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Ependymomas in adult patients: Results of adjuvant radiotherapy

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Background. *As ependymomas are rare tumours and experiences base on the results of retrospective studies, we assess the survival and pattern of recurrence in eight adult patients with intracranial or spinal ependymoma who were treated with adjuvant radiotherapy.*

Patients and methods. *The data of a series of adult patients with low/intermediate (7) or high-grade (1) ependymomas receiving postoperative radiotherapy are presented. Between 1985 and 1994, eight patients (mean age 41 years, range 18-55 years) with intracranial (2) or spinal (6) ependymoma were irradiated either after macroscopically complete surgery (4), or incomplete surgery (1) or for salvage after incomplete resection of local recurrence (3). Radiotherapy with a mean dose of 52 Gy (range, 50-54Gy) was given to generous local fields with boost, not to the entire craniospinal axis.*

Results. *Median follow-up was 101 months (range, 12-146 months); the 5-year overall survival and disease-free survival were 100 % and 8ž %, respectively. Infield failure occurred in one patient with intracranial and one with spinal ependymoma 77 months after radiotherapy in both cases. Initially, these two patients had been irradiated after incomplete resection of a recurrent tumour. Two patients with spinal cord tumours showed outfield failure in the spinal cord 38 and 86 months after radiotherapy. No irradiation induced late effects were observed.*

Conclusions. *Adjuvant radiotherapy after incomplete surgery and/or local recurrence and/or high-grade tumours seems to be efficient to prolong local control in this rare disease.*

Key words: ependymoma-surgery-radiotherapy; radiotherapy, adjuvant; adult

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Introduction

Ependymomas derive from ependymal cells lining the ventricular system and the central spinal canal. They are rare tumours and experiences base on the results of retrospective studies.[1-14] About 60% of the intracranial ependymomas are located infratentorially, most commonly in the fourth ventricle, while 40% evolve supratentorially.[15] About half of supratentorial tumours are located intraventricularly, while the remainder appear to be intraparenchymal, arising perhaps from remote fetal ependymal cell rests.[16] Intracranial ependymomas generally occur in children and young adults. Spinal cord tumours, however are seen more frequently in adult patients in the fourth and fifth decade with the lumbosacralis axis as a common site.

This study reviews survival and pattern of recurrence in eight adult patients with intracranial or spinal ependymoma.

Material and methods

Patients characteristics

From August 1984 through April 1995, eight adult patients with histologically proven ependymoma received radiotherapy at some phase in their treatment. Four patients were irradiated postoperatively after macroscopically complete surgery, one patient after incomplete surgery, and three patients underwent incomplete surgery and postoperative radiotherapy for salvage. Details are given in Table 1. There were 4 male and 4 female patients, their median age was 44 years (range, 18-55 years).

Two patients had an intracranial tumour; one supratentorial ependymoma was found in the third ventricle and one infratentorial tumour was located in the fourth ventricle. Six patients had ependymomas of the spinal cord, which were located in the thoracolumbar and lumbar region in three patients, respectively. No patient had evidence of distant metastases.

The tumours were classified according to the degree of histologic differentiation, there were seven low/intermediate-grade and one high-grade tumour. Myxopapillary subtype was found in one patient, papillary in three, cellular and anaplastic subtype in one case, respectively. No information on histologic subtype was evident in 2 patients.

In earlier years diagnostic evaluation of the primary tumour included ventriculography and myelography, whereas in recent years, computed tomography and magnetic resonance imaging have usually been performed.

Most frequent symptom in patients with spinal tumours was low-back pain. Few days before diagnosis, the tumour caused spastic hemiparesis in three patients. In one patient with spinal ependymoma no information about the kind and duration of symptoms was available. Both patients with intracranial tumours had suffered from headache for 3 years and 2 months, respectively. Few days before diagnosis, the symptoms of increasing intracranial pressure were recorded. Details are shown in Table 1.

External radiotherapy

Seven patients received a mean dose of 52 Gy (50-54 Gy) to the tumour bed including a safety margin and an additional boost; one patient had a whole-brain irradiation followed by a boost. No irradiation of the entire craniospinal axis was performed. Daily doses were 1.7 - 2.0 Gy 5 days per week. All fields were treated daily. Photon beams were used in five patients, two patients were irradiated with electrons and, in earlier years, one patient had a Cobalt-60 therapy. Treatment planning CT scans for the determination of the target volume were done routinely. No patient had chemotherapy additionally.

Table 1. Patient's characteristics including the treatment modality and outcome

Age	Site	Grade	Symptoms		Initial	Time to	Surgery and	Progression			Outcome
			Kind	Duration	surgery	failure	radiation dose	Intervall	Site	Treatment	
18	supratentorial	I	Headache Vertigo Neck stiffness	2 mos 3 days	R0	122 mos	R2 + 50 Gy	77 mos	Infield	Radiosurgery	111mos^{AWD}
30	supratentorial	cell.I- I	Headache Nausea, Emesis	3 years 6 days			R0 + 54 Gy				119 mos^{NED}
53	Th12- S1	I	Dysbasia Hemiparesis	3 mos 6 days			R1 + 52.2 Gy				12 mos^{NED}
44	TH12- L1	myxopap.II	Low back pain Hemiparesis	2 mos 4 days			R0 + 50 Gy	38 mos 23 mos	Outfield $^{(Th9)}$ Outfield $^{(L4-S3)}$	RX R2+50Gy	84 mos^{DOD}
55	L3-4	pap.II	Low back pain	2 mos			R0 + 54 Gy				111 mos^{NED}
44	Th10- L1	pap.I	?	?	R0	46 mos	R2 + 54 Gy	77 mos	Infield	~	91mos ^{DSM}
30	L3-4	anapl.III	Hemiparesis	2 days			R0 + 54 Gy				41mos^{NED}
52	L2- L4	pap.I	Low back pain	17 mos	R0	74 mos	R1 + 54 Gy	86 mos 44 mos	Outfield $^{(Th6-8)}$ Outfield $^{(Th2-3)}$	RX R1+ 52.2Gy	146 mos^{AWD}

mos: months; cell: cellulary; myxopap: myxopapillary; pap: papillary; anapl: anaplastic
AWD: Alive with disease, NED: No evidence of disease, DOD: Dead of disease, DSM: Dead of second malignancy
R0: Radical surgery; R1: Microscopically incomplete surgery; R2: Macroscopically incomplete surgery; RX: unknown radicality

Follow up

The median follow-up was 101 months (range, 12- 146 months). Patients were seen in follow-ups every 3 months for 3 years and every 6-12 months thereafter. Follow up investigations included myelography in earlier years, later on, computed tomography or /magnetic resonance imaging were performed.

Data analysis

Estimates of rates for overall and disease-specific survival were calculated using the Kaplan-Meier product limit method.[17] The timing of all events was calculated from the last day of radiotherapy.

Results

Radiation treatment was well tolerated. Acute discomfort included reversible focal loss of hair and/or moderate skin erythema; no late side-effects were observed.

All patients were evaluable for survival and local control. Overall 5-year survival was 100 %. The median disease-free survival was 86 months, the 5-year disease-free survival was 86 %.

Two patients failed locally within the radiation field. In one patient with an intracranial ependymoma, radiosurgery was performed for salvage, the other patient received no further treatment; he died secondary to primary pancreatic cancer. Initially, both patients had been irradiated for local recurrence. Two patients with spinal cord tumours developed outfield failures. Details are summarised in Table 1. No distant failures were observed.

Discussion

Failure to control disease at the primary site seems to be the major problem. Most patients

with intracranial ependymomas who develop spinal metastases also fail locally and die of their local disease. In rare cases, distant metastases have been reported.[14, 18]

Prognostic factors

Clinical variables like age,[2,3,12,13] gender,[3,13] tumour grade,[4,7,11-13] histological subtype[1,4] and tumour location,[3,6,12] have been discussed to be potential prognostic factors. Some reports have seen no significant difference in survival rates based on age, [2,3,13] others have found a trend for better progression-free survival [7,12] or a significant better actuarial survival in patients older than 16 years of age[7].

While some authors[3] have found no significant correlation with gender and survival, Vanuytsel et al.[13] obtained a significant better overall and progression-free survival in female patients. Tumour grade has been most frequently identified as significant variable. [4,7,11,13] Seven out of eight of our patients with spinal and intracranial ependymomas had low/intermediate-grade tumours with a 5-year disease-specific survival rate of 86 %; these numbers are in keeping with the results of other reviews.[2,4,11] Tumour location was the only factor that influenced absolute survival in a review of Mc. Laughlin et al.[6], these findings have not been confirmed by others.[3,12]

Another possible prognosticator which was evaluated by some authors is the duration of symptoms prior to diagnosis.[11,14] The clinical presentation of ependymoma depends on the location of the tumour; it can be unspecific like headache or low-back pain, which may lead to delayed diagnosis. Wen et al.[14] report a median duration time of 18 months in patients with spinal ependymomas, 40% of the patients had symptoms for more than 3 years prior to their initial visit. Median length of symptoms of 14 months was noted by Waldron et al.[11], but this clinical variable had no impact on recurrence-free and cause-specific survival on multivariate analysis.

Intracranial ependymoma

Surgical resection and radiotherapy are accepted as standard treatment, but it remains disagreement regarding the volume that should be irradiated. For the treatment of high-grade supratentorial ependymoma with no evidence of dissemination, some authors recommend craniospinal irradiation (CSI),[12] others however, saw no benefit of the use of CSI and found whole brain irradiation with boost a justifiable approach.[7,13] Craniospinal irradiation remains standard treatment when spinal seeding is radiographically or pathologically evident. For localised supratentorial low-grade tumours general agreement exists on local confined fields [7,13] either generous local irradiation or whole-brain irradiation with boost.

The spread to the subarachnoidal space is considered to be higher for tumours arising in the posterior fossa and for high-grade tumours. Therefore, for high-grade infratentorial tumours, CSI is considered as treatment of choice by most authors.[2,7,12] In case of low-grade infratentorial tumours, treatment policies include local fields [7,13] and CSI.[12]

Local infield failure occurred in one of our two patients with intracranial ependymomas 77 months after macroscopically incomplete resection of local recurrent tumour and postoperative radiotherapy (50 Gy); stereotactic radiosurgery was performed for salvage in this patient.

Spinal ependymoma

Spinal ependymomas have a long natural history. Both, the length of symptoms prior to diagnosis as discussed above and the development of late recurrences illustrate this. Recurrences later than 10 years following initial diagnosis and therapy have been reported[11] - therefore long-term follow-up is needed to assess treatment results.

Surgical resection is the mainstay of treatment for the majority of these tumours; with the improvement of neurosurgical instrumen-

tation, the morbidity of the radical approach has decreased extremely. However, radical surgery is not possible in all cases. The role of postoperative radiotherapy is controversial for the patients with spinal ependymomas. Some authors consider surgery alone to be efficient[9], others recommend postoperative radiotherapy only for intermediate/high-grade tumours[8,11] or after incomplete resection;[5,6,8,11,14] generally, a local field irradiation is considered sufficient.[6,10,11] Wen et al.[14] recommend a dose of 45-50 Gy if the tumour has been incompletely resected or if it has been removed in a piecemeal fashion and not in an en bloc fashion. If the tumour has been removed in a piecemeal fashion the authors recommend a thecal sac irradiation additionally. Waldron et al.[11] also suggest postoperative irradiation of intermediate or poorly differentiated tumours, irrespective of the degree of resection, as well as in incompletely resected tumours. Given the dose limitations by the spinal cord tolerance levels, the radiation doses reported in the literature range between 40 and 54 Gy.[2,7,8,12,14] A report by Stuben et al.[7] showed a significant difference in progression free survival (PFS) probability between the patients treated with doses up to 45 Gy and those patients receiving more than 45 Gy (36% vs. 54% 5-year PFS). In our patients with spinal ependymoma, a mean dose of 53 Gy was used and infield failure was obtained in one patient. He had been irradiated for local recurrence after macroscopically incomplete surgery; the patient died due to pancreatic cancer. In two patients, one papillary and one myxopapilary subtype, outfield failures were seen. (Table 1). One may argue, that larger fields might have reduced the risk of these events.

Conclusion

Adjuvant radiotherapy either after incomplete surgery and/or local recurrence and/or high-grade tumours seems to be efficient to prolong local control in this rare disease.

References

1. Schwartz TH, Kim S, Glick RS, Bagiella E, Balmaceda C, Fetell MR, et al. Supratentorial ependymomas in adult patients. *Neurosurgery* 1999; **44:** 721-31.
2. Schüller P, Schäfer U, Micke O, Willich N. Radiotherapy for intracranial and spinal ependymomas. *Strahlenther Onkol* 1999; **175:** 105-11.
3. Abdel Wahab M, Corn B, Wolfson A, Raub W, Gaspar LE, Curran W Jr, et al. Prognostic factors and survival in patients with spinal cord gliomas after radiation therapy. *Am J Clin Oncol* 1999; **22:** 344-51.
4. Schild SE, Nisi K, Scheithauer BW, Wong WW, Lyons MK, Schomberg PJ, et al. The results of radiotherapy for ependymomas: The Mayo clinic experience. *Int J Rad Oncol Biol Phys* 1998; **42:** 953-8.
5. Lee TT, Gromelski EB, Green BA, Weidner A. Surgical treatment of spinal ependymoma and post-operative radiotherapy. *Acta Neurochir* 1998; **140:** 309-13.
6. McLaughlin MP, Marcus RB Jr, Buatti JM, Mc Collough WM, Mickle JP, Kedar A, et al. Ependymoma: Results, prognostic factors and treatment recommendations. *Int J Radiat Oncol Biol Phys* 1998; **40:** 845-50.
7. Stüben G, Stuschke M, Kroll M, Havers W, Sack H. Postoperative radiotherapy of spinal and intracranial ependymomas: Analysis of prognostic factors. *Radiother Oncol* 1997; **45:** 3-10.
8. Shirato H, Kamada T, Hida K, Koyanagi I, Iwasaki Y, Miyasaka K, et al. The role of radiotherapy in the management of spinal cord glioma. *Int J Rad Oncol Biol Phys* 1995; **33:** 323-8.
9. Epstein FJ, Farmer JP, Freed D. Adult intramedullary spinal cord ependymomas: the result of surgery in 38 patients. *J Neurosurg* 1993; **79:** 204-9.
10. Clover LL, Hazuka MB, Kenzie JJ. Spinal cord ependymomas treated with surgery and radiation therapy: A review of 11 cases. *Am J Clin Oncol* 1993; **16:** 350-3.
11. Waldron JN, Laperriere NJ, Jaakkimainen L, Simpson WJ, Payne D, Milosevic M, et al. Spinal cord ependymomas: A retrospective analysis of 59 cases. *Int J Rad Oncol Biol Phys* 1993; **27:** 223-9.

12. Grabenbauer GG, Barta B, Erhardt J, Buchfelder M, Thierauf P, Beck JD, et al. Ependymomas: Prognostic factors and results of surgery and radiotherapy. *Onkol* 1992; **168:** 679-85.

13. Vanuytsel LJ, Bessell EM, Ashley SE, Bloom JG, Brada M. Intracranial ependymoma: Long-term results of a policy of surgery and radiotherapy. *Int J Rad Oncol Biol Phys* 1992; **23:** 313-9.

14. Wen B-C, Hussey DH, Hitchon PW, Schelper RL, Vigliotti AP, Doornbos JF, et al. The role of radiotherapy in the management of ependymomas of the spinal cord. *Int J Rad Oncol Biol Phys* 1991; **20:** 781-6.

15. Levin VA, Sheline GE, Gutin PH. Ependymoma. In: de Vita V Jr, Hellman S, Rosenberg SA, editors. *Cancer: Principles and practice of oncology*, Philadelphia: J.B. Lippincott; 1989. p.1588-9.

16. Molina OM, Colina JL, Luzardo GD, Mendez OE, Cardozo D, Velasquez HS, et al. Extraventricular cerebral anaplastic ependymomas. *Surg Neurol* 1999; **51:** 630-5.

17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958: **53:** 457-81.

18. Graf M, Blaeker H, Otto HF. Extraneural metastasizing ependymoma of the spinal cord. *Pathol Oncol Res* 1999; **5:** 56-60.