Outcome predictors in the management of intramedullary classic ependymoma
An integrative survival analysis

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Abstract
This is a retrospective study.

The aim of this study was to illustrate the survival outcomes of patients with classic ependymoma (CE) and identify potential prognostic factors. CE is the most common category of spinal ependymomas, but few published studies have discussed predictors of the survival outcome.

A Boolean search of the PubMed, Embase, and OVID databases was conducted by 2 investigators independently. The objects were intramedullary grade II ependymoma according to 2007 WHO classification. Univariate Kaplan–Meier analysis and Log-Rank tests were performed to identify variables associated with progression-free survival (PFS) or overall survival (OS). Multivariate Cox regression was performed to assess hazard ratios (HRs) with 95% confidence intervals (95% CIs). Statistical analysis was performed by SPSS version 23.0 (IBM Corp.) with statistical significance defined as P < .05.

A total of 35 studies were identified, including 169 cases of CE. The mean follow-up time across cases was 64.2 ± 51.5 months. Univariate analysis showed that patients who had undergone total resection (TR) had better PFS and OS than those with subtotal resection (STR) and biopsy (P = .002, P = .004, respectively). Within either univariate or multivariate analysis (P = .000, P = .07, respectively), histological type was an independent prognostic factor for PFS of CE (papillary type: HR 0.002, 95% CI (0.000–0.073), P = .001, tanycytic type: HR 0.010, 95% CI (0.000–0.218), P = .003).

It was the first integrative analysis of CE to elucidate the correlation between kinds of factors and prognostic outcomes. Definite histological type and safely TR were foundation of CE’s management.

Level of Evidence: 4

Abbreviations: CE = classic ependymoma, GCE = giant cell ependymoma, OS = overall survival, PFS = progression-free survival, RT = radiotherapy, SA = surgery alone, STR = subtotal resection, TR = total resection.

Keywords: ependymoma, neoplasm, prognostic factor, retrospective analysis, spinal cord, survival analysis, WHO grade 2

1. Introduction

Ependymomas are the most common primary intramedullary spinal cord tumor in adults, representing 30% to 45% of such lesions.[1–3] The World Health Organization (WHO) categorizes ependymomas into 3 grades, Grade I myxopapillary ependymoma and subependymoma; Grade II ependymoma, which represent classic ependymomas (CEs), including the cellular, clear cell, tanycytic, and papillary variants; and Grade III anaplastic ependymomas.[4] Although CEs can vary in histological classification, they account for 55.7% of spinal cord ependymomas.[5] Gross total resection (TR) of a spinal cord ependymoma may be accomplished in a majority of patients.[6–10] CEs with slowness of progression maintain the risk of late metastasis into the intraspinal or intracranial regions, with relatively poor prognosis.[11]

Demographic features, tumor grade, extension of surgery, and adjuvant radiotherapy (RT) are among the most studied variables in the existing CE literature, though the association of these factors and survival outcomes is quite variable. An integrative study performed by Kukreja et al[12] revealed that completeness of resection plays a crucial role in improving the prognosis of patients with spinal myxopapillary ependymomas (though younger patients have a less favorable outcome). On the contrary, adjuvant RT does not influence progression-free survival (PFS). In contrast, the study by Chen et al[13] suggested that adjuvant radiotherapies are considerable prognostic indicators in primary spinal anaplastic ependymomas, and age in this study was not significantly associated with the result. Various studies have attempted to clarify the prognostic factors of ependymomas,[12–15] but few have focused on CEs individually.

Lin et al[16] conducted a population-based study for pediatric Grade II spinal ependymomas. They elucidated that RT and female sex in the subtotal resection (STR) group were factors...
associated with decreased mortality. Considering that CEs are one of the most prevalent ependymomas,[17] further investigation of the survival outcome of CEs is urgent.

In this study, we reviewed the literature on patients with CE to evaluate the survival outcome and identify potential prognostic indicators.

2. Materials and methods

2.1. Search strategy

A Boolean search of the PubMed, Embase, and OVID databases was conducted in March 2017 by 2 investigators independently. The study language was limited to English. Search terms were (Spinal Cord Neoplasms [MeSH Terms] AND ependymoma [MeSH Terms] AND “humans”[MeSH Terms]). We excluded duplicate results and screened studies by reading the abstract and full text. References of relevant articles, conference abstracts, and books were used as an additional approach to data collection. The final result was coordinated by a third researcher.

2.2. Selection method

Inclusion criteria for original papers were all included studies were case reports and case series reviews. Single case information was presented and the diagnosis was verified by pathological evidence. According to the WHO classification,[4] the CE comprises a histologically heterogeneous group of tumors that include cellular, papillary, clear cell, and tanycytic subtypes. The articles focused on the patient outcomes by follow-up, providing events of recurrence, death, and others factors relevant to the progression of the disease.

Exclusion criteria were patients with other tumors and severe diseases, such as neurofibromatosis, the primary lesion being extramedullary, such as cauda equine and so on, studies did not focus on CEs or where data were not available, the follow-up data were not referenced, and studies performed in the same institution and during the same time frame were also excluded.

2.3. Data extraction

Data collection was comprised of patient characteristics (age, sex, complaints, etc.), location and length of tumor, extent of resection, strategy of adjuvant treatment, recurrence or progression of disease, mortality, time to recurrence or death, and follow-up duration. To analyze the potential prognostic factors of intramedullary CE, we identified the aforementioned factors into groups. The age of the patients was categorized into 2 groups (Age <18 and Age ≥18 years). The extent of resection was divided into 2 subgroups: TR and STR (STR, biopsy included). TR referred the tumors removed in both an en bloc and a piecemeal fashion. The extent of resection was defined on the basis of the author’s report or postoperative imaging. The adjuvant treatment fell into mainly 2 groups: RT and surgery alone (SA). The outcome of patients included all cause of death, tumor recurrence, and other complications. Disease progression was defined as tumor-relevant death, recurrence, and repeat surgery.

2.4. Statistical analysis

We depicted the characteristics of patients with intramedullary CE. The primary outcomes of our study were PFS and overall survival (OS), which were analyzed by Kaplan–Meier survival analysis with log-rank tests. Cox proportional hazard model was utilized for multivariate analysis. Hazard ratios (HRs) with 95% confidence intervals (95% CIs) were calculated. The covariates selected were determined by clinical experience and the result of the univariate analysis. Continuous variables were analyzed using the t test, and categorical variables were analyzed by the Pearson Chi-square test. P values <.05 were considered statistically significant. All the statistical operations were conducted using SPSS software (version 23.0; IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

3. Results

3.1. Study characteristic

A total of 1249 studies were found according to the search parameters, of which 246 replicated studies and 927 nonrelevant studies were excluded. During full-text review of the remaining 76 studies, 21 studies and 14 references of them[18–52] were deemed to meet the inclusion criteria. Among the 55 excluded studies, 15 were extramedullary ependymoma studies and 40 of the studies did not address CEs. The flowchart of selection is shown in Fig. 1. All included cases provided pathological diagnostic, treatment strategy, and follow-up data. Two studies[23,45] presented a rare subtype of Grade II ependymoma, which is alternatively referred to as giant cell ependymoma (GCE). GCE was first described in 1996,[53] characterized histologically by the presence of pleomorphic giant cells.

3.2. Demographic features

Thirty-five studies including 169 cases were eligible for survival analysis. The primary characteristics of the included patients are summarized in Table 1. The mean age was 35.2±17.8 years. Male to female ratio was 1.2:1. Magnetic resonance imaging (MRI) showed that 67.8% patients had over 3 level lesions. Of
the 163 patients who received surgical resection for CEs, 68.1% had undergone TR and 31.9% had undergone STR. The remaining 6 patients underwent biopsy alone. Around two-fifths of the included patients had received RT; however, it accounted 69.0% in people with none TR. Almost two-thirds of the 83 patients who were classified with the certainly histological subtype were deemed to have cellular ependymomas. The giant cell (2 cases), clear cell (3 cases), and papillary (6 cases) ependymomas were rare. During the follow-up (mean 64.2 ± 51.5 months), 10.1% of patients were deceased and 18.3% had suffered tumor recurrence. The recurrence rate at 1 year, 3 years, and 5 years were 4.1%, 8.2%, and 13.5%, respectively. The most common cause of death was tumor recurrence (70.6%), followed by unknown (17.6%) and cardiac disease (11.8%). It is worth noting that only 1 patient with T8-cauda lesions suffered death after TR.

### 3.3. PFS

PFS is a combined end-point that includes progression and death. Since the lower rate of death, it may enhance estimates of treatment effectiveness and improve power. Overall, conditions of 33 patients worsened after the treatment, of which 3 cases were upgraded to extraspinal metastasis. The median time to progression was 147.0 ± 23.4 months for the sample as a whole. Univariate analysis showed that PFS was not affected by patients’ age, sex, or tumor length (Table 2). A log-rank test further revealed a significant difference in the PFS between the TR and STR groups (P = .002). Overall, 9 of 111 patients with TR suffered recurrence or death, with the mean time to PFS being 185.2 ± 14.2 months. On the contrary, progression of the disease was observed in 27 (46.6%) patients with STR, with a mean time to PFS being 129.3 ± 16.0 months (Fig. 2). There was also a significant difference in PFS according to histological type (P = .000). Specifically, patients who were classified as papillary

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### Table 1

**Characteristics of classical ependymoma patients.**

| Variable                        | N (%)       |
|---------------------------------|-------------|
| Number of patients              | 169         |
| Age, mean ± SD, y <18           | 39 (23.1)   |
| ≥18                             | 130 (76.9)  |
| Sex                             |             |
| Male                            | 90 (54.2)   |
| Female                          | 76 (45.8)   |
| Tumor length in MRI<3 level     | 47 (32.2)   |
| ≥3 level                        | 99 (67.8)   |
| Pathology classification Cellular | 53 (67.1)   |
| Papillary                       | 6 (7.6)     |
| Clear cell                      | 3 (3.8)     |
| Tanyctyc                        | 15 (19.0)   |
| Giant cell                      | 2 (2.5)     |
| Surgery                         |             |
| TR                              | 111 (65.7)  |
| STR                             | 52 (30.8)   |
| Biopsy                          | 6 (3.8)     |
| Adjuvant therapy                |             |
| Radiotherapy                    | 66 (39.1)   |
| Chemotherapy<3 level            | 9 (5.3)     |
| Follow-up, mean ± SD, mo        | 64.2 ± 51.5 |
| Recurrence                      | 31 (18.3)   |
| Death                           | 17 (10.1)   |

*Three cases did not reference the data.

†These 22 cases reported the tumor location, but not tumor length.

‡Only 79 cases were available for further analysis.

§All patients who underwent chemotherapy also underwent radiation.

### Table 2

**K-M and Cox regression analysis of PFS in classical ependymoma patients.**

| Variable                        | K-M analysis | Cox regression analysis |
|---------------------------------|--------------|-------------------------|
|                                 | Mean, mo     | SD                      | P          | HR   | 95% CI        | P          |
| Age, y                          |              |                         | .326 .2856 | (0.391–20.919) | .301 |
| <18                             | 182.5        | 24.2                    | .580 .9055 | (0.338–2.113) | .818 |
| ≥18                             | 161.8        | 17.4                    | .711       |       |               |            |
| Sex                             |              |                         | .510 .7974 | (0.338–2.113) | .172 |
| Male                            | 172.6        | 18.8                    | .580 .9055 | (0.338–2.113) | .818 |
| Female                          | 125.6        | 9.8                     | .711       |       |               |            |
| Tumor length<3 level            | 200.8        | 31.9                    | .011 .1285 | (0.483–3.272) | .639 |
| ≥3 level                        | 171.9        | 18.5                    | .011 .1285 | (0.483–3.272) | .639 |
| Pathology subtype               |              |                         | .000       |       |               |            |
| Cellular                        | 98.3         | 16.3                    | .027 (0.001–0.521) | .017 |
| Papillary                       | 194.4        | 33.2                    | .002 (0.000–0.073) | .001 |
| Clear cell                      | 34.0         | 0.0                     | .010 (0.000–0.218) | .003 |
| Tanyctyc                        | 93.3         | 7.0                     | .010 (0.000–0.218) | .003 |
| Giant cell                      | 5.3          | 2.7                     | .010 (0.000–0.218) | .003 |
| Surgery                         |              |                         | .011 .1285 | (0.483–3.272) | .639 |
| TR                              | 185.2        | 14.2                    | .011 .1285 | (0.483–3.272) | .639 |
| STR and biopsy                  | 132.2        | 15.6                    | .011 .1285 | (0.483–3.272) | .639 |
| Adjuvant therapy                |              |                         | .000       |       |               |            |
| None                            | 225.7        | 19.7                    | .056 (0.233–1.846) | .424 |
| Done                            | 119.6        | 14.3                    | .056 (0.233–1.846) | .424 |

95% CI = 95% confidence interval, HR = hazard ratio, STR = subtotal resection, TR = total resection.

*Overall P value of model coefficients test is .000.

§As coefficients did not converge, no further models will be fitted in the multivariate analysis.
type had a longer progression-free time (mean 194.4 ± 33.2 months) than the other subtypes. When classified by adjuvant therapy, RT patients had a shorter progression-free time than SA, with a mean of 119.6 ± 14.3 months (P = .000, Table 2). Further analysis stratified by extent of surgery could not change this trend in neither TR nor STR group (P = .020). A multivariate Cox proportional hazards model for PFS was fitted using the following variables: age, sex, pathology subtype, extent of surgery, and adjuvant therapy. The results suggested that pathology type was independently associated with PFS (P = .016, Fig. 4, Table 2). Patients who had cellular, papillary, or tanycytic subtypes had lower risks of progression than those who possessed the clear cell type (HR = 0.027, 95% CI 0.001–0.521; HR = 0.002, 95% CI 0.000–0.073; HR = 0.010, 95% CI 0.000–0.218; HR = 0.142, 95% CI 0.005–3.923, respectively).

3.4. OS

Traditionally, improvement in OS is the gold standard for definitively demonstrating clinical benefit of the cancer therapy in a clinical trial. In our analysis, a total of 17 cases (8.7%) were deceased, mainly due to tumor metastasis (15 cases). The mean survival time was 229.7 ± 14.5 months. The 2 remaining cases were pronounced dead due to heart failure and high level of paralysis, respectively. The OS analysis was not performed on histological type, due to the unavailability of papillary and clear cell type data. Similar to the results of the PFS analysis, univariate analysis showed that neither age nor sex had significant effects on OS (Table 3). The 5-year OS rate of the STR group was 13.8%, which was significantly lower than 2.7% observed in TR group (mean time to OS 200.0 ± 20.7 vs 215.3 ± 4.4, P = .004, Fig. 5). RT did not improve OS compared with SA (mean time to OS 190.8 ± 23.8 vs 264.6 ± 7.5, respectively, P = .007, Fig. 6). Tumor length, surgery extension, and adjuvant therapy were included in Cox regression model, of which none had a statistical effect on OS (P = .196, Table 3).

4. Discussion

Intramedullary tumors are rare, with limited existing information regarding its prognostic factors. Thus, we conducted a comprehensive literature review and integrative analysis to clarify the correlation between potential predictors and outcomes. Here, we performed the first integrative study that specifically evaluated subjects with CEs. A total of 169 cases were included in our investigation, with a mean follow-up time of 64.2 months. We confirmed histological subtype as an independently prognostic indicator of CEs. We also found a substantially better outcome for patients who underwent TR compared with STR or biopsy. Further, we observed that SA was associated with a significant improvement in survival.

Some studies have demonstrated the influence of age on survival outcomes in patients with spinal ependymomas. In a previous analysis of the SEER database, Lin et al[14] demonstrated that younger age was associated with improved long-term survival (P = .01). Alshaya et al[11] similarly performed an autopsy case study and literature review of classic low-grade ependymoma, describing that younger age was the only risk factors for patients with TR of the lesion. Both of the 2 studies had a small sample size. The former was only conducted in 1 database, and the later restricted subjects with metastasis. Conversely, we held a comprehensive data retrieval in Pubmed,
OVID, and EMBase. Our research here suggested neither PFS nor OS was impacted by age, sex, or tumor length.

Although some studies have suggested histological grading as a significant predictor of survival, the prognostic value of pathological evidence in ependymomas has been questioned.\[54–56\] Waldron et al\[57\] undertook a review of 59 spinal ependymoma subjects, where they concluded that tumor grade was the major prognostic factor. However, Safaee et al\[8\] and Vera-Bolanos et al\[17\] concluded that there was no difference between patients with grades I and II tumors ($P = .708$, $P = .19$, respectively). The association between grade III histology and survival, on the contrary, remained significant in a multivariate model ($P = .008$, $P = .003$, respectively). In this study, histological subtype was significantly linked to tumor progression both in univariate and multivariate analysis ($P = .000$, $P = .007$, respectively). The papillary ependymoma, generally a slow growing tumor, had the longest time to progression (mean 194.4 ± 33.2 months), which implied that other classifications might have higher invasiveness. Hence, a specific subtype of patients with CEs should be confirmed in clinical practice.

In accordance with previous studies,\[6–8,10\] the extent of surgery was also considered as an indicator in our research. The 5-year mortality in the TR group was 2.7%, while 13.8% patients were deceased in the STR group. In the study by Schick et al\[9\] of 25 cases, 5 recurrent ependymomas were detected even after STR. Bostrom et al\[10\] found that complete resection was associated with improvement in the survival of spinal cord ependymomas. In general, most evidence points to the recommendation of maximally safe resection as the first-line of treatment for CEs.

The role of adjuvant radiation therapy in the treatment of CEs has remained controversial.\[20,58–60\] Wahab et al\[61\] reviewed 22 cases of spinal ependymomas who received radiation. They discovered that postoperative radiation after STR is safe and prolonged patient survival. On the contrary, a population-based investigation using the SEER database conducted by Amirian

### Table 3
K-M and Cox regression analysis of OS in classical ependymoma patients.

| Variable          | K-M analysis | Cox regression analysis |
|-------------------|--------------|------------------------|
|                   | Mean, mo     | SD                     | HR  | 95% CI       | P  |
| Age, y            |              |                        |     |              |    |
| <18               | 237.5        | 22.9                   | .429|              |    |
| ≥18               | 234.1        | 12.5                   | .853|              |    |
| Sex               |              |                        |     |              |    |
| Male              | 236.4        | 12.9                   | .240| 0.314        | .276|
| Female            | 156.4        | 9.5                    | .233| 0.690        | .679|
| Tumor length      |              |                        |     |              |    |
| <3 level          | 270.0        | 5.9                    | .240| 0.314        | .276|
| ≥3 level          | 233.3        | 18.7                   | .004| 0.119–3.977  | .679|
| Surgery           |              |                        |     |              |    |
| TR                | 215.3        | 4.4                    | .007| 0.383        | .276|
| STR and biopsy    | 200.0        | 20.7                   |     |              |    |
| Adjuvant therapy  |              |                        |     |              |    |
| None              | 264.5        | 7.5                    |     |              |    |
| Done              | 130.8        | 23.8                   |     |              |    |

95% CI = 95% confidence interval, HR = hazard ratio, STR = subtotal resection, TR = total resection.

*Overall $P$ value of model coefficients test is .196.
et al.\(^{[21]}\) revealed that RT in adults was detrimental to survival (univariate HR=2.13, 95% CI 1.72–2.65; multivariate model HR=1.22, 95% CI 0.97–1.56). Alternatively, the univariate analysis of the study herein showed that CE patients who underwent adjuvant therapy demonstrated improved 5-year mortality. However, the multivariate analysis could not verify this result, leading us to believe that there were other confounding factors affecting the results of the univariate model. Regarding RT, a relationship could not be judged from the result due to the fact that patients who experienced adjuvant radiation may have had a worse baseline compared with the others. Most of those RT patients (61%) had the neoplasm invading surrounding tissue and thus received STR. Seventy-three percent of RT patients had large tumor (≥3 level), which increases the potential risk of recurrence and metastasis of postoperation. Further clinical data are needed to investigate these findings in the future.

Some inherent limitations were inevitable due to the nature of the study. First, all the literature included were retrospective studies simply due to the lack of prospective studies in the literature. Nonrandomized intervention and observational analysis of original papers may have also caused a higher risk of bias. Second, as no individual data were available, integrated studies with large samples were not included in our research leading to a selection bias. Moreover, the deficit of clinical data restricted our interpretation of the results to a certain degree, for example, the standard of neurological function evaluation in each study was different. In addition, the span of time among the original studies was around 40 years, which led to heterogeneity of surgical methods and, subsequently, outcome assessments.

5. Conclusion

Ependymomas are the most common primary intramedullary spinal cord tumor, of which more than half were CE. Lots of reports generally investigated ependymoma based on WHO grade, but few focus on the CE, that is, WHO grade 2, alone. It would be beneficial to predict prognostic of patients with CE that making the pathological subtype clear in the clinical work. Specifically, papillary type was associated with prolonged PFS and OS. TR was recommended as the first goal of surgery, while adjuvant therapy could not improve outcomes after neither TR nor STR. Above all, definite histological type and safely TR were foundation of CE’s management. More experimental studies with control group should be performed in this issue.

6. Ethics statement

Study participants voluntarily agreed to participate in the study and provided written informed consent before enrollment. The study was approved by the Ethics Committee of Union Hospital Affiliated to Fujian Medical University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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