Ependymomas in Young Children

Lead Contributors:

Su Gülsün Berrak, MD
Rejin Kebudi, MD
Istanbul University, Oncology Institute
Istanbul, Turkey

Ibrahim Qaddoumi, MD, MS
St. Jude Children’s Research Hospital
Memphis, Tennessee, United States of America

A. Epidemiology

Ependymomas are the third most common type of brain tumor that affects children. In a recent study of Turkish children, ependymomas accounted for approximately 13.6% of all brain tumors. More than 50% of all patients with ependymomas are younger than 5 years of age, and 70-80% are younger than 8 years of age at the time of clinical presentation.

A. References

2Kutluk T, Yesilipek A, on behalf of Turkish Pediatric Oncology Group/Turkish Pediatric Hematology Association. Pediatric Cancer Registry. National Cancer Congress, 2007
B. Clinical Signs and Symptoms

Most children with ependymomas present with localized disease. The predominant location for this tumor is the posterior fossa; the main clinical signs and symptoms in young children with this tumor are irritability, lethargy, and gait disturbance. Other relevant clinical signs include a bulging fontanel, an increase in the circumference of the head, papilledema, meningismus, ataxia, cranial nerve palsy, and nystagmus. Although presenting features during first year of life are not specific, radiological studies reveal that they are larger tumors that involve the upper cervical canal and pontine cistern. Dissemination is a frequent finding in infants affected with these tumors.

B. References

C. Prognostic Factors and Treatment

Both brain stem involvement and disseminated disease in patients with ependymomas are known to have a poorer prognosis, probably because of the preclusion of complete resection.\(^1,2\) Younger children are also known to have a worse prognosis, presumably because of the presence of more immature neural tissue in young patients with ependymomas, which leads to more aggressive behavior.\(^1,3\) In a multivariate analysis performed in a recent study, both age (>3 years) and gross total resection (GTR) were independently found to have a significant impact on the survival of patients with ependymomas.\(^4,5\) In many previous studies the failure of the post-surgical imaging that indicates the presence or absence of gross total resection has lead to a lack of evidence of the impact of surgery on prognosis.\(^6\) The extent of resection is accepted as an independent prognostic factor in most studies.\(^4,5,7-14\) The 5-year survival of patients with ependymomas varies from 60 to 89 % after gross total resection (GTR) whereas the 5-year survival for incompletely resected tumors is about 21-46 %.\(^4,5,14-18\) Thus, optimal treatment of these tumors entails complete surgical resection,\(^5,10,11,15,19,20\) confirmed by post-operative contrast-enhanced MRI. The importance of achieving GTR justifies the implementation of second look surgery even with the help of adjuvant chemotherapy.\(^46-49\) Other prognostic variables such as histology and the site of occurrence appear to only impact survival marginally as compared with the extent of surgical resection.\(^4,5,7,12,13,21,22\) However, in spite of the utilization of novel surgical techniques in a randomized Children’s Cancer Group (CCG) trial, 53% of the participants had residual tumor on postoperative imaging.\(^19\) Nevertheless, in patients for whom complete resection cannot be obtained, the same trial suggests that less than 1.5 cm\(^2\) residual tumor predicts improved survival.\(^19\) To improve survival, maximal safe resection should be an aim in the treatment of ependymomas.
Local recurrence is the primary pattern of treatment failure, regardless of the tumor histology or completeness of resection, and postoperative focal radiotherapy is considered to be the second backbone of therapy in ependymomas. However, radiotherapy is known to cause several side effects, one of which is the risk of neurocognitive late effects, especially in children younger than 3 years of age.\textsuperscript{23-27} Thus, in order to find a balance between effective treatment and the preservation of neurocognitive development, treatment approaches for young children with ependymomas should aim to maximize surgical resection while deferring radiotherapy or reducing the volume of radiation dose. New radiotherapy techniques such as conformal or stereotactic radiotherapy have fewer acute and lower long-term toxicities than conventional radiotherapy. Stereotactic radiotherapy involves the application of high-doses of radiotherapy to a defined target while sparing normal tissues.\textsuperscript{28} There are several reports with promising 3 to 5 year local control rates using stereotactic irradiation as a boost after conventional radiation therapy or for the treatment of recurrent ependymomas; these reports include mostly information on adults.\textsuperscript{29-32} Hodgson et al\textsuperscript{32} reported a 3-year progression-free survival rate of 22% in 28 pediatric ependymoma patients. Jawahar et al\textsuperscript{33} demonstrated a 5-year progression-free survival rate of 32% in 22 patients with recurrent ependymomas. Combs et al\textsuperscript{34} achieved a 5-year progression-free survival rate of 77% in 19 ependymoma patients, who underwent stereotactic radiosurgery either as the primary postoperative modality (n = 6) or at the time of tumor recurrence (n = 12). These results support the idea that stereotactic radiosurgery is a local treatment option in young ependymoma patients since this type of radiotherapy is highly focal and precise; this therapy should only be administered by expert radiation oncologists as it requires special skills and techniques. It must be acknowledged, however, that in order to determine its efficacy, the long-term follow-up of patients treated using this method is still pending. Currently, conformal radiotherapy techniques are being used in many
treatment centers to avoid exposing normal brain tissue to radiation and therefore reducing the risk of potential neurocognitive late effects.\textsuperscript{35-38} Merchant et al\textsuperscript{39} have reported a 3-year progression free survival of approximately 75\% in 88 patients (aged 1–21 years) with localized ependymomas who were treated with conformal radiotherapy. However, 74 of the 88 children in this preliminary report had undergone complete tumor resection.\textsuperscript{39} Moreover, in the same study, 24 months after the start of conformal radiotherapy the neurocognitive functions were found to be within the normative mean for the appropriate age group.\textsuperscript{39} Current studies have also implemented a conformal approach for all patients older than 12 months. The American Pediatric Brain Tumor Consortium study for children younger than 3 years of age uses intrathecal chemotherapy, systemic chemotherapy, and conformal radiotherapy for patients with high-risk disease. The Children’s Oncology Group (COG) also uses conformal radiotherapy to treat a subgroup of patients older than 1 year with high-risk localized ependymomas.

The potential benefits of conformal radiotherapy will be realized only if no increase is noted in the rate of failure and if acute and late toxicities remain within the predicted limits. Conklin et al\textsuperscript{38} found that while the intellectual skill gain remained rate proportionate to their peer group, academic reading skills in children treated with conformal radiotherapy for local ependymoma were negatively affected. For that reason, the assessment of toxicity as well as the rate of failure requires a very careful assessment during follow-up.

Many early “baby” studies examined deferral or avoidance of radiotherapy among young patients with ependymomas and other brain tumors. Among those studies, the Pediatric Oncology Group (POG) and the CCG used a policy of delayed radiation in their first cooperative infant protocols, and the Societe Francaise d’Oncologie Pediatrique (SFOP) avoided the use of radiotherapy as first-line treatment in a study of infants and young children with ependymomas. In the Baby POG I study, the 5-year survival rate when radiotherapy was deferred for 2 years (while chemotherapy administered for 2 years) was found to be only
25.7% compared with 63.3% in patients for whom radiotherapy was deferred for 1 year (chemotherapy was given for only 1 year). The difference in survival rate with delayed radiotherapy was noted to persist even among children with good prognostic features, who had GTR, and no metastases at diagnosis. This data suggested that while ependymomomas may be chemotherapy-sensitive tumors, they cannot be cured with chemotherapy only; radiation may be deferred but usually cannot be eliminated. This data should not be used as an alternative to aggressive safe surgery to achieve GTR. GTR followed by tightly focal radiotherapy (such as conformal technique radiotherapy) is the standard of care at most centers. However, in cases of metastatic ependymoma in which focal radiation is not possible, extended chemotherapy, as given in the “baby” studies could be considered. Also, in children with residual tumors, using fewer courses (1-4) of chemotherapy to facilitate second surgery is a reasonable if neurosurgical expertise and supportive services are available. Finally, in very young (less than 1 year of age) patients, chemotherapy can be implemented to delay radiation until the patient reaches an age acceptable to local radiation oncology experts. In the SFOP Baby Protocol 90, infants were intended to receive multiagent chemotherapy over 16 months without radiation if they remained progression-free. Radiation could be avoided in 23% of patients in the study. That study had a 4-year overall survival rate (59%) similar to that of the Baby POG I study (63.3%). This finding demonstrates that a significant proportion of children with ependymoma can be cured without radiotherapy. Moreover, the deferral of radiotherapy up to the time of relapse or progression was not found to compromise the overall survival of the whole patient population in either of these studies. The prospective CCG-9921, HIT-SKK 87 and 92, and UKCCSG/SIOP studies also involved a similar concept of multiagent chemotherapy and the deferral of radiation up to the time of progression or relapse, and they achieved similar overall survival rates, i.e., 59%, (at 5 years), 55.9% (at 3 years), and 60% (at 5 years), respectively.
Another strategy to treat young children with brain tumors (including ependymomas) is to use myeloablative chemotherapy and autologous hematopoietic stem cell rescue according to the Headstart studies. The Headstart I&II studies found a 5-year survival rate of 38%, which is inferior to the outcomes achieved with the “baby” approach, which uses multi-agent chemotherapy and defers radiation to progression or relapse.

In conclusion, ependymomas are the third most common type of brain tumor that affects children. Most children with ependymomas present with localized disease. The most important prognostic factors for this tumor are gross total resection and young age. Recent studies could explain why young age is a poor prognostic factor. Witt et al showed that posterior fossa ependymomas in the young children are genetically different than other posterior fossa tumors in older patients.

The most important treatment modality is a multidisciplinary approach among the different disciplines involved in the treatment of children with ependymoma, including such as neurosurgery, neuropathology, radiology, radiation oncology and neuro oncology. If local expertise and the proper equipment for tight focal radiation fields are available, the child should receive focal radiotherapy post-GTR depending on age and metastatic status, since radiotherapy is the second-most important therapy for ependymoma.

However, chemotherapy before radiotherapy could be utilized in some cases as described above. The final role of chemotherapy in ependymoma is still under investigation. Currently, the overall survival of all children with ependymomas is in the range of 39-69%, suggesting the need for studies to improve survival rates. The development of new strategies whose purpose is to improve survival with minimum toxicity is the main goal of most current studies. It seems that this goal may be achieved in the near future as better understanding of genetics and biology of ependymoma will allow the identification of separate subgroups of ependymomas in different CNS regions or even within the same region. The ability to identify separate...
ependymoma subgroups will potentially enable the use of tailored therapies for different ependymoma types.  

C. References


