total doses (period)
	Extent of fields
Metastasis	CSF cytology
	MRI total neuraxis
	Myelography
	Extraneural sites
Recurrence	Time to recurrence
	Restart procedure at anamnesis
Death	

Survival

The survival of patients with an ependymoma depends among other factors on the localization of the tumour.[80] The average survival of patients who received radiotherapy supplementary to surgery and of patients who had surgery alone shows a difference in favour to radiotherapy.[10,16,18] Data from the literature concerning the overall survival of a patient with an ependymoma are shown in Table VIII. Concerning survival between intracranial and spinal ependymomas, and survival between low and high grade ependymomas, a trend in favour of the spinal (group D and E) and low-grade (group F and G) ependymomas can be recognized (Table VIII). Figures on survival in groups J,K,L and M on gross total removal versus partial resection have no significance owing to small numbers.

Conclusions

It is obvious from these data concerning ependymomas, that there is no clear understanding of the epidemiology, biology and treatment of choice in these tumours. Many authors have stressed the importance of prospective studies with protocol-based treatment strategies. Major drawbacks are the relatively small number of patients with ependymoma in each centre and the obvious lack of consensus among neurosurgeons, neuro-oncologists and neuropathologists.

We feel that it is justified to consider ependymomas of the spinal cord as a separate entity and we consider this as the only solid conclusion after our analysis of the available data for both intracranial and spinal tumours. On account of the heterogeneous data available in the reviewed literature neither positive nor negative judgement on the influence of localization and grade of the tumour, surgery, radiation and chemotherapy is possible at the moment.

Appropriate analysis of the results with the various therapeutic options can only be obtained by reliable data and on the basis of these data we strongly advocate a cooperative study of the effectiveness of treatments used. To allow reliable collection of data in the future, we wish to propose the multicentre use of a standardized format (standardized formats can be obtained by centres who wish to join this study at the authors' address) to stage and follow all patients with an ependymoma (Table IX). The collected data should provide insight into the biological and clinical course of ependymomas. Hopefully, this insight will lead to more effective treatment.

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