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Intracranial ependymoma in adult patients: results of postoperative radiotherapy

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Aim. to evaluate the results of postoperative radiotherapy in patients with intracranial ependymoma.
Material and methods. Twenty-four adult patients with intracranial ependymoma were treated between 1985 and 1998 with postoperative radiotherapy. Eighteen received craniospinal irradiation (median dose 30 Gy). The median dose given to the primary site was 57.6 Gy. The tumours were supratentorial in 13 (54%) and infratentorial in 11 (46%) patients. There were 6 anaplastic and 18 low-grade ependymomas. No patient received chemotherapy as the primary treatment. Pattern of failure, overall survival (OS), disease free survival (DFS) and survival after recurrence (SAR) were analysed. Age, tumour location, histology, extent of resection, performance and neurologic status were included in a univariate analysis in order to assess possible factors influencing overall survival.
Results. Median follow up for alive patients was 93 months. Actuarial 3-, 5- and 10-year OS rates were 67%, 56% and 41%, respectively. Actuarial 3-, 5- and 10-year DFS rates were 62%, 48% and 48%, respectively. In the univariate analysis age was the strongest prognostic factor. Five-year OS for patients younger than 35 years was 92%, whilst for older ones it was 18%, p=0.0003. Better OS was observed in patients with intraventricular rather than extraventricular tumours (77% vs. 0%, p=0.01). The tendency towards improved OS was observed for infratentorial tumour location. Patients with infratentorial tumours survived 5 years in 72%, whilst those with supratentorial tumors only in 42%, p=0.17. Five-year survival for patients undergoing complete vs. incomplete resection was 0% vs. 74%, p=0.03. Histology, performance and neurologic status had no significant influence on OS.
Tumour recurrence was observed in 12 (50%) patients. All recurrences were local. Two patients had simultaneous local and distant failure. Mean SAR was 26 months. SAR was longer for patients with failure occurring later (>1 year vs.≤1 year) after initial treatment (33 vs. 13 months).
Conclusions. Local recurrence is the most frequent site of failure in patients with intracranial ependymoma. Patient age is a strong prognostic factor. Extraventricular location of ependymoma in adults worsens survival. Patients with anaplastic ependymoma and those with incompletely resected tumours have a relatively good prognosis after irradiation, an important part of treatment.

Wyściółczak wewnątrzczaszkowy u dorosłych: wyniki pooperacyjnego napromieniania

Cel pracy. Ocena wyników pooperacyjnej radioterapii 24 dorosłych chorych na wewnątrzczaszkowego wyściółczaka.
Materiał i metoda. Poddano analizie 24 chorych na wewnątrzczaszkowego wyściółczaka, leczonych pooperacyjnym napromienianiem w II Zakładzie Teleradioterapii Centrum Onkologii im. M. Skłodowskiej-Curie, w latach 1985-1998. Osiemnastu chorych napromieniono na oś mózgowo-rdzeniową (mediana dawki 30 Gy). Mediana dawki na guz lub ložę wyniosła 57,6 Gy. Trzynaście (54%) guzów położonych było nadnamiotowo, 11 (46%) podnamiotowo. Leczono 6 anaplastycznych oraz 18 łagodnych wyściółczaków. Chorym nie podawano chemioterapii jako pierwotnego leczenia. Przeprowadzono analizę niepowodzeń leczenia, przeżycia ogólnego, przeżycia bez nawrotu choroby i przeżycia po wznowie (PPW). Oceny czynników rokowniczych dokonano w analizie jednowymiarowej, włączając wiek, lokalizację guza, stopień złośliwości nowotworu (anaplastyczne vs. łagodne), zakres resekcji, stan ogólny i neurologiczny.
Wyniki. Prawdopodobieństwo 3-, 5- i 10-letniego przeżycia ogólnego wyniosło odpowiednio 67%, 56% i 41%. Prawdopodobieństwo 3-, 5- i 10-letniego przeżycia bez nawrotu choroby wyniosło odpowiednio 62%, 48% i 48%. Wiek okazał się najsilniejszym czynnikiem prognostycznym w analizie jednowymiarowej. Pięcioletnie przeżycie ogólne dla chorych w wieku poniżej 35 lat wynosiło 92%, a dla starszych 18%, p=0,0003. Położenie guza zewnątrzkomorowe w stosunku do wewnątrzko-

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morowego skracało przeżycie, 0% vs. 77%, p=0,01. Obserwowano tendencję do dłuższego przeżycia chorych z lokalizacją guza podnamiotową. Pięcioletnie przeżycie pacjentów, którzy przebyli makroskopowo radykalny zabieg vs. nieradykalny wyniosło 0% vs. 74%, p=0,03. Stan ogólny i neurologiczny chorych nie miał wpływu na przeżycie.
U 12 (50%) chorych stwierdzono wznowę. Wszystkie niepowodzenia wystąpiły w pierwotnej lokalizacji guza, w 2 przypadkach towarzyszyły im przerzuty. Średnie PPW wyniosło 26 miesięcy. Średnie PPW u chorych, u których niepowodzenie wystąpiło po ponad roku od czasu leczenia, wyniosło 33 miesiące. U chorych z niepowodzeniem leczenia, występującym w ciągu roku po radioterapii, średnie PPW wyniosło 13 miesięcy.
Wnioski. Wznowa miejscowa jest najczęstszą przyczyną niepowodzeń u chorych na wyściółczaka. Wiek jest silnym czynnikiem prognostycznym. Lokalizacja zewnątrzkomorowa wyściółczaka u dorosłych wiąże się z gorszym rokowaniem. Chorzy na anaplastyczną postać wyściółczaka oraz zoperowani nieradykalnie mają relatywnie dobre rokowanie po zastosowaniu pooperacyjnego napromieniania.

Key words: intracranial ependymoma, radiotherapy
Słowa kluczowe: wyściółczak wewnątrzczaszkowy, radioterapia

Introduction

Intracranial ependymomas arise from the ependymal cells of the cerebral ventricles or from the extraventricular parenchyma. They are rare tumours, representing some 5--8% of intracranial gliomas [1]. Due to the location and invasive nature of ependymomas complete surgical removal is often impossible and postoperative irradiation is a standard treatment. Controversies remain concerning the exact target volume and the optimal extent of radiation fields.

Material and methods

Between 1985 and 1998 24 adult patients with a histological diagnosis of intracranial ependymoma received postoperative radiotherapy at Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw. The group consisted of 9 women and 15 men aged between 16 and 62 years (median age: 33 years). The tumours were supratentorial in 13 (54%) (including 7 extraventricular tumours) and infratentorial in 11 (46%) patients. In 2 cases the cerebral truncus was involved.

The patients underwent biopsy in 2, partial resection in 7, subtotal in 10 and total removal in 5 cases. There were 6 high--grade (anaplastic ependymoma) and 18 low-grade (including 2 subependymomas) tumours. Performance status according to the Zubrod score was estimated as follows: 0-2 pts, 1-12 pts, 2-7 pts, 3-2 pts, 4-1 pts. Neurological status according to EORTC\MRC Neurologic Deficits Score (Table I) [2] was 1 in 12 pts (50%), 2 in 8 pts, 3 in 3 pts and 4 in one case. Seven patients had a ventricular shunt placed during the surgical intervention. None had metastatic disease at the initial diagnosis and none received neoadjuvant chemotherapy.

The mean time lapse between surgery and radiotherapy was 46 days, range: 21-103 days.

Radiotherapy was performed using a Co60 unit or 4--15 MV linear accelerators. Craniospinal-axis irradiation was performed in patients with infratentorial tumours regardless of grade and in high-grade tumours regardless of location. The brain was treated with two opposed fields. The spine fields were irradiated with two direct posterior beams (electrons, photons) with appropriate shifting gaps. Partial brain fields were planned by estimating the tumour volume from radiographic studies made before surgery. Two or three wedged fields technique was applied. 3D treatment planning system was used in 4 cases irradiated after 1996.

Cranio-spinal irradiation was performed in 18 cases. Median dose given to the spinal cord was 30 Gy, ranged from 24 to 36.4 Gy (24 Gy was given to one patient with metastasis in mediastinum diagnosed during radical irradiation).

Median radiotherapy dose to the primary site was 57.6 Gy (mean 55 Gy, range: 46-60 Gy) in conventional fractionation. Mean radiotherapy duration was 65 days (range: 39-96 days).

Steroids were given to 8 patients in order to control cerebral oedema.

The length of overall survival was measured from the first day of irradiation. Actuarial overall and disease free survival were calculated using the Kaplan-Meier method. The following factors were analysed as predictors for overall survival: age (<35 years vs. ≥35 years), location (supratentorial vs. infratentorial and intraventricular vs. extraventricular), histology (low vs. high grade), performance status (Zubrod score 0-1 vs. 2-4), neurological status (no neurological deficits vs. any present neurological deficits) and extent of resection (total vs. subtotal, partial resection or biopsy and total-subtotal vs. partial-biopsy). Statistical analysis was performed using the log-rank test. Multivariate analysis was not performed because of the number of patients was too small.

Table I. EORTC\MRC Neurologic Deficits Score [2]

1. Absence of any neurologic deficits detectable
2. Minor neurologic deficits; without any impairment of normal activity
3. Neurologic deficits leading to some impairment of normal activity (paresis, minor mental changes)
4. Serious neurologic deficits leading to disability to care for himself: paralysis, aphasia, serious mental (emotional and\or cognitive) changes
5. Any communication with patient impossible

Results

Mean follow-up was 71 months (range: 8-209 months). Median follow up for alive patients was 93 months (range: 32-209 months).

The actuarial overall survival (OS) rates at 3, 5 and 10 years were 67%, 56% and 41%, respectively (Figure 1).

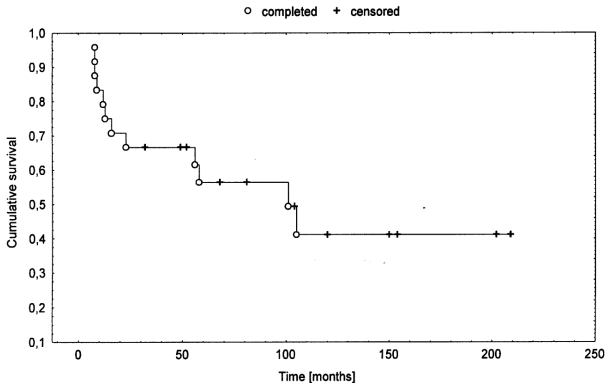

Figure 1. Overall survival of patients with ependymoma

The disease free survival (DFS) rates at 3, 5 and 10 years were 62%, 48% and 48%, respectively (Figure 2).

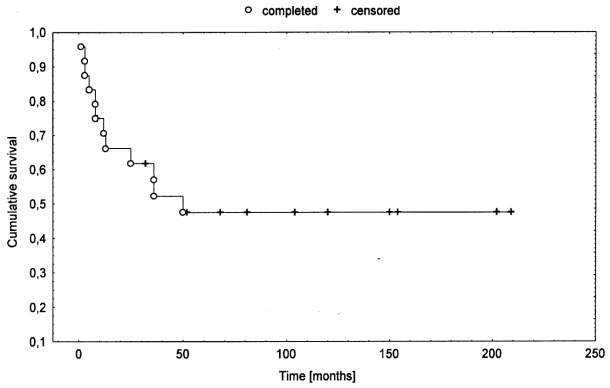

Figure 2. Disease-free survival of patients with ependymoma

Results of univariate analysis concerning the influence of prognostic factors at OS are presented in Table II.

Five-year OS for patients younger then 35 years was 92% whilst for older it reached 18% (Figure 3).

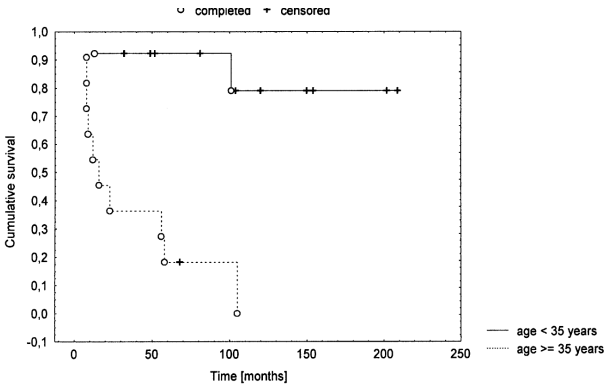

Figure 3. Overall survival according to patient age

OS at 5-years for patients with supratentorial (13 pts) and infratentorial (11 pts) tumours was 42% and 72%, respectively, however the difference was not significant (p=0.17).

Table II. Results of univariate analysis in patients with intracranial ependymoma

Factors	Number of patients	5-years OS	p-value
Age:			0.0003
≥35 year	13	92%	
(35 year	11	18%	
Location:			0.17
supratentorial tumours	13	42%	
infratentorial tumours	11	72%	
Location:			0.01
intraventricular tumours	17	77%	
extraventricular tumours	7	0%	
Histopathology:			0.41
benign ependymoma	18	58%	
anaplastic ependymoma	6	50%	
Performance status:			0.47
Zubrod 0-1	14	51%	
Zubrod 2-4	10	60%	
Neurological status:			0.26
EORTC\MRC 1	12	63%	
EORTC\MRC 2-4	12	50%	
Extent of resection:			0.03
total	5	0%	
subtotal/partial/biopsy	19	74%	
Extent of resection:			0.09
total/subtotal	15	45%	
partial/biopsy	9	78%	

Five-year OS of patients with intraventricular (17 pts) and extraventricular (7 pts) tumours was 77% and 0%, respectively (p=0.01) (Figure 4).

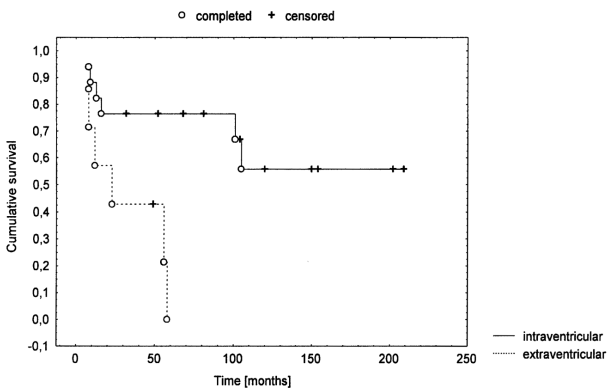

Figure 4. Overall survival according to location in relation to the ventricular system

Five-year OS of patients with benign (18 pts) and malignant (6 pts) ependymoma was 58% and 50%, respectively (p=0.41) (Figure 5).

There was no difference in survival between patients with good (0-1) and poor (2-4) performance status (51% vs. 60%), and with presence or not of neurological deficits (63% vs. 50%).

A marked difference in 5 year OS was noted between patients undergoing complete vs. incomplete resection (0% vs. 74%, p=0.03) (Figure 6), and those undergo-

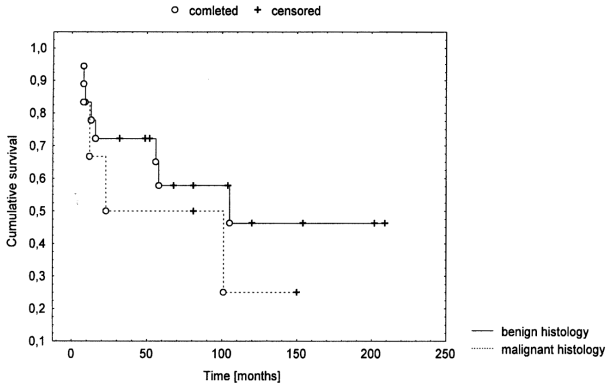

Figure 5. Overall survival according to tumour histology

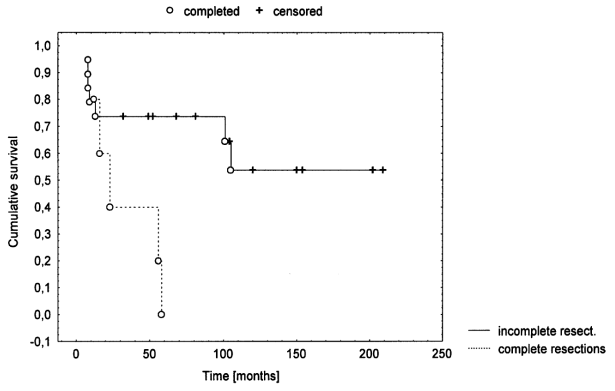

Figure 6. Overall survival according to the extent of resection

ing total-subtotal vs. partial resection or biopsy (45% vs. 78%, p=0.09). There were no significant early or late side effects of radiotherapy. Transient mild leukopenia (2 pts.), headache (8 pts) caused by cerebral oedema and epilatio were observed.

At the time of this analysis 12 of the 24 patients were known to be dead. One patient died of urinary bladder cancer progression without ependymoma recurrence. Eleven patients died of ependymoma recurrence, one is alive 24 months after surgery for failure. All recurrences were local. Two patients had simultaneous local and distant failure. The first one, a 37-year old patient, had local progression and metastasis in mediastinum diagnosed during the CNS irradiation. The second, with anaplastic ependymoma, developed local and spinal cord failure 50 months after craniospinal-axis irradiation. One patient with recurrence was treated with chemotherapy, 3 with surgery, 1 with radiotherapy and 1 using these all 3 methods. Recurrences occurred from 1 to 50 months of follow-up (mean 16,5 months). Survival after recurrence (SAR) ranged from 3 to 69 months (mean 26 months). Two-year SAR was 33%. Mean SAR for patients with DFS below 1 year was 13 months, whilst mean SAR for those with later failures (DFS ≥1 year) was 33 months.

Discussion

Overall survival and disease free survival in our group of patients are similar to those reported in literature, 5-years OS and DFS being 43-57% and 38-41%, respectively [1, 3-5, 14].

Similar to the reports on other brain tumours in adults, age is the most powerful prognostic factor in our material. Other authors state that age is a prognostic factor in ependymomas, but rather for children. Patients younger than 4 years at diagnosis fare worse than older ones [6]. Patients over 18 years have better OS, than 18 year-olds and younger [1].

Patients with infratentorial tumours had higher survival rates (72%) than those with supratentorial tumours (42%). Survival differences are in accordance to tumour site, as was also reported in the literature. Actuarial five-year survival was 30-35% for supratentorial, 57-59% for infratentorial, 57-100% for spinal cord and 83% for cauda equina tumours [8, 7].

Supratentorial ependymomas are extraventricular or have intraventricular extension. In our material 5-year OS of extraventricular tumours was significantly worse than intraventricular (0% vs. 77%). Six of seven patients with extraventricular ependymoma were older than 35 years. Maybe older age, a poor prognostic factor in the adult group, has influenced overall survival of the patients with extraventricular tumours. The differences in survival according to the tumour site in the brain are explained by some authors by differences in the ability to resect tumours from various sites. The review of pathologic aspects of ependymomas by Fokes and Earle [9] has shown that most supratentorial tumours exhibit infiltrative growth into the brain parenchyma, as compared to infratentorial tumours, which grow exophytically. This makes surgical resection of infratentorial tumours easier than in the case of supratentorial tumours. Also, supratentorial tumours are rarely encapsulated, whereas infratentorial tumours are usually entirely encapsulated [10], thus further increasing the possibility of their resection. However, this cannot be the explanation of the findings of present study. Another possible explanation is that supratentorial ependymomas are typically larger and that neurological problems occur later, thus causing worse survival.

The role of extent of surgery remains controversial. Some authors have suggested that the extent of resection is an important prognostic factor [11-13]. Others have found no attributable effect of the extent of surgery on survival [4, 7]. In our material patients with completely resected tumours had surprisingly worse OS, which indicates the importance of postoperative radiation therapy.

There is no significant correlation between benign and malignant ependymomas and the length of OS. It may be caused by the small number of patients, but also shows the efficacy of radiotherpy for malignant ependymomas. This trend was also observed by other authors [14, 15].

In our study, the dominant pattern of recurrence was the primary site (100% with 2 cases of simultaneous distant and local failure). We used to treat supratentorial low-grade tumours with local fields, according to recommendations from published data [16]. Infratentorial and

all high-grade tumours have been treated by craniospinal-axis irradiation. The pattern of failure and a review of the literature have indicated that prophylactic craniospinal-axis irradiation can be recommended only in patients with the highest risk of spinal seeding, i.e. in high-grade infratentorial tumours [1, 5, 16], even though some authors consider craniospinal-axis fields radiotherapy only in those cases where spinal seeding is radiographically or pathologically evident [3, 7].

In unison with other reports, the main reason of treatment failure in presented group is local recurrence. 2-year survival after recurrence was 33%. J.W.Goldwein reports a 29% rate of 2-year actuarial survival after recurrence and better results for patients with benign lesions and at the first relapse. Surgery, irradiation and chemotherapy based on cisplatin with etoposide appear to be the most active agents so patients with recurrence and better prognostic factors may benefit from such aggressive therapy [17]. Stereotactic radiosurgery provides good local control for patients with recurrent intracranial ependymoma (estimated 3-year control – 68%) and may have a favourable impact on survival [18].

Conclusions

1. Local recurrence is the most frequent site of failure in patients with intracranial ependymoma.
2. Patient age is a strong prognostic factor.
3. Extraventricular location of ependymoma in adult patients worsens survival.
4. Patients with anaplastic ependymoma and those with incompletely resected tumours have relatively good prognosis after irradiation, thus indicating that radiotherapy is an important part of the treatment.

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