

# Adjunctive treatment of myxopapillary ependymoma

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## Abstract

Myxopapillary ependymoma are rare tumors and optimal therapeutic strategy is remained controversial. The main treatments for myxopapillary ependymoma tumors include surgery and radiotherapy. Hence, the present study aimed to review adjuvant treatment of myxopapillary ependymoma, focusing on spinal myxopapillary ependymoma. The information sources of all articles were the English authoritative databases including PubMed, Web of science, Scopus, Science direct and Google scholar. In this review study, the keywords including adjuvant, treatment, myxopapillary and ependymoma were selected from MeSH medical library. Related articles were published from 2000 to 2020. Given radiation tolerance in the spinal cord is 10-15% lower than that of the brain, it also should be noted that with increased dose and scope of therapeutic field, the corresponding risks are increased, as well. Also, chemotherapy has never been used as the primary treatment approach. Radiotherapy's value is considered while involving with sensitive areas where chemotherapy is also recommended. Gross total resection is the preferred primary treatment.

But the role of adjuvant radiotherapy is debated in different tumor and patient scenarios and no standard treatment strategy had been defined yet. The bottom line is that as long as cellular and molecular methods or gene therapy can be used in the treatment of myxopapillary ependymoma, all the studies confirm that the best treatment method is still wide surgical resection as much as possible.

## Introduction

Myxopapillary ependymomas (MPEs) are uncommon and make up approximately 15% of all ependymomas. There are two types of Grade 1 ependymoma including myxopapillary and subependymoma. These tumors are very uncommon among adults.<sup>1-3</sup> The term *myxopapillary ependymoma* was first used by Kernohan showing an ependymoma with heavily branching papillary form, hyalinized blood vessels, and abundant intercellular and perivascular mucin.<sup>1,2</sup> Histopathologically, MPEs are low-grade tumors and according to World Health Organization (WHO) classification they are classified as grade 1 tumors.<sup>3</sup> The usual age of presentation is from third to fifth decade.<sup>4</sup> Intradural MPEs almost exclusively occur at the *conus medullaris* or *filum terminale*. Extradural MPEs most commonly present as subcutaneous soft tissues in the sacrococcygeal region. It may also be seen rarely in the brain.<sup>5-7</sup> The microscopic appearance of MPE is characterized by pseudopapillary formation with symmetrical zones of mucoid matrix surrounding branching tumescent vessels as well as accumulation of mucin within and between tumor cells.<sup>8</sup> The mean proliferating index of this subtype is 2.4 *versus* 21% for anaplastic ependymomas.<sup>9</sup>

Treatment of myxopapillary ependymal tumors has been established separately for each patient. Two main local therapies are generally used to treat myxopapillary ependymoma tumors, which include surgery and radiation therapy. Due to the fact that most of the myxopapillary ependymoma are located in a place where surgery is less likely to be complete resection, adjuvant treatments for MPE are very important. The side effects of surgery depend on the type and location of the tumor.<sup>10</sup> In adjuvant treatments where radiation therapy is employed in addition to surgery, long-term survival after total tumor resection was approximately 40%.<sup>11</sup>

Since the risk of recurrence with solely surgical treatment for myxopapillary ependymoma is high (about 38%)<sup>12</sup> standard treatment is maximal safe resection plus local radiotherapy of the involved area.<sup>13,14</sup>

Obviously, evaluating the status of adjuvant treatments can provide legal health strategies and policies, minimize the side

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effects of these treatments, and maximize their beneficial effects. Considering the above-mentioned explanations and the fact that there is no comprehensive study review of treatment of myxopapillary ependymoma, especially adjuvant treatment, this study aimed to review of adjuvant treatments of myxopapillary ependymoma.

## Methodology

In this review study, the keywords adjuvant, treatment, myxopapillary, and ependymoma were firstly selected from MeSH medical library in the databases including Google Scholar, Pub Med, ISI, Scopus and so on. Related articles published from 2010 to 2020 were reviewed.

## Epidemiology

Ependymomas are unusual tumors that are related to ependymal cells in the central canal of the spinal cord, filum terminale, choroid plexus, or brain parenchyma. MPE are a rare division of ependymoma categorized as grade I tumors in the WHO. That involve conus medullaris, cauda equina and filum terminale in more than 95% of cases.<sup>15</sup> The MPE incidence is about 0.05-0.08 per 100,000 persons each year, and it is predominant in male specially in the 20-40 years old.<sup>16</sup> Also 10-20 percent of this disease have been seen in pediatrics.<sup>17</sup>

In 2016 James *et al* determined the epidemiology, prognostic factors, and treatment-related outcomes for MPE with SEER database. The incidence of MEP in the USA was evaluated about 1.00 per million person-years.<sup>15</sup> Worldwide distribution of myxopapillary ependymoma prevalence shows a significant difference between more developed and less developed countries, with less prevalence in less developed countries. This could be due to the lack of recognition in cases of death in less developed countries.<sup>15,18-21</sup>

## Early symptoms of the disease

These symptoms usually include low-back pain for long time. At this time, physical examination may be normal and other signs of the disease may be absent. However weakness of bilateral lower limbs and related symptoms of dysfunction of bowel or bladder would be added to symptomatology.<sup>22</sup>

## Molecular markers

Some studies have tested the effect of molecular markers including Ki-67, MIB-1 and p53 on MPE dissemination; but these attempts at molecular sub-stratification of MPE have failed to convincingly recognize patients with high-risk future dissemination.<sup>23</sup>

## National Comprehensive Cancer Network guideline

According to the National Comprehensive Cancer Network (NCCN) guidelines version 3.2019, in MPE without capsule violation and negative cerebral spinal fluid (CSF) cytology, the gross-total resection (GTR) only should be used. When capsule violation and negative CSF cytology occur, the GTR or STR with adjuvant external

beam RT should be presented. When GTR and STR performed but evidence of metastasis or negative CSF cytology occurred, the craniospinal RT should be used as an adjuvant treatment.

## Primary treatment of myxopapillary ependymomas

According to reports in literatures the mainstay of spinal ependymoma is treated in primary step with surgery to gain a histologic diagnosis and cut off much of the tumor. Studies have shown that surgery is the treatment of choice in cases where the tumor has not spread and is in a specific focus. After surgery, radiotherapy is also used as adjuncts, although in cases where surgery is not possible these methods are considered as the main treatment.<sup>24-26</sup>

The highest possible rate of resection of tumor tissues during surgery is considerably important, and has been shown to increase the survival rate of patients, reduction of the need for adjunctive treatment, and increased effectiveness of radiotherapy.<sup>2,13,24,27</sup>

GTR shows better treatment outcomes compared to subtotal resection (STR) in local control [28,13]. It should be noted that the STR is accepted under certain conditions, such as the involvement of sensitive sites.<sup>28,29</sup>

The highest possible amount of tumor resection by surgery is an important factor in determining prognosis. In addition, spinal myxopapillary ependymoma (sMPE) is an uncommon primary spinal neoplasm infiltrating the spinal cord, conus medullaris (CM), and nerve roots. It is associated with low resection and high recurrence rates.

## Adjuvant radiotherapy in the treatment of myxopapillary ependymomas

Although the surgical resection is considered as a treatment of MPE, the adjuvant radiotherapy (RT) has been helpful in increasing progression-free survival (PFS) in pediatric and adult patients.<sup>30-33</sup> Also RT provide control of disease in the long term for the patient with recurring after surgery.<sup>34,35</sup> Use of 3D-conformal radiation or IMRT is suitable and under investigation. In addition, a dosage of 5400 cGy is suitable for spinal myxopapillary ependymoma.<sup>36</sup> Lately, the Rare Cancer Network reported the largest series of 85 patients to date on spinal MPE that most of whom were adults. On multivariate analysis, adjuvant high-dose RT (>50.4 Gy) was associated with a major enhancement in 5-year PFS.<sup>37</sup> Also, the M.D. Anderson described a significant development in PFS and a reduced failure rate related to the adjuvant RT regardless of the extent of initial surgery in the adult patients treatment with MEP.<sup>30</sup>

Many studies investigated RT effect on treatment of MPE in adult and pediatric. Al-Halabi *et al* evaluated RT role in the controlling of primary and MPE after surgery. They conducted a review of MPE patients that treated at the Montreal Children's Hospital/McGill University Health Centre between 1985 and 2008. They showed RT has good effect on control of residual, metastatic and/or recurrent disease and routine adjuvant RT can improve outcomes in pediatric MPE.<sup>1</sup>

On the other hand, while extent of resection has been shown to correlate with outcomes after MPE resection, the effect of capsular violation has not been well studied. As a result, the role of adjuvant radiation also remains controversial. To this end, importance of capsule integrity upon myxopapillary ependymoma resection was examined by Abdulaziz *et al*.<sup>38</sup> They found a considerable correla-

tion between capsular violation and recurrence after removal of myxopapillary ependymoma.

### Adjuvant radiotherapy in the treatment of myxopapillary ependymomas in pediatrics

For pediatric cases, the treatment is constantly more complicated. Decision making for management of pediatric patients is considered to be more difficult as they usually have a worse outcome. Use of adjuvant radiotherapy is suggested by many authors in pediatric patients even after GTR of tumor. In doing so, Pędziwiatr *et al.*, investigated spinal cord ependymoma among children. They found the histological type of ependymoma myxopapillary as a statistically significant favorable prognostic factor. In their study, GTR along with adjuvant RT provided a 100% survival rate.<sup>39</sup> Therefore, RT is strongly recommended following GTR in children suffering from myxopapillary ependymoma. In a similar study the effect of adjuvant RT was evaluated on sixteen pediatric patients with MPE.<sup>2</sup> All patients received GTR or a subtotal resection (STR) surgery as the initial treatment modality. Their conclusion showed that Adjuvant RT enhanced local control compared to surgery alone and should be considered after surgical resection in MPE pediatric patients.<sup>4</sup> Lucchesi *et al.* assessed treatment modalities, demographics, and the associated outcomes of children with MPE by the Epidemiology, Surveillance, and End Results (SEER) national cancer database to achieve an enhanced estimation of these tumors. Survival was over 95% at the 5- and 10-year mark, regardless of treatment procedure. However, patients who treated with GTR had survival rate about 100%. But STR plus radiation treatment had 91% survival rate.<sup>40</sup> In clinical investigation the role of adjuvant RT in pediatric with MPE was assessed. In this study patients had surgery including of a GTR or a STR at initial time, then all patients receiving RT in 50.4 Gy dose. Their result showed adjuvant RT enhanced treatment of local control compared to surgery alone<sup>2</sup> (Table 1).

The optimal RT administration timing was assessed by Liu *et al.*, they identified 31 patients that had intracranial ependymoma in childhood. All patients received surgery initially, 39% of patients received upfront RT, 32% had delayed RT and 29% of them had no RT. Their study support the early initiation of adjuvant RT in the multi-modal management of pediatric ependymomas.<sup>41</sup>

### Metastases of spinal myxopapillary ependymoma

Regarding spinal myxopapillary ependymoma, Kraetzig *et al.*, for the first time analyzed the characteristics of distant metastases of spinal myxopapillary ependymoma according to their clinical and biological behavior in one of the largest case series. Their evaluation showed Metastases occurring in all parts of the neuroaxis but it mainly localized in the thoracic and sacral spine in 38.9% and 33.3%, respectively. They recommend the GTR of the primary tumor as the initial action and additional radiation therapy should be undertaken upon a STR. Furthermore, additional resection or irradiation as salvage therapy should be performed if metastases become symptomatic.<sup>21,14,42,43</sup> In cases with seeding, when craniospinal irradiation is planned, new radiotherapy equipment such as Helical TomoTherapy may provide more effective radiation with less side effects.<sup>44</sup>

### Other adjuvant therapy

Accordingly, temozolomide (TMZ) is usually used in the treatment of glioblastoma and, recently, it has been reported to be effective for the lower grade spinal gliomas including spinal intramedullary ependymomas. However, for myxopapillary ependymomas, there has been no report that TMZ is effective. For this purpose, Fujiwara *et al.*, represented TMZ as a possible option for adjuvant therapy in multiple recurrent myxopapillary ependymomas. They described a case in that TMZ showed remarkable efficacy on a recurrent spinal myxopapillary ependymoma.<sup>45,46</sup>

### Conclusions

Although the results of this study are helpful, definitive conclusions need to be drawn from prospective multicenter studies with regard to underlying and confounding factors. The bottom line is that as long as cellular and molecular methods or gene therapy can be used to treat myxopapillary ependymoma tumor, the widest possible surgical resection is still the best treatment accordingly. Also, the following relevant topic are proposed to be investigated with more case studies and research since they have still

**Table 1. Summary of studies in myxopapillary ependymomas treatment.**

Authors and year of publication	Pediatric or adult	Resection	Adjuvant therapy	Overall survival
Bandopadhyay <i>et al.</i> <sup>43</sup>	Pediatric	GTR	RT	Overall survival (100%) is excellent
Kukreja <i>et al.</i> <sup>44</sup>	Pediatric and adult	GTR	RT	The influence of adjuvant RT was significant in younger age
Akyurek <i>et al.</i> <sup>32</sup>	Adult	GTR	RT	RT appears to significantly reduce the rate of tumor progression
Al-Habibi <i>et al.</i> <sup>4</sup>	Pediatric	STR and GTR	RT	RT resulted in control of residual, metastatic and/or recurrent disease
Akyurek <sup>32</sup>	Adult		RT	Adjuvant RT appears to significantly reduce the rate of tumor progression
Kucia <sup>45</sup>	Adult		RT	Postoperative radiation therapy may improve outcome
Harold C <sup>5</sup>	Adult and pediatric	GTR	RT	Adjuvant RT improved local control compared to surgery alone
Kukreja <sup>44</sup>	Adult and Pediatric	GTR	RT	Influence of adjuvant RT was significant in younger age groups
Nagib <sup>46</sup>	Pediatric	GTR	RT	Radiotherapy appeared to have no proven value in completely resected tumors in children
William <sup>47</sup>	Pediatric	GTR and STR	RT	Gross-total resection alone is associated with decreased recurrence rates compared with STR with or without radiotherapy.
Nakamura <sup>48</sup>	Adult	GTR and STR	RT	Surgical margin obtained at the initial surgery and the extent and amount of postoperative radiation can be crucial factors determining the prognosis of patients

GTR, gross-total resection; RT, radiotherapy; STR, subtotal resection.

areas of uncertainty: management of subtotal resection and negative CSF cytology, management of GTR and capsule violation, management of recurrences, metastatic MPE and role of chemotherapy.

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