Surgical outcomes of spinal cord ependymoma: Postoperative motor status and recurrence for each WHO grade in a multicenter study

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Abstract

Background: The goals of the study are to analyze postoperative outcomes and recurrence in cases of spinal cord ependymoma in each World Health Organization (WHO) Grade, and to examine the influence of extent of surgical removal on prognosis. Spinal ependymoma has a relatively high frequency among intramedullary spinal cord tumors. The tumor is classified in WHO guidelines as grades I, II, and III, but few studies have examined postoperative prognosis based on these grades.

Methods: The records of 80 patients undergoing surgery for spinal cord ependymoma were examined in a multicenter study using a retrospective database. Neurological motor status, pathological type, extent of resection, and tumor recurrence were evaluated.

Results: The histopathological types were grade I in 23 cases (myxopapillary: 21, subependymoma: 2), grade II in 52 cases, and grade III in 5 cases (including all anaplastic cases). Total resection was performed in 60 cases (83%), and eight cases had recurrence, including 2 in WHO grade I, 2 in grade II, and 4 in grade III. The 5-year recurrence-free survival rates were 90%, 91%, and 20% in grades I, II and III, respectively. Adjuvant radiotherapy for the local site was performed in 8 cases, including 3 in grade I and 5 in grade III; however, 4 of the 5 grade III cases (80%) had recurrence after radiotherapy. Among 59 patients with normal ambulation or independence without external assistance (McCormick Grade I or II), 53 (90%) maintained the same mobility after surgery. In cases that underwent total resection, the recurrence rate was significantly lower ($p<0.01$). A good preoperative motor status also resulted in significantly better postoperative recovery of motor status ($p<0.05$).

Conclusions: Total resection of spinal cord ependymoma leads to postoperative motor recovery and may reduce tumor recurrence. Therefore, early surgery for this tumor is recommended before aggravation of paralysis.

Introduction

Spinal cord ependymoma is a primary tumor of the central nervous system (CNS) that comprises 2-6% of CNS tumors [1,2]. This tumor has a relative high frequency of 30-88% among intramedullary spinal cord tumors [2,3] and exhibits a variety of clinical features based on lesion location. Most spinal ependymomas are benign, slowly progressive, and well-demarcated neoplasms with little infiltrative potential [4], but recurrence may occur [5,6]. These tumors can cause progressive myelopathy by compression of the surrounding spinal cord, rather than infiltration into surrounding neural tissues [7]. Spinal cord ependymomas are amenable to complete surgical resection with acceptable morbidity and mortality and a low incidence of recurrence with local infiltration, invasion or malignant transformation [8].

In World Health Organization (WHO) guidelines, ependymomas are classified into grades I, II, and III [9]: grade I ependymomas are myxopapillary or subependymomas; grade II may be tanycytic, papillary, or classic; and grade III is referred to as anaplastic or malignant ependymoma. Despite their probable common cell of origin, histological subtypes of ependymomas have wide molecular heterogeneity [10] and few reports have examined outcomes for different WHO grades [2,11,12]. In the current series, we examined the influence of several factors on prognosis, focusing chiefly on the extent of surgical resection and WHO grade, with the goal of using postoperative motor status and recurrence as a basis for treatment decisions in future cases.

Materials and Methods

Patients and clinical data

The subjects were 80 patients undergoing surgery for spinal cord ependymoma at five institutions in the Nagoya Spine Group (NSG). Surgery was performed by seven surgeons, who were certified by the Japanese Spine Surgery and Related Research (JSSR) society at each facility. Approval for the study was obtained from Institutional Review Boards, and all data were obtained from medical

records. A review of medical records was performed to evaluate neurological motor status, pathological type, extent of resection, and tumor recurrence.

Neurological Assessment

Patients were assigned a preoperative neurological clinical grade using the modified McCormick scale (grade I = normal gait, II = mild gait disturbance not requiring support, III = gait with support, IV = assistance required, and V = wheelchair needed) [13]. McCormick grades 1 and II were defined as stable gait with no support required for walking, which indicates independent gait ability [14-16]. Grades were assigned on the basis of documented neurological examinations. Functional assessments were conducted preoperatively, postoperatively, and regularly during follow-up.

Surgical Procedures

None of the patients had previously received surgical treatment. Tumors were operated on using standard dorsal approaches as indicated by the location of the lesion, in the prone position. All tumor resections were performed using microscopes and intraoperative spinal cord monitoring. The extent of tumor resection was categorized as total resection, subtotal resection, partial resection, and biopsy. Total resection was attempted in all surgical cases. We used the standard definition of total resection: removal of 100% of the tumor based on no residual tumor documented microscopically and on intraoperative ultrasonography at the end of the procedure. The procedure was considered to be subtotal resection when a small tumor fragment was deliberately left in place, based on documented removal of 80-99% of the tumor on intraoperative ultrasonography. We performed subtotal resection in this series when intraoperative evoked potential monitoring changes heralded impending neurological paralysis. A 50-80% resection was defined as partial resection and < 50% resection was defined as a biopsy [14-16]. The extent of resection was confirmed using MRI postoperatively. Intraoperative neurophysiological monitoring (IONM) was performed using transcranial electrical

stimulation motor evoked potential (TcMEP) monitoring [17]. The operation was interrupted and the operative field was filled with warm saline if a ≥70% decrease in amplitude was detected as an alarm point for spinal cords damage [18]. The operation was resumed when the waveform recovered [16].

Histopathological analysis

The tumor was pathologically diagnosed postoperatively based on the histological type. Histologic review of microsections stained with hematoxylin and eosin was used to classify tumors using the WHO classification [9] for tumors derived from ependymal cells as grade I, myxopapillary, or sub-ependymoma; grade II, tanycytic, papillary, or classical ependymoma; and grade III, anaplastic, or malignant ependymoma. Ki67 activity was determined as an index of cell proliferative activity.

Statistical Analysis

Differences between groups were evaluated by t test or analysis of variance (ANOVA) with a post-hoc Tukey test, and by Pearson chi-square test. Differences among three groups were analyzed by Tukey Kruskal-Wallis test and one-way ANOVA. A p value < 0.05 was considered to be significant. Survival analysis based on tumor recurrence or progression was performed using the Kaplan-Meier method with between-group survival comparisons by log-rank test. All analyses were performed using SPSS ver. 23; IBM Inc., Chicago, IL).

Results

Demographics

The 80 patients (39 males, 41 females; Table 1) had an average age of 45.6 (range 6-75) years (Figure 1). The most common age was 50 years and the average age was only 18.2 years in WHO grade III cases. The average follow-up period was 7.2 years, with a range of 34 to 184 months. In the WHO classification, there were 23 cases in grade I (29%) (myxopapillary: 21, subependymoma: 2),

52 in grade II (65%) (all classical cases), and 5 in grade III (6%) (all anaplastic cases). At admission, 27, 28, 15, 10, and 0 patients were classified into McCormick grades I, II, II, IV, and V, respectively.

Clinical characteristics

In the WHO classification, grade I tumors were most commonly thoracolumbar junction-lumbar lesions (n=21, 84%); grade II tumors were commonly located in the cervical (n=28, 54%) and thoracic (n=21, 40%) regions, and 4 of the 5 grade III lesions were located in the thoracic region. All cervical lesions and 80% of thoracic spine lesions were grade II, whereas 80% of conus-lumbar lesions were grade I (Figure 2). In preoperative MRI [19], all grade II cases were isointense or hypointense on T1-weighted MRI, 45 (87%) were hyperintense on T2-weighted MRI, 43 (83%) showed surrounding cord edema, 46 (89%) had associated cysts, and 7 (13%) had syringomyelia. Of the 52 tumors, 18 (35%) showed the “cap sign”, a rim of extreme hypointensity seen around the tumor on T2-weighted images, which is due to hemosiderin. In gadolinium-enhanced MRI, all cases were enhanced, and 24 (46%), 16 (31%), 9 (37%), and 3 (6%) showed homogeneous, heterogeneous, rim and nodular enhancement, respectively. All 5 grade III tumors were heterogeneously hyperintense on T2-weighted MRI, 2 (40%) had an associated cyst, and 1 (20%) showed the “cap sign”. In gadolinium-enhanced MRI, 3 (60%) had a heterogeneous pattern, and 2 (40%) had a homogeneous pattern. Thus, the grade II and grade III tumors had similar MRI characteristics and were difficult to differentiate using these findings.

Preoperative duration from disease onset

The mean preoperative duration from disease onset was 17 months (range 1-85 months). Details for each WHO classification are listed in Table 1. There was no significant difference between the amount of tumor resection and the preoperative disease duration (Table 3). Patients with stable gait (McCormick I and II) just before surgery had a significantly shorter preoperative disease duration

from onset compared to those with unstable gait (McCormick III, IV, and V) ($p<0.05$) (Figure 6a), and the preoperative time of disease from onset was also significantly shorter in patients with stable gait at final follow-up ($p<0.05$) (Figure 6b).

Extent of resection and postoperative outcome

The extent of resection was total in 60 cases (79%), subtotal in 9 (11%), partial in 11 (14%), and biopsy in 0 (0%). For cases in WHO grades I, II and III, total resection was performed in 18, 41 and 1; subtotal resection in 3, 6 and 0; and partial resection in 3, 5 and 4 cases, respectively (Table 1). Total resection was performed in both cases of subependymoma of WHO grade I. Of the patients who did not undergo total resection, the main reason for curtailing resection was prevention of neurological injury due to an adherent tumor (n=15: 5 grade I, 6 grade II, and 4 grade III), followed by waveform deterioration of Tc-MEP in neuromonitoring (n=5: all grade II). The rates of total resection were 78% ,79%, and 20% in WHO grades I, II and III, respectively, with a significantly lower rate in grade III cases compared to other grades ($p<0.05$) (Table 2). Ki67 activity in WHO grade III cases was significantly higher than in WHO grades I and II.

In our series, there were no cases in which surgery was delayed until paralysis worsened. However, there were five cases (2 myxopapillary and 3 classical ependymoma) in which paralysis worsened due to difficulty in diagnosis. Pre- and postoperative neurological status (McCormick classification) for each grade is shown in Figure 3. Significantly more cases with preoperative McCormick grades I or II underwent total resection compared to limited resection ($p<0.01$) (Table 3). Among 59 patients with normal ambulation or independence without an external aid (McCormick grade I or II), 53 (90%) maintained the same mobility after surgery. Cases in McCormick classes I and II at final follow-up had better preoperative McCormick grades. In contrast, only 28% of patients in preoperative McCormick classes III, IV and V achieved independent ambulation postoperatively ($p<0.05$). In cases in WHO grades I and II, the percentage of cases in McCormick classes I and II at final follow-up was

also related to the preoperative independent ambulation status ($p<0.05$) (Figure 4).

Adjuvant radiotherapy

Postoperative adjuvant radiotherapy of 40-45 Gy at the local site was given in 8 cases (10%), including 1 with total resection, 3 with subtotal resection, and 4 with partial resection. Stratified by WHO grade, 3 of 21 myxopapillary WHO grade I tumors received adjuvant radiotherapy, of which all had undergone subtotal resection and none underwent total resection, and 2 subependymomas in WHO grade I did not receive adjuvant radiotherapy. All 5 patients with grade III tumors underwent radiotherapy, of whom 1 had undergone total resection, and 3 had undergone partial resection. There were no side effects of myelotoxicity. Recurrence was found in 4 of 8 cases treated with radiotherapy and in 4 of 72 cases that did not receive radiotherapy (Table 4). There was recurrence in both myxopapillary cases with subtotal or partial resection that did not receive radiotherapy.

Tumor recurrence and progression

There were 8 cases (10%) with recurrence (Table 5), including 2 grade I (both myxopapillary), 2 grade II and 4 grade III cases, and 5 cases underwent reoperation. Subependymoma showed no recurrence. Distant recurrences to the brain and cervical cord were eventually observed in 3 cases, and these metastases resulted in death. The 5-year recurrence-free survival (RFS) rates were 90% (72/80) in all patients, 91% (21/23) for WHO grade I cases (subependymomas showed no recurrence in), 96% (50/52) for grade II, and 20% (1/5) for grade III. Recurrence was significantly more frequent in WHO grade III cases ($p<0.01$), and Ki67 activity as an index of cell proliferative activity was significantly higher in WHO grade III cases (Table 2). In cases with total resection, recurrence was significantly reduced compared to those with subtotal and partial resection ($p<0.05$) (Table 3). Survival rates for recurrence depending on extent of resection are shown for WHO grades I, II and III in Figure 5.

Discussion

Spinal cord ependymoma is the most common primary intraspinal neoplasms in adults and accounts for 15-30% of primary spinal intramedullary tumors [3]. However, the tumor is generally relatively uncommon and assembling a sizeable case series is difficult. Furthermore, subgroup analysis by histological grade requires review of all pathological specimens according to current WHO guidelines. A previous evaluation of spinal cord ependymoma using the WHO classification [20] showed that myxopapillary ependymoma (grade I) is mainly capsuled and mostly occurs in the conus medullaris or filum terminale [21-23]. Tumor growth occurs between nerve roots and along arachnoid membranes, and multifocal disease (i.e., cerebrospinal fluid dissemination) and early cerebrospinal fluid metastasis may occur [11,24].

Subependymomas (grade I) rarely occur in the spinal cord, and subependymoma is histologically benign and usually well marginated, which makes a good clinical outcome likely after complete removal [25]. Total resection should be attempted with a microsurgical technique based on protection of spinal function if a frozen biopsy confirms the subependymoma [26,27]. Most lesions showed no adhesion to the spinal cord, and total removal was achieved easily using microsurgical techniques. However, if the lesion is densely adherent to neural tissue or poorly demarcated from the cord, which indicates difficulty in total removal even though the tumor is benign, subtotal removal for decompression of the spinal cord from the intramedullary lesion is acceptable to improve myelopathic symptoms and avoid severe operative complications [28,29]. Classical ependymoma (grade II) is mostly a benign, slow-growing tumor that is most commonly a cervical lesion, and patients with grade II tumors have significantly longer PFS than those with grade I ependymoma [12]. Anaplastic ependymoma (grade III) is a rare and malignant subtype [30] associated with dissemination of intracranial anaplastic ependymoma and recurrent or metastatic spinal anaplastic ependymoma.

Most ependymomas are benign, slow-growing, and tend to compress, rather than infiltrate, the

adjacent cord parenchyma. Such tumors present a relatively clear surgical plane and are curable with total resection. In older reports, the total resection rate was 70% or less [31], but this rate is now as high as 80-90% [31,32] due to improvements in surgical techniques and diagnostic imaging. However, despite improved microsurgical techniques, the potential morbidity resulting from surgery is still a formidable challenge, even for experienced surgeons. Although total resection is the ultimate goal of surgery, preservation of spinal cord function should always take priority. Thus, it is important to modify surgical plans based on preoperative status, intraoperative findings, and degree of invasion of the tumor of the spinal cord, which differs in each WHO classification. Cases with motor weakness often have waveform deterioration in IONM [17,33], which reflects plasticity and a vulnerable spinal cord. In cases with intraoperative waveform deterioration, total resection may have to be switched to subtotal or partial resection.

Several recent publications have recommended surgery before symptoms become severe [14-16]. Total surgical resection is desirable, and all cases in our series that underwent total resection had no recurrence and postoperative McCormick class I or II. However, infiltration into the spinal cord differs among tumors in each WHO classification, and total resection may not always be possible. In particular, WHO grade III cases, which includes all pathologically highly proliferative cases, are likely to infiltrate into the spinal cord, making it difficult to perform total resection. Grade III tumors had a high recurrence rate and worsening of symptoms, despite postoperative radiotherapy. The preoperative disease duration from onset was significantly shorter in patients with stable gait just before surgery and in patients with stable gait at final follow-up. These findings are consistent with previous reports [14,15] and show that early diagnosis of spinal ependymoma is important for recovery of postoperative motor status.

In this series, total resection was possible in 60 (75%) of the 80 cases. For patients who were walking normally without support before surgery (grades I and II), comparable gait was maintained in 90% of the cases and total resection was possible in 83%. Total resection was not achievable at a such

a high rate in cases of anaplastic-type ependymoma, in which the boundary between the tumor and spinal cord was unclear in 4 (80%) of the 5 cases. Good preoperative ambulatory ability was associated with postoperative independent ambulatory ability and total excision of tumors.

Several studies have examined the surgical outcomes for spinal ependymomas of all WHO grades [6,11,12]. For tumors in grades I and II, the clear boundary often permits complete removal. Tarapore et al. reported 10-year recurrence rates of 40% and 19% [12] and Boström et al. found 5-year recurrences rates of 18% and 5% for grades I and II, respectively [11]. In our series, the respective 5-year recurrence rates were 7% (2 cases treated with subtotal and partial resection) and 4% (2 cases, both partial resection). In contrast, grade III tumors grow rapidly and are likely to recur and metastasize, which leads to a poor prognosis (5-year recurrence rates were 80 %) [6,12]. For these tumors, Tarapore et al. found a total resection rate of only 33%, a 10-year recurrence rate of 66%, and 10-year mortality of 66% [12]. In our series, the 5-year recurrence rates for grade III tumors were 80%. Of the 5 cases, only one underwent total resection (20%), radiotherapy was performed in all 5 cases (100%), regrowth and metastasis occurred in 4 cases (80%), and the mortality was 60%. These data are consistent with the poor prognosis of WHO grade III spinal ependymomas found in previous reports.

Adjuvant radiotherapy may be effective for spinal cord ependymoma. For grade I tumors, Chan et al. found postoperative intracranial metastasis in 3 of 5 patients who did not receive radiotherapy, even after complete tumor resection, and suggested that radiation to the entire brain and spinal cord (including local radiation; total dose 30-50 Gy) prevented further tumor progression [34]. Nakamura et al. reported that 14 of 15 patients with grade I tumors who received whole brain and spinal cord radiation or local irradiation survived without tumor recurrence. In our series, the two myxopapillary cases that underwent subtotal or partial resection without radiotherapy both had recurrence. Sakai et al. have previously suggested that adjuvant therapy should be applied for postoperative residual or unresectable tumors [23], and our results are consistent with this viewpoint. Radiotherapy after

subtotal resection is recommended for grade II tumors to prevent dissemination and anaplastic disease [2,11,12], but it has been suggested that postoperative radiotherapy for spinal ependymoma may not lead to better tumor control [35]. In our series, radiotherapy was performed for cases in WHO grades I and III, and was appeared to be effective in grade I cases that could not undergo total resection, and in all grade III cases. Radiotherapy was performed in 3 patients in grade I who underwent incomplete resection. In these patients, recurrence did not occur during follow-up, and there was no side effect of radiation myelopathy.

This study has limitations of a short follow-up period, a small number of subjects, use of radiotherapy in only a few patients, and operations performed in multiple facilities. Within these limitations, all pathological data were collected retrospectively, and we were able to obtain complete details on intraoperative findings and neurological outcomes. Early surgery for spinal cord ependymoma is important before aggravation of paralysis, with consideration of infiltration of the tumor into the spinal cord differing for each WHO classification, and is desirable even for a case without severe neurological deficits. Cases with good preoperative motor status are likely to be amenable to total resection without Tc-MEP waveform deterioration in IONM, and are also likely to have better postoperative motor performance. Although the effectiveness of radiation cannot be judged from our series, side effects such as myelotoxicity did not occur.

Conclusion

We have reported the surgical results for 80 cases of intramedullary spinal cord ependymoma in the multicenter study. In this series, we described the pre- and postoperative ambulatory status, extent of tumor resection, use of adjuvant radiotherapy, surgical outcome, lifespan, and pathological findings for cell proliferative activity. The 5-year recurrence-free survival rates were 90%, 91%, and 20% in WHO grades I, II and III, respectively. Among 59 patients with prospective normal ambulation or independence without external assistance (McCormick Grade I or II), 53 (90%) maintained the same

mobility after surgery. Cases with preoperative independent gait ability were commonly able to undergo total resection, and total resection frequently led to postoperative motor recovery and prevented tumor recurrence. Therefore, early surgery for spinal cord ependymoma is recommended before aggravation of paralysis.

Disclosure

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Figure Legends

Figure 1: Age distribution of cases in each WHO grade

Figure 2: Localization of 80 spinal ependymal tumors in each WHO grade.

Figure 3: Neurological status in pre-op and post-op (McCormick classification) of each WHO grade (a) grade I, (b) grade II, (c) grade III (n=80).

Figure 4: Better preoperative ambulatory ability was significantly associated with good postoperative ambulation, with probabilities of achieving good postoperative results for patients in preoperative class I and II of 90% in all patients, 90% in WHO grade I, 92% in grade II, and 66% in grade III. In contrast, improvement of postoperative independent ambulatory ability was difficult for cases with severe preoperative symptoms, with probabilities for patients in preoperative classes III, IV, and V of 29% in all patients, 20% in WHO grade I, 36% in grade II, and 0% in grade III.

Figure 5: Survival rate for recurrence depending on extent of resection was shown in each WHO grade I (a), II (b), III (c)

Figure 6: Comparison of patients with stable (McCormick I and II) and unstable (McCormick III, IV, and V) gait just before surgery. (a) Patients with stable gait just before surgery had a significantly shorter preoperative disease duration from onset ($p<0.05$). (b) The preoperative disease duration from onset was significantly shorter in patients with stable gait at final follow-up ($p<0.05$).