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Management of Pediatric Myxopapillary Ependymoma: The Role of Adjuvant Radiation

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Abstract

Introduction—Myxopapillary ependymoma (MPE) is a rare tumor in children. The primary treatment is gross total resection (GTR), with no clearly defined role for adjuvant radiation therapy (RT). Published reports, however, suggest that children with MPE present with a more aggressive disease course. The goal of this study was to assess the role of adjuvant RT in pediatric patients with MPE.

Methods—Sixteen patients with MPE seen at Johns Hopkins Hospital (JHH) between November 1984 and December 2010 were retrospectively reviewed. Fifteen of the patients were evaluable with a mean age of 16.8 years (range, 12–21 years). Kaplan-Meier curves and descriptive statistics were used for analysis.

Results—All patients received surgery as the initial treatment modality. Surgery consisted of either a GTR or a subtotal resection (STR). The median dose of adjuvant RT was 50.4 Gy (range, 45–54 Gy). All patients receiving RT were treated at the involved site. After a median follow-up of 7.2 years (range, 0.75–26.4 years), all patients were alive with stable disease. Local control at 5 and 10 years was 62.5% and 30%, respectively, for surgery alone versus 100% at both time points for surgery and adjuvant RT. Fifty percent of the patients receiving surgery alone had local failure. All patients receiving STR alone had local failure compared to 33% of patients receiving GTR alone. One patient in the surgery and adjuvant RT group developed a distant site of recurrence 1 year from diagnosis. No late toxicity was reported at last follow-up, and neurologic symptoms either improved or remained stable following surgery with or without RT.

Conclusions—Adjuvant RT improved local control compared to surgery alone and should be considered after surgical resection in pediatric patients with MPE.

Introduction

Myxopapillary ependymomas (MPEs) were first recognized as a distinct histologic variant of ependymomas in 1932 by Kernohan (1). The designation “myxopapillary” is based on the histologic appearance of MPEs. They produce mucin and, due to their branching vasculature, form tumor cells arranged in papillae (2, 3). These ependymomas are categorized as grade 1 tumors by the World Health Organization and are considered benign tumors characterized by slow, indolent growth and a long disease course (4). MPEs typically arise in the lumbosacral spine, specifically in association with the conus medullaris, cauda equina, or filum terminale (5, 6). Rarely do these tumors arise in other sites in the spinal cord, brain, or outside the neuroaxis (7). Most patients are male, and MPEs are diagnosed in the third or fourth decade of life (5). While the exact incidence is unknown, MPE is estimated to represent 13% of ependymal tumors (6). These tumors appear to be rarer in the pediatric population than in adults. MPEs are also capable of distant spread. A recent study found that one-third of treatment failures occurred at distant sites with or without a primary site failure (7). MPEs are reported to be more aggressive in children and associated with higher incidences of intracranial and spinal dissemination (2, 4, 5, 7, 8). A study from St. Jude Children’s Research Hospital reported a higher-than-expected rate of subarachnoid dissemination at presentation that resulted in the use of craniospinal radiation therapy (RT) rather than involved field radiation in 3 of 4 pediatric patients with MPE (8). Maximal safe resection is considered the standard of care for management of MPE. Currently, there is no clearly defined role for adjuvant RT, although it has been recommended following subtotal resection (STR). Some studies have recommended adjuvant RT for all patients following surgery regardless of extent of resection (4, 7). Other studies have advocated adjuvant RT in patients receiving piecemeal gross total resection (GTR) as opposed to en bloc resections, based on the increased local recurrence rates in the former (9). In this study, we report the results of a large single institutional experience of pediatric patients with MPE treated with either surgery alone or surgery and adjuvant RT.

Methods and Materials

Patients

Between November 1984 and December 2010, 16 pediatric patients with histologically confirmed MPE treated at Johns Hopkins Hospital were retrospectively reviewed from a database approved by our institutional review board. Of these patients, 15 patients were evaluable. Data were obtained from paper charts and electronic medical records and included age at diagnosis, sex, presenting symptoms, location of disease, date and extent of surgery, RT dose and volume, imaging (myelography, MRI, CT), recurrence (local or distant), toxicity, and date of last follow-up. The mean age at diagnosis was 16.8 years (range, 12–21 years). All 15 patients were male.

Surgery

All patients in this study underwent either GTR or STR as the initial treatment modality. GTR encompassed tumors removed in both an en bloc and a piecemeal fashion. The extent

of resection was defined based on the operative note and evidence of the presence or absence of residual disease on postoperative imaging.

Radiation treatment

Seven patients received adjuvant RT following the initial surgery. The median dose of RT was 50.4 Gy (range, 45–54 Gy) delivered by external beam to the tumor bed. RT was offered following GTR if the patient had a bulky disease, nerve root or bone invasion, and/or piecemeal resections. RT was offered following STR for gross disease and neurologic symptoms. In the era of computed tomography (CT)-based planning and International Commission on Radiation Units and Measurements definitions, the gross tumor volume (GTV) was defined as residual disease, if present, based on postoperative imaging. The clinical target volume (CTV) was defined as the initial location and extent of disease based on both pre- and postoperative imaging. The planning target volume was a geometric expansion of the CTV created to account for setup error. Margin expansion for the planning target volume ranged from 0.5 mm-1 cm depending on the radiation and immobilization techniques used. Table 1 summarizes the radiation techniques.

RT toxicity was assessed by reviewing the patient's radiation treatment records for on-treatment visits and follow-up notes. Toxicity was rated based on National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Definitions of local control, progression-free survival and overall survival

Failure was defined as either local or distant (outside the tumor bed and/or the volume irradiated). Local control (LC) was defined as the time from diagnosis to first local failure. Progression-free survival (PFS) was measured from diagnosis to first recurrence of disease (ie, local or distant metastasis). Overall survival was measured from the date of diagnosis to the date of death or last follow-up.

Statistical analysis

GraphPad (GraphPad Software, Inc, La Jolla, CA) software was used to calculate survival rates based on the Kaplan-Meier method. Descriptive statistics were used for analysis when applicable. A *P* value of .05 was considered statistically significant.

Results

Surgery was the initial treatment for all patients in this study. Ten patients had GTR and 5 had STR. Four of 10 patients who had GTR received adjuvant RT compared to 3 of 5 patients who had STR. The median follow-up time was 7.2 years (range, 0.75–26.4 years), and all patients were alive with stable disease at the time of last follow-up. Table 2 summarizes the patient characteristics.

Results from this study showed a statistically significant reduction in local failure rate for patients receiving adjuvant RT following surgery ($P=.04$). Estimated LC at 5 and 10 years was 62.5% and 30%, respectively, for the group undergoing surgery (GTR and STR) alone and 100% at both time points for the group receiving surgery and adjuvant RT (Fig. 1). For

patients receiving GTR alone, the estimated 5 and 10 year LC rates were 80% and 42.5%, respectively (Fig. 2). No patients receiving GTR and adjuvant RT experienced local failure. The 2 patients who received STR alone had local failures compared to 2 of the 6 patients who received GTR alone. Overall, 4 of 8 patients who received surgery alone had local failure.

Estimated PFS rates at 5 and 10 years were 62.5% and 30%, respectively, for the group receiving surgery (GTR and STR) alone (Fig. 3). These data matched the LC rate as all failures in this cohort were local. Conversely, the estimated PFS rates for the surgery and adjuvant RT groups were 80% at 5 and 10 years. These data reflect the fact that 1 patient in the surgery and adjuvant RT group developed a distant site of recurrence 1 year from diagnosis.

Five patients (33%) in this study developed recurrence that required salvage treatment, 4 of which were local. Patients were treated according to 1 of the following modalities: 1 patient underwent salvage treatment with surgery alone, 2 patients received surgery followed by radiation, and 2 patients received RT alone. Of the 4 patients with local failures, 2 failures occurred following STR, and the other 2 failures occurred following GTR. None of the patients who developed a local failure received adjuvant RT.

Of the 5 patients who developed a recurrence, 2 patients developed a second recurrence after salvage therapy. Both of these patients were treated with RT. One patient was treated with local RT at the initial site of his tumor. He then developed a distant recurrence in the brain 5 months later and underwent salvage treatment with craniospinal irradiation (CSI) followed by stereotactic radiosurgery (SRS) boost to 2 brain lesions. The second patient was treated with a craniotomy followed by whole-brain RT and intensity modulated RT boost to the postoperative tumor bed. He also received an SRS boost to 2 additional sites of disease in the brain. He was later found to have distant metastasis to the thoracic spine 2 years later that was salvaged with RT. Both of these patients had LC of their disease at last follow-up in 2011.

Several patients developed mild, acute RT-related toxicities (Table 1). Grade 1 or 2 nausea and vomiting were experienced by 6 patients, and 1 patient developed grade 3 nausea and vomiting. Two patients reported grade 1 or 2 lower back and/or extremity pain that worsened acutely from baseline. No late toxicity was reported at last follow-up. Two patients who did not receive adjuvant radiation following surgery developed disease recurrence that required salvage treatment to larger RT fields. One patient experienced mild symptoms, while the other patient developed grade 3 nausea and vomiting requiring intravenous fluids and antiemetics. He subsequently lost 15–20 pounds and continued to experience nausea for 2 months following completion of RT. His symptoms subsequently resolved. Despite this exception, RT was well tolerated by most patients, and an excellent toxicity profile was demonstrated.

Discussion

MPE is a rare tumor in the pediatric population, and historically, the primary treatment modality has been maximal safe resection with no clearly defined role for adjuvant RT (5, 9–11). The purpose of this study was to evaluate the outcomes of pediatric patients treated at a single institution with long-term follow-up in an effort to assess the role of RT after gross total or subtotal resection.

MPE is generally regarded as a benign malignancy, compared to the more aggressive, higher grade ependymomas (grade 2) and anaplastic ependymomas (grade 3). MPE is also unique in that it presents in the lumbosacral spine and not in the posterior fossa and fourth ventricle, the usual location of grade 2 and 3 ependymomas. A possible explanation for the benign prognosis of MPEs may be due to their anatomic location rather than their histologic features (5, 10, 12). The location of MPE in the distal lumbosacral spine and cauda equina region limits its access to direct lymphatic spread and other means of dissemination (12). Although the prognosis of MPE is more favorable than that of other ependymomas, the literature suggests a more aggressive pattern of disease in younger patients. A retrospective study from the Rare Cancer Network, which represents the largest series published on spinal MPE, showed a 5-year PFS benefit in patients aged 36.9 years and older (88% vs 52%, $P=.01$) compared to that in younger patients and children (3). Another study reported more frequent multiple recurrences in younger patients (2). Bagley et al (10) found that pediatric patients had a much higher rate of local recurrence and metastases within the neuroaxis (64% vs 32%). The reason for this more aggressive disease course in children remains unclear. One possible explanation is that adults are more likely to communicate their symptoms to physicians than children and are therefore diagnosed earlier, before the disease has spread (8). While published pediatric case reports have limited patient numbers, a high rate of tumor dissemination at initial presentation has been reported (8, 13). An alternative explanation that has been suggested is that children present with more aggressive tumor biology (4). Unfortunately, no histopathologic features or the MIB-1 index have been shown to successfully predict the natural history, patterns of recurrence, or distant metastases in this group of tumors (2, 5, 10, 12).

Surgery is widely regarded as the first-line treatment for pediatric patients with MPE. This recommendation is based on the number of retrospective studies evaluating both children and adults with spinal ependymomas (5, 6, 9, 10, 14, 15). Surgical skills have improved, with modern microsurgery techniques, resulting in a greater percentage of patients being able to receive GTRs and specifically en bloc resections. MPEs are believed to be more difficult to resect given their irregular shape and contact with surrounding nerve roots, and therefore, a GTR may be associated with increased morbidity (7). Some physicians have recommended limited resection compatible with a good neurologic outcome followed by adjuvant RT in MPE patients (8). However, studies have shown improved overall and PFS rates for patients treated with GTR compared to those receiving STR (2, 5, 10). A study evaluating 77 patients with MPE found that patients receiving GTR compared to those receiving STR had increased overall survival (19 vs 14 years), decreased recurrence rates, and a reduced likelihood of sustaining or developing significant neurologic sequelae (2).

These results are consistent with our data, which indicated a reduction in the number of local failures in patients treated with GTR alone compared to those treated with STR.

A number of studies have shown the utility of adjuvant RT following STR in patients with MPE, and this treatment paradigm is widely regarded as the standard of care with little controversy (8, 15–18). One study, however, failed to demonstrate a clear role for adjuvant RT and favored aggressive surgical techniques in pediatric patients with MPE, in which the goal was to achieve GTR (5). Another study found the only prognostic factor that correlated with longer time to progression was a maximal resection (15). However, as all patients received postoperative RT, the prognostic significance of adjuvant RT could not be assessed, and it was recommended for patients who had STR or biopsy. Volpp et al (9) made a distinction between GTRs that resulted in en bloc vs piecemeal resections and recommended adjuvant RT for the latter. It should be noted that the last 2 studies included adults and all spinal ependymomas. Our study, which specifically examined MPE in children, found no recurrent disease in the 3 patients treated with STR and adjuvant RT compared to local failure in both patients treated with STR alone, further supporting the role of adjuvant RT in this group of patients.

This study goes a step further to support the use of postoperative RT in all patients, regardless of extent of resection. Our results showed no local failures in any patient receiving adjuvant RT following either GTR or STR. Of the 6 patients in our study who were treated with GTR followed by observation, 2 patients developed local recurrence. The recommendation for adjuvant RT following GTR is in line with those of other published reports. Ross et al (11) showed no local recurrences in 3 pediatric patients receiving adjuvant RT following GTR. Similarly, a retrospective review by Al-Halabi et al (4) reported 7 cases of pediatric patients with MPE and recommended adjuvant RT regardless of initial extent of surgery. That study found that 2 of 3 patients treated with GTR alone failed initial treatment and required salvage RT. Chan et al (19) performed a similar study and found both local and distant recurrences in 2 patients treated with GTR alone. Despite their small sample sizes, these studies represent some of the largest published data to date in the pediatric MPE literature (4, 19). In a study by Akyurek et al (7), MPE patients with a median age of 35 years, were found to have better 10-year LC rates if they received adjuvant RT after GTR compared to patients who received GTR alone (90% vs 58%, respectively). These results are comparable to our data, which showed an estimated 100% and 42.5% actuarial LC at 10 years for the GTR and adjuvant RT group, respectively, compared to the group receiving GTR alone. Based on our data and those of other studies showing similar results, we believe adjuvant RT should be considered following all surgeries, including GTR, in order to improve long-term disease control in children with MPE. Questions that remain are whether distant metastases are more likely to occur following GTR alone and whether adjuvant local RT will result in fewer disseminated neuroaxis recurrences (4). One patient in our study developed recurrence at a distant site following GTR and adjuvant RT, but his recurrence in the brain was found to be a grade 2 ependymoma on final pathology.

As MPEs represent a radiosensitive tumor, establishing the optimal radiation dose and determining whether there is a benefit to dose escalation are important questions that have been addressed. Akyurek et al (7) did not find a benefit when treating patients to doses

exceeding 45 Gy. However, most of their patients had doses of 50 Gy or higher, and only 4 patients had doses less than 45 Gy. Another study also failed to observe a dose-response relationship in the analysis of 80 patients with ependymomas and recommended a total dose of 50.4 Gy (17). However, on subgroup analysis of the 12 patients with MPE, a dose-response relationship was found. The 5-year LC rates were 100% with doses exceeding 50 Gy and 67% with lower doses (20). Another study evaluating patients with MPE found improved disease control in patients treated with high-dose RT (50.4 Gy) (3). In our study, the median dose to the tumor was 50.4 Gy, and all patients showed locally controlled disease with no evidence of a dose-response relationship.

One of the larger concerns with treatment in this patient population, which is expected to have excellent long-term survival, is the potential for RT toxicity. RT was well tolerated, with only 1 patient with grade 3 nausea and vomiting and 2 patients with grade 2 nausea and pain. All other acute toxicities were grade 1, and there were no significant long-term sequelae noted in any patients at last follow-up. No patient developed radiation myelopathy. Although the long-term follow-up is short, given the relatively benign course of this disease, there were no radiation-induced second malignancies noted to date. These findings are consistent with previous reports in this patient population (4, 6, 18).

Limitations to this series include the retrospective nature of the study and the small number of patients included in the study. However, this study represents 1 of the largest studies to date that analyzes the clinical outcomes exclusively in pediatric MPE over a 25-year period in a single-institution experience. Although further follow-up is needed to determine the rate of late effects such as RT-induced malignancies, our extended median follow-up to date has not demonstrated evidence of significant late sequelae. There are certainly potential risks in delivering RT in young patients at initial diagnosis, but these risks should be weighed against the potential complications that may accompany salvage treatment at time of recurrence, including the need for further surgical resection and the possibility of larger RT fields (eg, craniospinal radiation) that may be required in the setting of distant recurrence.

Conclusions

A definitive treatment paradigm for pediatric patients with MPE has not been established. While the role of adjuvant RT following STR is widely accepted, the role of RT following GTR has not been well studied. This study demonstrates improvement in LC and PFS with the use adjuvant RT after surgery, regardless of the initial extent of resection. RT was well tolerated in our patient cohort, with expected acute toxicities and without significant long-term side effects. Adjuvant RT should be considered following surgical resection in all pediatric patients with myxopapillary ependymoma.

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Summary

Myxopapillary ependymoma (MPE) is a rare tumor in children. The primary treatment is gross total resection, with no clearly defined role for adjuvant radiation therapy (RT). Fifteen pediatric patients with MPE treated at Johns Hopkins Hospital were retrospectively reviewed. We found that adjuvant RT improved local control compared to surgery alone and should be considered after surgical resection in pediatric patients with MPE.

Fig. 1.
LC rates with surgery alone compared to surgery and adjuvant RT.

Fig. 2.
LC rates with GTR alone compared to GTR and adjuvant RT.

Fig. 3.
PFS rates with surgery alone compared to surgery and adjuvant RT.

Table 1

Radiation planning, technique, and toxicity

Patient	Radiation dose and treatment plan	RT technique	Length of follow-up (months)	Acute toxicity	Late complications
1	Plan 1: 39.6 Gy/22 Fr to residual disease and tumor bed from T10-S3 Plan 2: 9 Gy/5 Fr boost to T10-S3. Total dose = 48.6 Gy Recurrence Plan 1: 36 Gy/20 Fr CSI with inferior margin at top of T10 Plan 2: 20 Gy/10 Fr boost to 2 brain mets Plan 1: 36 Gy/20 Fr to residual disease and tumor bed from T11-S4 Plan 2: 14.4 Gy/8 Fr boost to T11-S4. Total dose = 50.4 Gy Plan 1: 36 Gy/20 Fr to tumor bed in lumbosacral spine Plan 2: 14.4 Gy/8 Fr boost to lumbosacral spine. Total dose = 50.4 Gy 1 st Recurrence Plan 1: 36 Gy/20 Fr WBRT Plan 2: 18 Gy/10 Fr boost to left temporal lobe tumor bed. Total dose = 54 Gy Plan 3: 20 Gy/1 Fr to 2 cerebellar mets 2 nd Recurrence Plan 4: 36 Gy/20 Fr to thoracic spine Plan 5: 10.8 Gy/6 Fr CD to T1 met. Total dose = 46.8 Gy Plan 6: 10.8 Gy/6 Fr CD to T5-T8. Total dose = 46.8 Gy Plan 1: 45 Gy/25 Fr to tumor bed from T7 to cauda equina Plan 2: 9 Gy/5 Fr CD from L3 to cauda. Total dose = 54 Gy Plan 1: 34.2 Gy/19 Fr to residual disease and tumor bed from L spine to cauda equina Plan 2: 16.2 Gy/9 Fr boost to L spine and cauda equina. Total dose = 50.4 Gy Plan 1: 50.4 Gy/28 Fr to tumor bed from T10-S2 Plan 1: 45 Gy/25 Fr to residual disease and tumor bed in lumbosacral spine Plan 2: 5.4 Gy/3 Fr CD to sacrum. Total dose = 50.4 Gy Plan 1: 39.6 Gy/22 Fr to gross disease in thoracolumbosacral spine	AP/PA Opposed laterals Opposed laterals (brain) & PA (spine) Fractionated SRT AP/PA 3DCRT AP/PA 3DCRT Opposed laterals 3DCRT Gamma knife SRS AP/PA RPO & LPO wedge pair 3DCRT Tomotherapy Tomotherapy PA photons 20 MeV PA electrons Opposed laterals 3DCRT 3DCRT 3DCRT	71 86 99 9 317 216 111 98	Grade 1 fatigue and diarrhea Grade 1 fatigue, nausea, vomiting, and esophagitis Grade 1 dermatitis Grade 1 fatigue and nausea; grade 2 right > left buttock pain requiring NSAIDs Grade 1 nausea and vomiting Headache, grade 1 nausea, dermatitis, and alopecia Grade 1 fatigue None Grade 2 nausea and grade 1 vomiting Grade 1 nausea; grade 1 right leg pain and posterior thigh pain (left > right) Grade 1 nausea, vomiting, and dermatitis Grade 1 dermatitis Grade 3 nausea and vomiting	None None None None None None None None None None

Patient	Radiation dose and treatment plan	RT technique	Length of follow-up (months)	Acute toxicity	Late complications
	Plan 2: 5.4 Gy/3 Fr CD from T11-S3	3DCRT			
	Plan 3: 9 Gy/5 Fr CD from L2-S3. Total dose = 54 Gy	3DCRT			
14	Plan 1: 45 Gy/25 Fr to tumor bed in the sacrum	3DCRT	75	None	None
15	Plan 1: 54 Gy/30 Fr to tumor bed in the sacrum	IMRT	51	Grade 1 diarrhea	None

Abbreviations: Fr =fraction; CD =cone down; met =metastasis; AP =anterior-posterior; PA =posterior-anterior; CSI =craniospinal irradiation; SRT = stereotactic radiation therapy; 3DCRT = 3-dimensional conformal radiation therapy; SRS = stereotactic radiosurgery; NSAIDS = nonsteroidal anti-inflammatory drugs; WBRT = whole brain radiation therapy; RPO = right posterior oblique; LPO = left posterior oblique; IMRT = intensity modulated radiation therapy.

Table 2
Patient characteristics, treatment details, and patterns of recurrence for 15 pediatric patients with MPE

Patient	Age	Tumor location	Signs/symptoms	Surgery	Adjuvant RT	Recurrence	Salvage treatment after initial surgery	Postsalvage recurrence	Salvage treatment after second recurrence
1	14	T11, L2-5	Proximal left LE, hip and proximal right LE pain	STR	No	local	RT	Yes, distant	CSI
2	18	L3-S1	Back and buttock pain	STR	Yes	No	NA	NA	NA
3	13	L1-2; L4-5	Limping and left hip pain	GTR	Yes	Distant	Surgery (STR) + RT	Yes, distant	RT
4	15	L2-3	Back pain	GTR	No	No	NA	NA	NA
5	12	T12-L3	Constipation, bilateral hip and LE pain	STR	Yes	No	NA	NA	NA
6	12	L5-S2	Back and hamstring pain	GTR	No	No	NA	NA	NA
7	21	T12-L1	LBP, dysesthesia in abdomen and Les	STR	No	Local	Surgery (STR)	No	NA
8	13	S2-3	Right LE pain	STR	Yes	No	NA	NA	NA
9	21	L1-2	Severe, progressing back pain	GTR	Yes	No	NA	NA	NA
10	20	T12-L2	Back pain, urinary incontinence	GTR	No	No	NA	NA	NA
11	14	L2-3	Back and groin pain, right LE weakness	GTR	No	Local	Surgery (STR) plus RT	No	NA
12	20	L1-2	Back pain, LE weakness and sensory changes; neurogenic bladder	GTR	No	Local	RT	No	NA
13	18	L1-2	Back pain with radiation to LEs	GTR	No	No	NA	NA	NA
14	20	S2-5	LBP and decreased sensation in both LEs	GTR	Yes	No	NA	NA	NA
15	21	L5; S1-5	LBP; right gluteal pain	GTR	Yes	No	NA	NA	NA

Abbreviations: CSI = craniospinal irradiation; GTR = gross total resection; LBP = lower back pain; LE = lower extremity; NA = not applicable; STR = subtotal resection.