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IS IT POSSIBLE TO REDUCE THE NUMBER OF SURGERIES IN EPENDYMOMAS?

Dinali Obeysekera, *Assama Riaz, Kelsie Rushlow, Narindra Anmolsingh, Maya Itani

MUA Medical School, (Medical University of the Americas), C/O R3 Education Inc. 27 Jackson Road, Suite 302 Devens, Massachusetts 01434, United States.

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ABSTRACT

Purpose of Study design: This review reported the surgical management of ependymoma and its related concerns, possibly to find out the way to reduce surgical repetition by other available treatment options. The better management strategies and future perspectives also analyzed. **Study Findings:** Surgical resection is reportedly the safest and recommended management strategy in most of the ependymoma cases with better survival rates. Although, surgical treatment has its associated side effects but these can be managed if handle efficiently. Other available options like radiotherapy and chemotherapy have limited efficacy and potential adverse effects. More efficient surgical methods are now been introduced with better management strategies. Other methodologies which are in the progress phase include proton beam therapy and the development of Immunotherapeutics.

Keywords: ependymomas, ependymomas treatment, ependymomas management, brain tumor, ependymomas surgical treatment, radiotherapy, Chemotherapy.

INTRODUCTION

Ependymomas are primarily the tumors of the central nervous system (CNS) and also known as neoplasm's of pediatrics and young children or adults. These tumors can develop in all age groups but children are more frequently affected than adults. Central Brain Tumor Registry of the United States (CBTRUS) published a report in 2014 that ependymomas are responsible for 5.2% CNS and brain tumors between 0–19 years of individuals in comparison with adults who had 1.9% of reported frequency. Another interesting fact of its prevalence is racial disparity; whites have 100,000 of 0.40 incidence rate versus 0.27 incidence rate were seen in African Americans [Armstrong and Gilbert, 2016; Ostrom *et al.,* 2014]. However, there is no gender discrimination reported. Yearly 1000–2000 adult cases of spinal or intracranial ependymoma are reported in the United States, 75 % cases reported in the spinal canal, 25 % from the intramedullary spinal cord, and 2 % from primary central nervous system (CNS) malignancies [Celano *et al.,* 2016; Chamberlain, 2003]. Ependymomas possibly initiate from the cerebral ventricle lining or the central canal of the spinal cord. However, some studies reported its origin from radial glial stem cells [Armstrong and Gilbert, 2016; Louis *et al.,* 2007]. Ependymomas may appear at any site of the ventricular system and spinal cord but its presentation varied according to the age group and sub grouping of histopathology [Armstrong and Gilbert, 2016]. The classification and tumor grading of ependymomas is an important prognostic factor. Ependymomas classified by the World Health Organization (WHO) into three grades, on the basis of anaplasia [Armstrong and Gilbert, 2016; Tarapore *et al.,* 2013]. Grade I: Myxopapillary ependymomas and subependymomas Grade II: Classic ependymomas (includes cellular, clear cell, papillary cell, giant cell, and tanycytic) Grade III: Anaplastic ependymomas [Armstrong and Gilbert, 2016; Tarapore *et al.,* 2013]. This grade classification is very important to guide in treatment choice; however, the prognostic value is still disputed. Pediatric ependymomas grading is also more complex and debatable to distinguish the prognostic value of grade II and III. Additionally, if followed the WHO guidelines alone; it's difficult to establish tumor and degree of prognosis due to the genetic heterogeneity among different subtypes of ependymomas and even between the same grades but from different origin like brain or spine [Tarapore *et al.,* 2013]. For better prognosis of ependymoma patients, other considerable factors are the location of ependymoma tumor, resection extent, presentation of clinical symptoms, neurological examination, examination for distant metastasis presence, and adjuvant radiotherapy [Tarapore *et al.,* 2013]. However, the management of ependymomas according to the grading system has not been systematized. Surgical and radiological therapies are the recommended available choices. Chemotherapy is an additional option with limited efficacy. According to CBTRUS 2014 report, the overall 10-year survival rate of ependymomas patients is 79.2%. The highest survival rate was seen in 20 – 44 years of patients. With increased age, the "10 years" survival rate decreases and seen only in 28.1% of patients. However, in children and young adults between 0 –19 years, a 66% survival rate was reported [Armstrong and Gilbert, 2016]. There were discrepancies reported in survival rate reports among different countries, which possibly are due to the availability of cancer drugs, lack of specialized medical care, and poor cancer management [Armstrong and Gilbert, 2016; Gatta *et al.,* 2014; Visser *et al.,* 2015]. Ependymomas are considered as slow-growing benign tumors that respond well to radiation. Ependymoma progresses by compressing the parenchymal cord rather to infiltrate it. The conventional and most adapted management of ependymoma is a surgical treatment to resect all possible material and perform histopathological testing [Verstegen *et al.,* 1997; Li *TY et al.,* 2014]. Gross-total resection (GTR) is the obvious surgical plane in most ependymoma tumor cases [Schwartz and McCormick, 2000]. After surgical management, some patients may also undergo radiotherapy. However, after refined microsurgical techniques and experienced surgeons, the survival of patients is crucial and controversial, and highly influenced by clinical and histopathological characteristics of the ependymoma tumor [Verstegen *et al.,* 1997; ; Li *TY et al.,* 2014]. This report is designed to evaluate the possibility of surgeries in ependymomas patients and its impact on their prognosis.

***Corresponding Author: Assama Riaz,**
MUA Medical School, (Medical University of the Americas), C/O R3 Education Inc. 27 Jackson Road, Suite 302 Devens, Massachusetts 01434, United States.

Ependymomas And Its Challenging Management

Surgical Treatment

Surgical treatment or resection is undoubtedly the most crucial management of all histological grades of ependymoma and always the preferred chosen treatment in both intracranial and spinal cord ependymoma [Armstrong and Gilbert, 2016; Zhang *et al.,* 2016]. The surgical resection is important to set up a definite diagnosis and collect tissue samples for pathological genomic testing to identify each ependymoma's distinctive molecular profile. Surgical resection also depends on the tumor's location; if resection is not possible due to the crucial location of the tumor the lesion biopsy is still required prior to the management of ependymoma. In the cases where tumor resection is possible, Gross-total resection (GTR) is always advisable. Many case studies have reported the experience of extensive resection and its association with progression-free survival (PFS) and overall survival (OS) of ependymoma patients [Armstrong and Gilbert, 2016; Metellus *et al.,* 2007; Paulino *et al.,* 2004; Healey *et al.,* 1991]. The Gross-total resection (GTR) technique or total tumor removal has been advanced and developed with time. Advancement of micro neurosurgery, computer-assisted technology – neuronavigation, and imaging techniques including Intraoperative ultrasound (IOUS), magnetic resonance (NMR), and Intraoperative neurophysiological monitoring (IONM) are beneficial for better outcome [Zhang *et al.,* 2016; Merchant and Fouladi, 2005]. According to the published data of spinal ependymoma, the nervous ability of 79% of the surgically treated patients was got better and improved health status [Zhang *et al.,* 2016; Nakamura *et al.,* 2009]. Although, there is limited data available; based on patient's case studies that those who underwent complete removal of ependymoma had better survival rates and improved quality of life [Zhang *et al.,* 2016]. Tumor resection is the best-reported treatment of ependymoma, where tumor resection is possible; the most substantial resection is recommended [Metellus *et al.,* 2007]. Gross-total resection (GTR) is not feasible in all cases depending upon the tumor's location, and subtotal resection (STR) would be the possible choice. STR is usually followed with radiation therapy and even underwent through radiation, these patients have a higher probability of progressive disease development [Armstrong and Gilbert, 2016]. Myxopapillary ependymomas are belonged to WHO grade I and comparatively different from all other intramedullary ependymomas originated from the spinal cord. Myxopapillary ependymomas are always occurred in conus medullaris and possibly extend to cauda equine. Several case reports evidently demonstrated that GTR without damaging the tumor capsule may be the possible cure. In this case, maintenance of tumor integrity is important to prevent tumor spread [Gilbert *e al.,* 2010; Nakamura *et al.,* 2009].

Radiotherapy

Radiotherapy is also a traditional treatment method of ependymoma along with surgical resection. Radiotherapy is provided postsurgical to improve prognosis and better patient recovery. With time it's been evident that total resection patients won't need additional radiation therapy and if there is no cerebrospinal fluid dissemination. In the case of intramedullary ependymoma, scientific scholars believed that radiotherapy can improve a patient's survival rate when it's total resection or partial. However, this belief is controversial and not all scholars agreed on that [Zhang *et al.,* 2016]. Local irradiation is usually helpful in supratentorial ependymoma, other conditions like Subtentorial ependymoma also adapts the entire brain or entire spinal cord irradiation with the approach to fall off the ependymoma cells. This methodology is controversial in recent research reports due to the possibility of local recurrence and spinal metastasis [Vanuytsel and Brada, 1991; Vanuytsel *et al.,* 1992]. National Comprehensive Cancer Network (NCCN) published the guidelines in 2006 for clinical practices; According to NCCN guidelines, ependymoma can be managed with regular radiotherapy treatment. The treatment protocol depends upon the spinal MRI and CSF reporting. Reduced radiotherapy dose to 80% is advisable in children than adult patients [Zhang *et al.,* 2016]. Radiotherapy is associated with many side effects including cognitive disability, vision and listening impairment, patient's growth especially in children, retardation, endocrine disorders, etc. However, new developments in this field like "intensity-modulated radiation therapy", may be helpful to reduce adverse effects [Korshunov *et al.,* 2004].

Chemotherapy

The management of ependymomas by chemotherapeutic methodology is yet not well established. It is usually performed in young adults to avoid radiation therapy due to nervous system development. The benefits, survival rate, and adverse effects of Chemotherapy has been studied and reported in detail; whether or not chemotherapy improves the survival rate is still disputed. NCCN published the guidelines in 2014 and recommended the chemotherapy only in patients with recurred ependymoma after radiation management or ependymoma with palliative care. Clinical trial studies reported the chemotherapy has a limited effect on ependymoma management. Platinum-based chemotherapy is considered to be one of the primary therapeutic agents to cure ependymoma. Other chemotherapeutic agents used in clinical trials are procarbazine and carboplatin, etoposide and cisplatin, and vincristine and cyclophosphamide after ependymoma surgery [Armstrong and Gilbert, 2016; Zhang *et al.,* 2016]. Chemotherapy treatment has limited efficacy and can be helpful in disease control but the contribution of each chemotherapeutic agent alone or in combination is yet uncertain to determine [Gilbert *et al.,* 2014].

Proton Beam Therapy (PBT)

Proton beam therapy (PBT) is usually indicated in children with intracranial ependymoma. This treatment is usually performed to reduce or avoid harmful effects on the endocrine, hearing, and cognitive abilities. However, large-scale clinical trials are suggested for a better understanding of PBT and its related concerns [Toescu, and Aquilina, 2019]. This treatment could be an effective treatment choice in pediatric patients because these ependymoma pediatric patients are in great danger of radiation therapy due to its potential adverse events. The preliminary clinical studies reported a favorable treatment profile [Amsbaugh *et al.,* 2012].

Surgical Treatment And Its Related Complications

Surgical procedures are always linked with related complications like infections and hematomas. However, it's rare due to perioperative antibiotics administration and electrocautery. Aseptic meningitis also reported after 5 days of surgical procedure [Morris *et al.,* 2009]. CSF sampling would be the only way to diagnose the presence of bacterial infection. Other post-operative concerns are alteration of CSF flow which may to leakage of CSF or pseudomeningocoele. These concerns can be preventable or treatable by dural hitch stitches, nuchal muscle suturing, and repeated lumbar puncture, depending upon the situation. In case of persistent complain permanent CSF diversion need to perform. Neurological morbidity is one of the major concerns of respective surgery. Other related concerns are aspiration pneumonia and respiratory distress [Toescu, and Aquilina, 2019].

DISCUSSION

The standard and adapted treatment of ependymoma is the ultimate surgical resection followed by radiotherapy at the primary tumor site. Instant postoperative radiation is not recommended and practiced in pediatric patients of < 3 years of age. In these cases, multi-agent chemotherapy is advised to avoid radiation therapy. This chemotherapy treatment is not recommended for patients > 3 years due to well-established trials. Resection alone is well successfully treated patients; Hukin et al treated 10 cases of pediatric ependymoma and reported GTR as the only primary successful therapy [Hukin *et al.,* 1998]. Another report by Palma et al reported well-responded success of supratentorial ependymoma treatment by GTR alone [Palma *et al.,* 2000]. GTR is not possible and accomplished in all tumor cases; this is more successful in supratentorial locations and some of the locations of the fourth ventricle roof. Aggressive attempts to remove tumors of other sites may lead to increased morbidity [Toescu, and Aquilina, 2019]. GTR alone and first complete resection is not possible in most ependymoma cases. Although, there is a high rate of complete first resection, very limited studies are available to report the second resection. The second resection decision and its correct timing difference from the first resection are also disputed. The chemotherapy is administered before the second resection decision to make a tumor more accessible in resection and to prevent its progression [Toescu, and Aquilina, 2019]. Radiotherapy treatment in ependymoma management is still debated due to related adverse effects. Stereotaxic radiosurgery is emerging in intracranial tumors due to better management outcomes. Other future developments include spinal radiosurgery. Advancements in imaging techniques and surgical methodologies may lead to successful tumor removal with a low morbidity rate [Toescu, and Aquilina, 2019]. Medical therapeutics also administered in different cases depending upon the patient's condition. However, it is also crucial if tumor cure is not possible and medicine is only using to control it, it would be tougher to decide whether to continue or not [Toescu, and Aquilina, 2019]. Development of Immunotherapeutic Strategies for cancer management is a new treatment direction including Cancer Vaccines as a Novel Therapeutic Approach. The pediatric studies of Immunotherapeutic reported the risk of pseudoprogression. The new trial designs should include comprehensive monitoring, management, and established guidelines [Pollack et al., 2013]. A recent study of Behmanesh et al. evaluated the surgical treatment and conservation management of intramedullary spinal cord ependymoma patients. The study consists of 56 patients, 33 underwent surgical resection and 22 were conservatively managed and evaluated for return to workability [Behmanesh *et al.,* 2020]. This study surprisingly reported the significantly better outcome of conservatively managed patients as compared to surgically treated ones, in terms of ability to return to work which is an important life factor after tumor diagnosis and treatment [Behmanesh *et al.,* 2020]. Another meta-analysis evaluation of complete and partial surgical resection of intramedullary ependymoma evaluated that complete resection can lead to progression-free survival (PFS) and improved follow-up neurological improvement. However, the overall survival rate was not linked to the degree of surgery performed. This study concluded that the partial resection is still acceptable due to its almost similar overall survival rate [Salari *et al.,* 2020]. Surgical treatment or surgical resection is the most recommended and adapted management of ependymomas. It is agreed by general consensus that GTR or complete resection in one attempt with leaving no residual tumor has a very low possibility in ependymoma cases. However, there are plenty of associated surgical risks like neurological deficits, sensory deterioration, sensory loss, dysfunction of dorsal column, bladder, and bowel, and dysesthetic syndrome, especially in the early postoperative days. Infections and CSF leakages also reported, mostly in the cases where radiotherapy involved. Radiation therapy is significantly associated with severe neurological damage and deformities, especially in pediatric patients. Identification of treatment-related potential issues is very crucial to manage their prevention, early diagnosis, improved quality of life and better survival rate.

Conclusion

The recent cases and research on better management of ependymomas are very critical. New treatment strategies with the better outcomes are essential. Reports with conservative management and microsurgical techniques and other methods like cancer vaccines are paths towards a better patient's future.

Conflict of interest

No conflict of interest is stated.

Disclosure of interest

I undoubtedly disclose that I didn't receive any financial aid during this research writing. This is my solely intellectual contribution to the medical field.

Ethical statement

This study fulfilled all required ethical parameters; reporting no human and animal's right violation.

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