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Clinical Study

Treatment of spinal cord ependymomas by surgery with or without postoperative radiotherapy

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Summary

Purpose: To evaluate the effectiveness of complete resection and postoperative radiotherapy in spinal cord ependymomas.

Methods and materials: We conducted a retrospective study over 20 patients (13 males and 7 females) with histologically confirmed spinal cord ependymomas between July 1985 and April 2001. Among them, 13 patients had ependymomas, 6 had myxopapillary ependymomas, and 1 had anaplastic ependymoma. All patients received radical surgery for tumor removal with 13 patients achieving complete resection and 7 incomplete resection due to technical difficulty. Among those with incomplete resection, 6 patients received postoperative radiotherapy to tumor bed and only one patient with anaplastic ependymoma received surgery alone. The total tumor dose ranged from 50 to 60 Gy.

Results: Among the 20 patients, 19 patients were alive and showed local control. The median survival time of all patients was 109 months, with 104 months in the complete resection alone group and 135 months in the incomplete resection with postoperative radiotherapy group. One patient with anaplastic ependymoma and no postoperative radiotherapy developed leptomeningeal seeding 9 months after surgery. Salvage therapy of radiotherapy and chemotherapy maintained normal neurological functions. The patient expired 34 months from the initial diagnosis due to progression of leptomeningeal seeding.

Conclusion: Complete resection alone in spinal cord ependymoma can achieve excellent local control and survival. Patients should receive complete resection if technically possible. Postoperative radiotherapy is not recommended for complete resection. For incomplete resection, postoperative local radiotherapy is recommended and it can also achieve excellent local control and survival. Local radiotherapy with 50–60 Gy is effective and safe. Salvage radiotherapy improves quality of life for local recurrence or leptomeningeal seeding patients.

Introduction

Ependymoma arises from ependymal cells that form the lining of the ventricles and central canal of the spinal cord. It is a clinically diverse group of gliomas that vary from aggressive parenchymal intraventricular tumors of children to benign spinal cord tumors in adults. Ependymoma is the most common intraspinal tumor [1]. It comprises 15% of spinal cord tumors and up to 60% of spinal cord gliomas [2,3]. Clinical trials on the treatments of spinal cord ependymomas are rare because the number of cases is often limited in one single institute. It is therefore important to review the long-term outcome of the patients with spinal cord ependymomas for further improvement.

Ependymoma can be classified differently. In general, it includes ependymoma, anaplastic (malignant) ependymoma, and myxopapillary ependymoma. Ependymoma includes cellular, papillary, clear cell, and tanycytic subtypes [4]. Spinal cord ependymoma is usually benign and curable with surgical resection or in combination with radiotherapy. The prognosis after radical resection of myxopapillary ependymoma is excellent. Anaplastic ependymoma is less common and has worse prognosis.

The primary sites of spinal cord ependymoma occur in the cervical and cervico-thoracic segments [4], with the myxopapillary subtype found frequently in the cauda equina region, mostly arising from the filum terminale [5].

Standard treatment usually includes radical resection followed by radiotherapy for known or suspected residual tumors [6,7]. Surgery is crucial for the establishment of a histologic diagnosis and the primary removal of the tumor. Patients with complete resection may not need postoperative radiotherapy. However, complete resection is not always possible because of its location. In such cases, postoperative radiotherapy is often necessary. Reported series have shown that postoperative radiotherapy can decrease local failure rate, achieve local tumor control, improve neurologic function, and increase survival [8–10].

The present study is a retrospective, single-institution report on 20 patients with spinal cord ependymomas

treated by surgery with or without postoperative radiotherapy. Treatment options were evaluated to determine their relationship to survival and disease control.

Methods and materials

Patients

Twenty patients with histologically confirmed spinal cord ependymomas between July 1985 and April 2001 were identified from the Cancer Registration Data Base of Taipei Veterans General Hospital. Patient age ranged from 12 to 72 years, with a median age of 39 ($\pm$17.59) years. There were 13 males and 7 females. Characteristics of patients are presented in Table 1. The diagnosis was confirmed by histological study in all cases.

Statistical methods

Survival and local control rates were the primary endpoints of the study. Local failure was defined as progression of local symptoms as well as tumor growth documented on neuroimaging studies. All statistics and tables were done by Statistical Package for the Social Sciences (SPSS) 11.0. Follow-up time ranged from 34 to 223 months, with a median follow-up time of 109 months.

Surgery

The preoperative evaluation included a careful history and physical examination, computer tomography (CT), CT myelogram, myelogram, or magnetic resonance imaging (MRI) of the clinically involved portion of the central nerve system (CNS). Sixteen patients received preoperative MRI and 2 had CT and myelogram only. The other 2 patients should probably have received preoperative CT or MRI according to our standard procedure. However, this part of medical records was missing.

All patients underwent laminectomy and posterior myelotomy for tumor removal. The extent of tumor resection was determined by a careful review of operative findings. Gross total resection and subtotal resection were classified by the neuro-surgeons subjectively. Gross total resections achieved in 13 (65%) patients, subtotal resections in 7 (35%) patients (Table 1). Ten out the 13 patients with complete resection received postoperative MRI according to clinical indications within 3–108 months after surgery. No evidence of residual tumor was found. Only 3 patients did not have postoperative MRI. Seven patients with incomplete resection were identified by the neurosurgeons. All had minimal residual tumor. Four patients received postoperative MRI, one received CT scan and two had no followed-up images. Two patients showed residual tumor in postoperative MRI. Six patients were referred for radiotherapy.

Pathologic examination

The pathological classifications are based on WHO Classification of Tumors (2000). Myxopapillary ependymoma is classified as Grade I, ependymoma as Grade II, and anaplastic ependymoma as Grade III. Among the 20 patients, there were 13 patients with ependymomas (WHO Grade II), 6 with myxopapillary

Table 1. Patient characteristics and treatment results

Case no.	Age (years)	Sex	Diagnosis	Histology	Surgery	OP[a] site	RT[b] dose (Gy)	RT Fx[c] dose	RT site	Quality of life (KPS[d])	Survival (months)	Status
1	31	F[e]	1987/12	ME[f]	ST[g]	L2–S1	60	2	S1–S2	70	194	NED[h], alive
2	30	M[i]	1991/2	ME	ST	L5	54	2/1.8	L4–L5	90	156	NED, alive
3	45	F	1992/4	ME	ST	T12–L2	51	1.2 BID	T12–L2	90	142	NED, alive
4	39	M	1993/6	E[j]	ST	C3–C6	50	1.8	C2–C6	70	128	NED, alive
5	38	M	1996/9	ME	ST	L3	52	2	L1–S3	90	89	NED, alive
6	31	F	1998/7	E	ST	L1–L3	54	2	L1–L3	70	67	NED, alive
7	21	F	1997/7	AE[k]	ST	T7,T8				0	34	REC[l], dead
8	19	M	1985/7	E	T[m]	C1–C7				90	223	NED, alive
9	65	M	1993/6	E	T	C5–T1				90	128	NED, alive
10	67	F	1993/7	ME	T	L1–L3				90	127	NED, alive
11	40	M	1994/2	E	T	L1–L2				90	120	NED, alive
12	72	M	1994/2	E	T	T7–T9				10	120	NED, alive
13	29	F	1994/9	E	T	C4–C6				90	113	NED, alive
14	52	M	1995/6	ME	T	L1–L3				90	104	NED, alive
15	64	M	1997/10	E	T	L1–L2				90	76	NED, alive
16	52	M	1999/4	E	T	C3–C5				90	58	NED, alive
17	12	M	2000/2	E	T	C3–C4				30	48	NED, alive
18	21	F	2000/12	E	T	T3–T8				70	38	NED, alive
19	33	M	2001/4	E	T	C2–C7				70	34	NED, alive
20	56	M	2001/4	E	T	T9–T10				70	34	NED, alive

[a] OP – operation; [b] RT – radiotherapy; [c] Fx – fraction; [d] KPS – Karnofsky performance status; [e] F – female; [f] ME – myxopapillary ependymomas; [g] ST – subtotal resection; [h] NED – no evidence of disease; [i] M – male; [j] E – ependymomas; [k] AE – anaplastic ependymomas; [l] REC – recurrence; [m] T – total resection.

ependymomas (WHO Grade I), and 1 with anaplastic ependymoma (WHO Grade III). All of the pathological samples were reviewed again by the same neuropathologist for this study in January 2004. In regard of tumor sites, 7 patients had involvement in the cervical cord, 5 in the thoracic cord, and 8 in the lumbar cord.

Postoperative radiotherapy

Among the 7 patients with incomplete surgical resection, 6 received postoperative radiotherapy using megavoltage radiation (6- or 10-MV X-rays) by linear accelerator. Radiotherapy was performed within 4 weeks after surgery in 5 patients and 6 months in one patient. Radiation fields included the gross tumor plus 1.5–2 cm margin above and below the tumor bed. The total tumor dose ranged from 50 to 60 Gy. All patients received 1.8 or 2 Gy per fraction per day except one who received 1.2 Gy twice per day. Radiotherapy was performed 5 days per week.

Results

Survival

The patients were treated between July 1985 and April 2001, and the data were analyzed in February 2004. Among the 20 patients, 19 patients were alive. One patient with anaplastic ependymoma and no postoperative radiotherapy expired 34 months after diagnosis due to progression of leptomeningeal seeding. The median survival time of all patients was 109 months, with 104 months in the complete resection alone group and 135 months in the incomplete resection with postoperative radiotherapy group.

Neurological function

The 6 patients with incomplete resection and postoperative radiotherapy showed excellent performance status in neurological functions during the follow-up. The 13 patients with complete resection survived and no surgical-related deterioration in neurological functions (Table 2).

Most patients suffered from neurological symptoms such as lower back pain or sciatica which affected their daily life. This was why they sought help. All patients showed improvement after surgery. The condition of six patients with radiotherapy has remained stable till now. One patient with anaplastic ependymoma and no postoperative radiotherapy developed leptomeningeal seeding. Salvage therapy of radiotherapy and chemotherapy achieved the goal of maintaining quality of life and normal neurological functions until the patient expired 34 months from the initial diagnosis due to progression of leptomeningeal seeding. There were two patients who showed decline in Karnofsky Performance Status (KPS) scores in the surgery alone group. One patient is now 76 years old and bedridden. The patient remained bedridden after surgery. No postoperative MRI was done considering the patient's age and poor performance status. Because the tumor size was large ($6.5 \times 1 \times 0.8$ cm), spinal cord injury caused by tumor compression was more likely than recurrence or surgical complication. The other patient is now 17 years old with neurofibromatosis type II, complicated with brain and spinal meningioma, spinal ependymoma, and schwannoma. Although recurrence of meningioma and schwannoma was proven by surgery, there was no evidence of recurrence over the primary site of ependymoma in the follow-up MRI. Therefore, the decline of the patient's performance status was caused by the progression of meningioma and schwannoma. These are the only two patients with distinct KPS decline in this study. No clinical evidence of long-term radiation damage was found in our study.

Table 2. Patient status by the end of follow up

KPS [a]	100–90	80–70	30–20	10	0
Complete resection	8	3	1	1	0
Incomplete resection + RT	3	3	0	0	0
Incomplete resection without RT	0	0	0	0	1

[a] KPS – Karnofsky performance status; RT – radiotherapy.

Patterns of recurrence

All patients who had complete resection or incomplete resection with adjuvant radiotherapy achieved local control. Only one patient with anaplastic ependymoma and no postoperative radiotherapy had recurrence with leptomeningeal seeding 9 months after surgery. Salvage therapy including craniospinal irradiation (32 Gy/20 fractions) with focal boost (43.2 Gy/27 fractions) and oral chemotherapy with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (130 mg/m^2) monthly for 12 courses were applied to the patient at another hospital. When the second recurrence was found, the second RT achieved the goal of maintaining quality of life and normal neurological functions. The patient expired 34 months from the initial diagnosis due to progression of leptomeningeal seeding.

Discussion

The present analysis was performed to define the long-term outcome of patients with spinal cord ependymomas. Existing studies indicated long survival and relatively low recurrence rate in patients [2,8,9,11,12]. Our evidence from this study is consistent with that of the previously published results.

Surgery

Existing series showed that complete resection of ependymomas was critical for tumor control and recurrence [11–13]. In our study, surgeons usually performed radical resections as possible. All patients

with spinal cord ependymomas who received surgery after 1998 achieved complete resection. Our study showed that complete resection of ependymomas could be achieved with a relatively high percentage (65%, 13 out of 20 patients), as compared to the quarter patients reported in other series [14–18]. There are two explanations for the higher rate of complete resection: the improvement of surgical techniques and the collaboration with radiology. The neurosurgeons have served in our hospital for several decades and are responsible for numerous surgeries. The resection of spinal tumor requires high technique. These experienced neurosurgeons are capable of performing complete resection with minimal surgical defects. No surgical-related neurological damage was found according to the postoperative records. With the advancement of equipment and the increasing experiences, the radiologists were able to provide better suggestions to the neurosurgeons for complete resection. We collaborated with the radiologists well. Sixteen out of 20 patients received preoperative MRI, which enabled the surgeons to evaluate tumor extension to achieve complete resection.

Some patients with complete resections were at shorter postoperative times than those with incomplete resections. With a small number of samples in this study, it was difficult to have even distribution. As the surgical techniques improved, patients with ependymoma were more likely to achieve total resection in our hospital. Seven patients enrolled since October 1997 all had ependymomas; 6 of them had complete resection. Ependymoma is easier to achieve complete resection than myxopapillary ependymoma. This could be another explanation why there were more patients with shorter postoperative times in complete resection group.

In this study, complete resections of ependymomas have demonstrated good tumor control and survival with low morbidity, as reported in other series [9,13,14]. McCormkck et al. reported excellent long-term control and low morbidity in 23 patients over a period of 12 years [19]. It is recommended that resection should be conducted as complete as possible for spinal cord ependymomas.

Among the 7 patients in the incomplete resection group, 4 were subtyped as myxopapillary ependymomas, 2 as ependymomas and 1 as anaplastic ependymoma. Myxopapillary ependymoas are usually found encapsulated and originated in the cauda equina region, which makes complete resection more difficult than other subtypes. Myxopapillary ependymoma is relatively difficult to achieve complete resection. So the incomplete resection group had a higher proportion of myxopapillary ependymomas, which was almost exclusive in lumbar spine. This resulted in the bias in tumor location.

In our study, those who could not achieve complete resection still had maximal safe resection. No detailed information was available in other series about this issue. According to our clinical experiences, maximal safe resection is recommended.

Radiotherapy

Clinical series have shown that postoperative radiotherapy improved local control and survival in incomplete resection of ependymomas [2,9,11, 15]. Our result showed that incomplete resection patients with postoperative radiotherapy had excellent local control and survival. This is consistent with the results reported in other series (Table 3) [20–22].

In Table 3, although the number of those with a biopsy followed by radiotherapy is very small, the recurrence rate seems low. There is no detail on their surgical procedures. If the primary tumor is small, biopsy can be considered as incomplete resection with very small residual. Ependymoma is relatively sensitive to radiotherapy. Radiotherapy is possible to achieve local control in these biopsy patients.

The patient with anaplastic ependymoma had recurrence with leptomeningeal seeding. The salvage therapy with radiotherapy and chemotherapy actually relieved the symptoms and improved the quality of life. This is the only death in our study. The patient died 34 months due to uncontrolled progression of tumor after the initial diagnosis. According to Whitaker et al., tumor control and long-term survival in patients of spinal cord ependymomas with recurrence were poor; the effect of extensive salvage measure was limited to low-grade tumors [16]. In Whitaker et al. the patients with Grades III/IV tumors had poorer survival. In our study, survival was also poor in patients with recurrent ependymomas. This is similar to the results of Whitaker et al. In their study, the data of patients were collected from earlier period (1950–1987). With the improvement of surgical techniques and equipments,

Table 3. Tumor recurrence in different series

Authors	R1[a]		R0[b]		Bx[c]
	OP + RT	OP alone	OP + RT	OP alone	RT
Wen et al. [20]	0/9[d]	1/1	0/1	1/6	0/3
Clover et al. [21]	3/7	1/1	–	0/1	0/1
Kochbati et al. [22]	1/9	0	0/2	0	1/4
Total	4/25 (16%)	2/2 (100%)	0/3	1/7 (14%)	1/8 (12.5%)

[a] R1 – subtotal resection; [b] R0 – total resection; [c] Bx – biopsy; [d] The numerator indicates the number of recurrence; the denominator indicates the total number of patients.

our study (1985–2001) achieved higher rate of complete resection (with 13/20 in our study vs. 14/58 in Whitaker et al.). The patients with total resection showed good survival up to 100% in 10-year overall survival rate. Those who did not achieve complete resection could still have maximal safe resection with postoperative radiotherapy. This may be the reason that we have only one recurrence in our study. Whitaker et al. concluded that radiotherapy might achieve long-term tumor control in over half of the patients with residual spinal ependymoma. Our study confirms this conclusion with better results.

For patients with unresectable residual tumor, local radiotherapy is recommended. One patient with myxopapillary ependymoma did not receive radiotherapy immediately because the symptoms subsided after surgery. However, persistent residual tumors in MRI and mild lower back pain were noted. This patient finally received radiotherapy 6 months after surgery. There are series reporting favorable outcomes for patients with low-grade (including myxopapillary) tumors of the lumbar spine or cauda equina having undergone en bloc complete resection alone [2,16–18]; therefore, the option of observation following en bloc complete resection for patients with low-grade spinal cord ependymomas is a reasonable one. If the tumor persists on the postoperative MRI, radiotherapy is recommended [23].

Some reported series increased the dose of radiation above 60 Gy in order to control high grade ependymomas. This measure could result in neurological damage. The dose in our study was limited to 50–60 Gy. The tumor dose of 60 Gy for spinal cord is relatively high. In our study, the only patient who received 60 Gy had tumors located over L2-S1 spine. The risk of radiation myelitis may not be as severe in this location. However, 60 Gy is not recommended for cervical spine. Moderate dose radiotherapy to the tumor bed is preferred. It is difficult to show a dose–response relationship with the limited patient number. A total dose of 50.4 Gy in 28 fractions seems reasonable.

Advantages and disadvantages

Major limitations of this study are biases which may have been introduced by the retrospective nature of the data collection and the relatively small number of patients. Relatively small changes in this distribution could make a big difference in the results.

Survival and local control of tumor are defined as endpoints, but since most patients are still alive, it is difficult to compare survival and recurrence between both groups. This is why the reports in other series are introduced in Table 3 for further discussion. The data in other series are consistent with ours. Surgical resection alone is effective for the complete resection patients. Although the case number is limited, incomplete resection alone is not effective, with 100% recurrence rate (Table 3). Postoperative radiotherapy is effective in reducing recurrence rate for incomplete resection patients. We are able to benefit the incomplete resection patients with postoperative radiotherapy in 100% local control and survival rate.

In our study, there is no data of patients with less than maximal safe resection for comparison. From other series, complete resection is important. Despite the small number of patients, several series reported that high recurrence rate was found in subtotal resection (Table 3). Although the lack of control group is disadvantageous for study, the best interest of the patients is our priority.

In addition, ependymoma is a low-grade tumor with slow progression. Although most patients in our study had long follow-up, there were some patients with a relatively short follow-up. Longer follow-up would be better. However, this is one of the studies of successfully treatment of adult spinal cord ependymomas in the literature and it has generally long-term follow-up (median follow-up was greater than 5 years). Moreover, reports of series of ependymomas are few and number. Most existing published series are based on experience in Western countries. Our report supplies data on the experience with the treatment of patients with ependymomas in Asian patients.

Conclusion

According to our experience with Asian patients with ependymomas and reported series in Western patients, complete resection alone in spinal cord ependymoma can achieve excellent local control and survival. Patients should receive complete resection if technically possible. Postoperative radiotherapy is not recommended for complete resection. For incomplete resection, postoperative local radiotherapy is recommended and it can also achieve excellent local control and survival without neurological damage. Local radiotherapy with 50–60 Gy is effective and safe. Salvage radiotherapy improves quality of life for local recurrence or leptomeningeal seeding patients.

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