Outcomes following myxopapillary ependymoma resection: the importance of capsule integrity

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OBJECT While extent of resection has been shown to correlate with outcomes after myxopapillary ependymoma (MPE) resection, the effect of capsular violation has not been well studied. The role of adjuvant radiation also remains controversial. In this paper the authors' goals were to evaluate outcomes following resection of MPE based on intraoperative capsular violation and to explore the role of adjuvant radiotherapy in cases of capsular violation.

METHODS A retrospective review of patients undergoing resection of MPE at 2 academic institutions between 1990 and 2013 was performed. Cases with dissemination at presentation, less than 12 months of follow-up, or incomplete records were excluded. Extent of resection was defined as en bloc if all visible tumor was removed without capsular violation, gross-total resection (GTR) if all visible tumor was removed, but with capsular violation, and subtotal resection (STR) if a known residual was left at the time of surgery. Postoperative MR images were reviewed to confirm the extent of resection. Primary outcomes were progression-free survival (PFS) and overall recurrence rates. The effects of extent of resection, capsular violation, and adjuvant radiotherapy on recurrence rates and PFS were analyzed using Kaplan-Meier statistics. Associations between recurrence and preoperative variables were evaluated using Fisher exact methods and t-tests where appropriate.

RESULTS Of the 107 patients reviewed, 58 patients (53% were male) met inclusion criteria. The mean age at surgery was 40.8 years (range 7–68 years). The median follow-up was 51.5 months (range 12–243 months). Extent of resection was defined as en bloc in 46.5% (n = 27), GTR in 34.5% (n = 20), and STR in 18.9% (n = 11). No recurrences were noted in the en bloc group, compared with 15% (n = 3) and 45% (n = 5) in the GTR and STR groups. En bloc resection was achieved most frequently in tumors involving the conus. Twelve patients (20%) underwent adjuvant radiotherapy following either STR or GTR. The overall recurrence rate was 13.8% (n = 8), and the 5-year PFS was 81%. Capsular violation was associated with a higher recurrence rate (p = 0.005). Adjuvant radiotherapy showed a nonsignificant trend of lower recurrence rates (16.7% vs 31.6%, p = 0.43) and longer PFS at 5 years (83.3% vs 49.9%, p = 0.16) in cases of capsular violation.

CONCLUSIONS A strong correlation between capsular violation and recurrence was found following removal of MPE and should be assessed when defining extent of resection in future studies. Although the use of adjuvant radiotherapy in cases of capsular violation showed a trend toward improved PFS, further investigation is needed to establish its role as salvage therapy also appears to be effective at halting disease progression.

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KEY WORDS myxopapillary ependymoma; surgery; capsule; radiation therapy; tumor recurrence

ABBREVIATIONS GTR = gross-total resection; MPE = myxopapillary ependymoma; PFS = progression-free survival; STR = subtotal resection.

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MYXOPAPILLARY ependymoma (MPE) was first described by Kernohan in 1932.¹³ Histologically, the WHO classified MPE as a Grade I ependymoma,¹⁴ a distinct tumor from Grade II (ependymoma) and III (anaplastic) tumors as it compresses rather than infiltrates normal adjacent tissue.¹¹ The majority of MPEs occur in the lumbosacral spine and involve the conus medullaris and/or cauda equina.^{11,16} Despite being classified as a benign tumor (Grade I), MPE can locally invade and recur in up to 41% of patients, especially following incomplete resection.²⁰ Even with complete resection, capsular violation can result in CSF tumor dissemination and lead to spinal, intracranial, and systemic metastases.^{5,7,8,15,17,22} MPEs have a male predominance, most commonly presenting in the 3rd or 4th decade of life and often preceded by a 6- to 24-month history of low-back pain; bladder dysfunction; and motor, sensory, and gait abnormalities.^{2,4,9} Magnetic resonance imaging remains the preferred modality to diagnose MPE, as it identifies the tumor and its relation to the surrounding soft tissues and the cauda equina. It also helps detect leptomeningeal spread along the spinal axis.⁴

Because of the rarity of these tumors, there are no definitive therapeutic guidelines for treating MPE. Nevertheless, surgery is widely regarded as first-line treatment with a primary goal of achieving complete tumor resection. Complete resection without capsular violation—the so-called marginal en bloc resection—can be curative, and is often simply accomplished by snipping the filum above and below the mass. Nevertheless, this technique can be technically difficult in a given tumor based on tumor size, shape, and anatomical relation to the cauda equina or spinal cord. Most series simply report gross-total resection (GTR) and subtotal resection (STR) or biopsy; however, we felt that GTR and en bloc resections may carry different prognoses. Additionally, in some series, adjuvant radiotherapy has been used following partially resected tumors as an additional means to control the spread of the tumor cells. Despite these opinions, some authors report favorable outcomes in the management of MPE using surgery alone. In this study, we share our multicenter experience of 58 MPE patients treated either with surgery alone or with surgery and adjuvant radiotherapy, specifically noting the surgical approach and factors predicting the resectability of the lesions.

Methods

The study involved patients with histologically confirmed MPE (WHO Grade I ependymoma) treated at Mayo Clinic Rochester and Johns Hopkins University between 1990 and 2013. Following institutional review board approval, a retrospective review of 107 patients was conducted. Patients of all ages were included, and the minimum follow-up was set at 1 year. Patients who presented with evidence of tumor dissemination or who had incomplete medical records were excluded from the study.

Records were reviewed for baseline characteristics including age, sex, length of follow-up, size, and location. Tumor size was recorded as the largest diameter measured on imaging. Tumor location was classified based on prox-

TABLE 1. Definitions for extent of resection

Extent of Resection	Definition
En bloc	Complete tumor removal by inspection under the operative microscope w/o capsular violation & absence of nodular enhancement on postop MRI
GTR	Complete removal, however, w/ capsular violation & no nodular enhancement on postop MRI
STR	Visible tumor remnant at the time of op &/or nodular enhancement noted on postop MRI

imity to the conus. Tumors above L-1 were classified as involving the thoracolumbar cord. Those arising at L1–2 were considered as arising from the conus, and those at L-3 or lower were considered to be arising from the cauda equina. All patients underwent surgery with the intent of complete resection without capsular violation. Patients were subgrouped as having undergone en bloc resection, GTR, or STR as determined by operative impression and review of postoperative images by an independent radiologist (Table 1). No patient who underwent en bloc resection received adjuvant radiotherapy. Patients who had either a GTR or STR were referred to radiation oncology for consideration of radiotherapy. The decision to treat was made on an individual patient basis. Adjuvant radiotherapy was initiated within 6 months of initial surgery and before radiographic evidence of recurrence. Primary outcome measures were progression-free survival (PFS) and overall recurrence rates. Survival time was defined from the date of surgery to local or distant recurrence on imaging or from surgery to last follow-up in those without evidence of recurrence. Recurrence was defined as either documented growth of known residual tumor in cases of STR or by new nodular enhancement in en bloc resection or GTR cases as documented by postoperative MRI. Complications after surgery were also recorded.

Preoperative variables were compared between those undergoing en bloc resection and those with either GTR or STR using chi-square or Fisher exact tests when appropriate for categorical variables and t-tests for continuous variables, respectively. PFS curves were determined using Kaplan-Meier estimates. Log-rank statistics were used to assess the effect of extent of resection and adjuvant radiotherapy on PFS. Fisher exact methods and t-tests were used to assess for additional correlations between preoperative characteristics and recurrence. Statistical analysis was performed using JMP software (version 10.0, SAS Institute Inc.).

Results

Of the initial 107 patients who were available for the study, 58 met the inclusion criteria. Of the excluded patients (n = 49), 34 did not have more than 12 months of follow-up, 14 had evidence of dissemination at time of presentation, and 1 patient was excluded due to incomplete medical records. The mean age at presentation was 40.8

TABLE 2. Comparison of baseline characteristics in cases with and without capsular violation

Variable	No Capsular Violation (n = 27)	Capsular Violation (n = 31)*	p Value
Mean age in yrs (SD)	42.9 (15.7)	38.9 (16.6)	0.35
Sex, no. (%)			0.45
Male	13 (48.2)	18 (41.9)	
Female	14 (51.8)	13 (58.1)	
Mean follow-up in mos (SD)	61.3 (44.6)	77.1 (62)	0.28
Mean size in cm (SD)	2.6 (1.5)	3.1 (2.0)	0.32
Location, no. (%)			0.01
Above L-1	8 (29.6)	5 (16.1)	
Conus	13 (48.1)	5 (16.1)	
CE	6 (22.2)	21 (67.7)	

CE = cauda equina.

* Includes both GTR and STR.

years (range 7–68 years). The majority of the cohort comprised males (53%). Median follow-up was 51.5 months (range 12–243 months). Data on tumor size were available for 45 patients. Median tumor size was 2.5 cm (range 0.2–10.6 cm). The majority of MPEs were located in the cauda equina region (50.0%) followed by the conus (31.0%). The tumor was above the conus in 19.0%. The extent of resection was defined as en bloc in 46.5% (n = 27), GTR in 34.5% (n = 20), and STR in 19.0% (n = 11). Twelve patients (38.7%) with capsular violation (GTR or STR) received adjuvant radiation therapy (median dose 50.4 Gy [range 41.4–54 Gy]). Baseline differences according to capsular violation are shown in Table 2. No differences were found with respect to age or sex between those who underwent an en bloc resection and those who underwent GTR or STR. The median length of follow-up was similar between groups (54 vs 50 months for non-en bloc and en bloc). There was a trend toward a larger size in cases of capsular violation (3.1 vs 2.6 cm, $p = 0.3$) and propensity to involve the cauda equina (67.7% vs 22.2%, $p = 0.01$).

The overall recurrence rate was 13.7% (n = 8). The overall PFS survival was 81% at 5 years (Fig. 1). Median

FIG. 1. Overall PFS. Kaplan-Meier curve showing the overall PFS in 58 patients undergoing surgery for MPE. The 5-year PFS was 81%.

time to recurrence was 32 months (range 3–53 months). Seven of the 8 recurrences occurred locally, whereas 1 patient had leptomeningeal spread following STR without radiation therapy. The majority of recurrences were treated with repeat surgery (n = 6); only 2 patients had salvage radiation therapy. Further details regarding patterns of failure and salvage therapy are given in Table 3. The majority of patients at last follow-up had no evidence of disease (n = 46) or evidence of progression (n = 11). No deaths were seen at a mean follow-up of 69.5 months.

No recurrences were noted in patients who underwent en bloc resection compared with 25.8% of patients with capsular violation ($p = 0.005$). A trend toward a higher recurrence rate was noted in patients who had an STR compared with those who underwent GTR (45.5% vs 15.0%, $p = 0.09$). Overall PFS at 5 years was higher in en bloc cases than in GTR/STR cases (100% vs 65%, $p = 0.005$) (Fig. 2). A trend toward a longer PFS at 5 years was noted after GTR compared with STR (78.4% vs 38.9%, $p = 0.06$). Lower recurrence rates (16.7% vs 31.6%, $p = 0.43$) and longer PFS at 5 years (83.3% vs 49.9%, $p = 0.16$) were seen in patients who received adjuvant radiotherapy (Fig. 3). Four of 6 patients who underwent STR without additional adjuvant radiotherapy eventually experienced a recurrence compared with 2 of 13 patients who underwent GTR ($p = 0.05$). In contrast, only 1 of 7 patients following GTR and 1 of 5 patients following STR who underwent adjuvant radiotherapy experienced a recurrence.

Review of preoperative variables demonstrated no statistically significant correlations between recurrence and age or tumor size. No recurrences were noted in patients (n = 18) who had tumors involving primarily the conus ($p = 0.04$). Two patients in this subgroup underwent adjuvant radiation therapy after GTR. The extent of resection in this subgroup was defined as en bloc in 13 patients and GTR in 5 patients. No recurrences were seen in the 6 pediatric patients (age < 18 years) in this cohort. Of note, all pediatric patients who did not undergo en bloc resection received adjuvant radiotherapy (n = 4). A nonsignificant trend toward higher recurrence rates was seen in males than in females (22.6% of males vs 3.7% of females, $p = 0.06$). Refer to Table 4 for further details regarding variables associated with recurrence.

Postoperative complications were observed in 8 patients, the majority of which were wound related. Two patients had wound infections that were treated with debridement and intravenous antibiotics. Two patients developed asymptomatic pseudomeningoceles that did not require revision, and 1 patient required repair of a CSF leak. One patient developed a deep venous thrombosis and another patient developed aseptic meningitis. One patient experienced permanent bladder dysfunction after GTR of tumor involving the conus. No statistically significant correlations were found between postoperative complications and extent of resection (4.2% in en bloc vs 22% in non-en bloc, $p = 0.12$) or tumor location ($p = 0.19$).

Discussion

A variety of biological and tumor-specific factors affecting posttreatment tumor progression in MPE have

TABLE 3. Patterns of failure following primary surgical treatment

Age (yrs), Sex	Region	EOR	Adjuvant RT	Site of Recurrence	PFS (mos)	Salvage Therapy	Status at Last Follow-Up
46, M	CE	STR	Yes	Local	28	RT (45 Gy)	NEP at 98 mos
24, F	CE	STR	No	Local	51	Op	NEP at 56 mos
19, M	CE	STR	No	Local	36	Op	NEP at 184 mos
53, M	TC	GTR	No	Local	44	Op	NEP at 153 mos
58, M	CE	STR	No	Local	11	Op	AWD at 106 mos
59, M	CE	STR	No	CSF spread	12	Chemo/RT (54 Gy)	NEP at 119 mos
61, M	CE	GTR	No	Local	3	Op	NEP at 109 mos
35, M	CE	GTR	Yes	Local	36	Op	NEP at 40 mos

AWD = alive with disease; Chemo = chemotherapy; EOR = extent of resection; NEP = no evidence of progression; RT = radiotherapy; TC = thoracic cord.

been studied. Age at diagnosis, tumor location, duration of clinical history, and histological findings have all been linked to PFS and overall survival of ependymomas.^{2,18,19} The strongest predictor of PFS in MPE, however, is negative surgical margins obtained at the initial resection.^{8,14} In our study, we sought to examine the effect of extent of resection, and more specifically, the effect of capsular violation on recurrence. No recurrences were observed in patients who underwent complete tumor removal without capsular violation. Additionally, a strong trend toward longer PFS was observed in patients who underwent GTR compared with STR (78.4% vs 38.9% at 5 years, $p = 0.06$). This trend became even more prominent when considering patients who underwent GTR compared with STR and did not receive adjuvant radiotherapy (73% vs 0% 5-year PFS, $p = 0.07$). Other series have also demonstrated a correlation between recurrence rates and extent of resection. Feldman et al. systemically reviewed 475 patients with MPE. The total recurrence rate was 15.5% in 232 patients who underwent complete resection, compared with 32.6% in 135 patients who underwent partial resection.⁹ Though not exclusively MPEs, in 31 cases of spinal ependymomas Chang et al. also found a correlation between extent of resection and PFS.⁶ Neither of these studies, however, differentiated between gross-total removal with capsular

violation (en bloc) and GTR. As en bloc resection theoretically precludes tumor spillage and microscopic residuals, it therefore may reduce or eliminate tumor progression. This concept has been previously explored by Nakamura et al., who studied 15 MPE patients who underwent complete resection.¹⁵ Six patients had their tumor resected completely with a deliberate attempt to not violate the capsule (en bloc) and 9 had piecemeal resections with adjuvant radiotherapy. Interestingly, no recurrences were noted in those undergoing piecemeal resection with adjuvant radiotherapy, whereas the only observed recurrence occurred in an attempted en bloc removal in which the authors felt the capsule was violated and the patient did not receive subsequent adjuvant radiotherapy. This case is not fully explained in the paper, but this statement would have resulted in the patient being included in our GTR category due to capsular violation, not the en bloc subset. In our study, 3 patients who underwent GTR and 5 patients who underwent STR eventually experienced a recurrence. While the small numbers in this study preclude making definitive conclusions, our data suggest that capsular violation, in addition to extent of resection, may be predictive of recurrence.

MPE is a unique intradural tumor as many arise solely

FIG. 2. Influence of extent of resection on PFS. Kaplan-Meier curve showing the PFS in patients who had an en bloc (red) compared with those who had a GTR (green) or STR (blue). The 5-year PFS was 100%, 78%, and 49%, respectively ($p = 0.002$).

FIG. 3. Influence of adjuvant radiation therapy on PFS in cases with capsular violation. Kaplan-Meier curve showing the PFS in patients who had either a GTR or STR grouped by those who received adjuvant therapy (blue) and those who did not (red). The 5-year PFS was higher in those who received adjuvant radiation therapy (83% vs 50%, $p = 0.16$).

TABLE 4. Associations with recurrence in 58 patients undergoing MPE removal

Variable	No Recurrence	Recurrence	p Value
Age in yrs			
Mean	40.2 (2.3)	44.4 (5.8)	0.50
Pediatric, no. (%)	6 (10.3)	0 (0)	0.58
Adult, no. (%)	44 (75.9)	8 (13.8)	
Sex, no. (%)			0.06
Female	26 (44.8)	1 (1.7)	
Male	24 (41.4)	7 (12.1)	
Tumor location, no. (%)			0.06
CE	22 (37.9)	7 (12.1)	
Conus	18 (31.0)	0 (0)	
Above L-1	10 (17.2)	1 (1.7)	
Mean tumor size in cm (SE)	2.9 (0.3)	2.6 (0.7)	0.71
Extent of resection			0.001
En bloc	27 (46.6)	0	
GTR	17 (29.3)	3 (5.2)	
STR	6 (10.3)	5 (8.6)	
Capsular violation			0.005
No	27 (46.6)	0 (0)	
Yes (GTR/STR)	23 (39.7)	8 (13.8)	
Adjuvant radiation*			0.43
Yes	10 (32.3)	2 (3.4)	
No	13 (41.9)	6 (10.3)	

* Cases with capsular violation (n = 31).

from the filum; thus, an en bloc resection may be as simple as cutting the filum above and below the tumor, and lifting it out without violating the capsule. However, as the present series demonstrates, MPE can also be found higher up in the spinal cord and vary with respect to size and intimacy with surrounding neurological structures. Therefore, en bloc resection may not always be feasible. Interestingly, we found that the tumors arising from the conus were more likely to be amenable to en bloc resection and GTR than tumors arising primarily below or above the conus. We also found that capsular violation was much more common in tumors involving the cauda equina (67.7% vs 22.2%, $p = 0.01$). A trend was also found between larger tumor size and capsular violation, though not significantly ($p = 0.32$). No association was found between the development of a postoperative complication and the extent of resection. While this study is likely not adequately powered to detect differences, the qualitative findings do suggest that tumor size and location partially dictate the extent of resection that is achievable. Regardless, it is our opinion that meticulous measures should be taken to avoid tumor spillage and dissemination at the time of surgery. For example, it has been the practice of the senior author and colleagues at the Johns Hopkins University to barricade the proximal and distal canal with Gelfoam and cottonoids prior to tumor removal. If capsular violation is unavoidable due to size and/or poorly defined margins or preexisting dissemination, the operative strategy should shift from en bloc resection to maximal safe resection. In these cases, we find it helpful to divide the operative field into smaller subsections with cottonoids and work from superior to in-

ferior to remove as much tumor as possible under the operative microscope. Tumor that cannot be safely dissected from roots or the cord is amputated and further debulked to leave as small of a remnant as possible. An ultrasonic aspirator can be a useful adjunct for debulking to avoid further tumor spillage. Once we have cleared one section of all removable tumor, we move down to the next section. We will repeat these maneuvers 1 or 2 more times to remove as much of the tumor as possible without causing neurological injury. Further studies which correlate preoperative imaging features (specifically tumor size and proximity to the conus) would be useful in defining which tumors are amenable to en bloc removal.

The role of adjuvant radiation therapy remains controversial in MPE. Some authors did not find a beneficial role for radiotherapy regardless of extent of resection,⁹ while others successfully used adjuvant radiotherapy to reduce the rate of tumor progression.^{2,5,15} In the large systematic analysis by Feldman et al., radiotherapy did not improve the overall tumor recurrence regardless of the extent of resection.⁹ In our study, no patient with an en bloc resection underwent adjuvant radiotherapy. Of those with capsular violation (GTR or STR), we did find a trend of lower recurrence rates (16.7% vs 31.6%, $p = 0.43$) and longer PFS at 5 years (83.3% vs 49.9%, $p = 0.16$) in patients who received adjuvant radiotherapy. A higher risk of recurrence was seen after STR than after GTR when no adjuvant radiotherapy was administered (66% vs 15%, $p = 0.05$). Despite these trends, salvage therapy also appeared to be effective at preventing further disease progression. More recently, Tsai et al. reported improved local control in patients who underwent radiation after an STR, but no difference in patients who underwent a GTR. Of note, patients were not further stratified on the basis of capsular violation.²¹ While both our experience and that of Tsai et al. noted improved PFS with adjuvant radiotherapy, especially in the case of GTR with capsular penetration, we currently recommend careful observation and initiation of radiotherapy at the time of salvage as this approach does not appear to compromise overall survival in our series, and there is a paucity of evidence demonstrating a survival advantage of adjuvant over salvage radiotherapy. Furthermore, our study does not explore potential toxicities of radiation treatment, which may further influence the decision to defer radiotherapy until progression. Larger studies are needed both to confirm the findings in this study and to compare the difference in outcomes between salvage and adjuvant radiotherapy.

MPE may be a more aggressive tumor in children; the systematic review performed by Feldman et al. compared 43 children with MPE (mean age 11 years) who shared the same treatment paradigm with 432 adults (mean age 37.8 years) and found that the overall recurrence rate was significantly higher in the pediatric population (40.5% vs 23.4%; $p = 0.02$).⁹ Chan et al. found that 3 of 5 children treated with surgery alone had intracranial metastasis.⁵ Despite being aggressive, there is more evidence in pediatric patients that surgery and adjuvant radiotherapy is more beneficial than surgery alone for treating MPE.^{1,3,4,7,10,12} In a pediatric population of 15 children with MPE from the Johns Hopkins Hospital, the local control rate at 5 and 10

years was 62.5% and 30%, respectively, for the group undergoing surgery alone and 100% at both time points for the group receiving surgery and adjuvant radiotherapy ($p = 0.04$).¹ Finally, Al-Halabi et al. treated 7 children with MPE with a median of 78 months of follow-up.³ Resection and adjuvant radiotherapy were performed in 4 patients; 3 of these patients remained disease-free compared with 2 of 3 patients with GTR alone who experienced disease recurrence. Only 6 pediatric cases were available for analysis in the present series. Of note, they were more likely to undergo a non-en bloc resection ($n = 4$). Adjuvant radiotherapy was administered in all cases and no recurrences were seen, which suggests a potential role for adjuvant radiotherapy in this subset. However, the small number of pediatric cases precludes any conclusions regarding the role of adjuvant therapy in this subset.

As with many retrospective series on rare diseases, this study is prone to bias. Foremost, as this tumor is fairly rare, we were only able to find 58 cases over a 20-year timespan at 2 large tertiary referral centers that met our inclusion criteria. The large timespan and multicenter nature increase the variability of technique and management paradigm of these patients, particularly regarding the role of adjuvant therapy. Additionally, only 8 recurrences were observed, which further limits both statistical power of the study and the type of analyses that can be performed in assessing for risk factors for recurrence and independence. For example, as tumor size and location partially dictate feasibility of en bloc resection, ideally they should be included in multivariate analysis or in a matched cohort. This study was underpowered for this type of analysis. Therefore, the trends found with the predictive variables examined in this study may reflect codependence. This study, however, does add further information to the literature on outcomes after MPE and shows some important trends that warrant further investigation. Capsular violation strongly correlated with recurrence. Thus, future analysis should include capsular violation when defining the extent of resection. This study also suggests that certain patients may benefit from upfront adjuvant radiotherapy as evidenced by the absence of recurrence in pediatric patients who were more likely to undergo non-en bloc resection and lower recurrence rates in patients who received adjuvant radiotherapy after STR.

Conclusions

The overall recurrence rate in cases of nondisseminated MPE is fairly low (13.8%) and seems to correlate with extent of resection. While the present series suggests an additional benefit in PFS in cases without capsular violation, further investigation is needed to affirm this finding. Adjuvant therapy should be considered in cases of subtotal resection and in patients at higher risk for recurrence. However, the decision to treat should be made on an individual basis as salvage therapy (surgery or radiotherapy at the time of recurrence) also appears to be effective, and the effect on long-term survival of adjuvant therapy is not currently known.

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