Ependymoma

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Creation date: February 2004

Scientific Editor: Professor Riccardo Riccardi

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Abstract
Ependymoma accounts for 10% of all pediatric central nervous system tumors and originates in ventricular spaces or from residual intra-parenchymal ependymal cells. The most common location in children is infratentorial. Symptoms depend upon the location of the tumor and can vary from intracranial hypertension for tumors originating in posterior fossa, behavioural changes and pyramidal signs for supratentorial tumors, to dysaesthesia for spinal ones. Etiology is unknown. A cytogenetic alteration involving chromosome 22 is commonly reported. Many questions are still under debate: the optimal radiotherapy volumes, doses and techniques, the usefulness of chemotherapy, the prognostic impact of grading, patient's age, tumor site. Prognostic factors related to genetic and molecular pattern are under evaluation. Surgery remains the main treatment for ependymoma, but complete resectability can be difficult, especially when tumor occurs infratentorially. Surgery should be therefore performed in one or more operations, according to the patient's neurological conditions, to decrease surgical morbidity, thereby increasing chances to implement subsequent treatment. Chemotherapy regimens adopted so far may enable a further surgery by reducing volume or infiltrating aspects of residual tumor. Radiotherapy allows controlling ependymoma; new radiotherapy treatment techniques, such as 3-D conformal radiotherapy, may enable the delivery of high radiation doses to small tumor volumes, improving the therapeutic ratio.

Keywords
Ependymoma, pediatric tumor, prognostic factors, morbidity, second-look surgery

Disease name
Ependymoma

Definition
Ependymomas are rare neuroectodermal tumors arising from ependymal cells of the ventricular system, choroid plexus, filum terminale, and central canal of the spinal cord. Ependymal cells are also present in the brain parenchyma as a result of migration from periventricular areas to the cortex during the embryonal stage (Centeno *et al*., 1986).

Diagnostic criteria and differential diagnosis
Ependymomas are composed of cells that form characteristic ependymal rosettes, perivascular pseudorosettes with blepharoplasts, which are basal bodies of cilia contained in cells surrounding a lumen. The World Health Organization (WHO) classification identifies three histological variants of ependymomas: cellular, papillary and clear-cell (Wiestler *et al*., 2000). These tumors are very similar as to their clinical outcome. The WHO classification allows distinguishing these ependymal variants from anaplastic gliomas, choroid plexus tumors and oligodendrogliomas. Anaplastic ependymomas are histologically recognized on the basis of their relative hypercellularity, cellular and nuclear pleomorphism, frequent mitosis and endothelial proliferation.

Etiology
Very little is known about the etiology of ependymomas. Some data about a possible infectious etiology were reported by Bergsagel *et al*. (1992) and Ledwicky *et al*. (1995). Using PCR techniques, Bergsagel analyzed 31 tumors from children for the presence of polyomavirus T-antigen gene sequences, and amplification products hybridizing preferentially to probes specific for simian virus 40 (SV 40), a monkey poliomavirus, were found in 10/11 analyzed ependymomas. SV40 infections are traditionally thought to be uncommon and harmless. Given these studies, this belief must be re-evaluated. Sources of SV40 infections remain unknown. Millions of people were inadvertently inoculated with SV40 *via* contaminated poliovaccine. It is also possible that SV40 is present in human populations and is transmitted similarly to human polyomaviruses. Further epidemiologic studies are required to clarify this hypothesis.

Genetics
The most common chromosomal abnormality found in ependymomas is an allelic loss of chromosome 22. This chromosomal region probably carries a *tumor suppressor* gene characteristic of ependymoma that is distinct from the *NF-2* gene (Bijlsma *et al*., 1995) and also from the *tumor suppressor* gene *hSNF5/INI1*, which has been located to 22q11.23, a region known to contribute to the pathogenesis of renal and extrarenal rhaboid tumors (Kraus *et al.*, 2001). A recent study, using comparative genomic hybridization on 42 primary and 11 recurrent pediatric ependymomas has shown three distinct genetic patterns in the primary tumors characterized by: a) structural, few, mainly partial imbalances; b) 13 or more chromosome imbalances with a non-random pattern of whole chromosome gains and losses; and c) a balanced genetic profile significantly associated with younger age at diagnosis, suggesting that ependymomas arising in infants are biologically distinct from those occurring in older children. The group with structural imbalances had a significantly worse outcome compared to tumors with a numerical or balanced profile (Dyer *et al*., 2002).

Clinical description
The signs and symptoms manifested in ependymomas depend upon the tumor size and location.
In *posterior fossa ependymomas*, symptoms are related to the obstruction of the fourth ventricle, leading to hydrocephalus. The most common presenting symptoms are nausea and vomiting, followed by headache. Signs such as ataxia and hemiparesis, and symptoms including visual disturbances, dizziness, and neck pain are related to compression of the posterior fossa structures. Children under 2 years of age present with vomiting, lethargy and irritability, which reflect the presence of open sutures enabling hydrocephalus to expand.
Supratentorial ependymomas are characterized by signs and symptoms usually associated with mass effect or focal neurological deficits, such as memory impairment, behavioral change and lethargy. Obviously, none of these symptoms are specific for ependymomas.
In most of *spinal ependymomas*, the first symptom is segmental dysaesthesia, because tumor originates in the region of the central canal expanding symmetrically and circumferentially, thereby compressing the crossing spinothalamic segmental fibres.

Prognosis
The standard grading criteria for ependymoma in the literature are controversial and their prognostic significance remains debatable (Mørk *et al*., 1977; Perilongo *et al*., 1997; Schild *et al*., 1998; McLaughin *et al*., 1998; Duffner *et al*., 1993; Goldwein *et al*., 1990).
In a recently published Italian study (Massimino *et al., in press*) one third of tumors were classified as grade 3 or anaplastic. In the literature, the histological distribution is very heterogeneous, with some series containing a high percentage of anaplastic tumors (Grill *et al*., 2001; Horn *et al*., 1999), especially if they include children below 3 years of age, and other series reporting only grade 2 tumors (Needle *et al*., 1997; Shaw *et al*., 1987; Tomita *et al*., 1998; Awaad *et al*., 1996).
In a recent comment on histological classification and prognostic criteria, Packer (2000) observed that the lack of an accepted grading system prevents any conclusions as to the prognostic

values of histological features. In the Italian series, histological grading was the most powerful prognostic indicator, grade 2 tumors being associated with a progression-free survival (PFS) at five-years of 66% and an overall survival (OS) of 87%, while anaplastic ependymoma only reached 29% and 37% for PFS and OS, respectively. The recent paper by Merchant *et al* (2002) using the same histopathological criteria on a retrospective series confirmed the prognostic impact of grading.
Growth fraction, measured with the proliferation marker Ki-67, correlates with tumor grade, thus malignant ependymoma corresponds to the highest growth fraction (Schroder *et al*., 1993). The immunohistochemical detection of the Ki-67 antigen on archival material is feasible and results can be used for prognostic evaluation (Figarella-Branger *et al*., 2000). The ERBB2 and ERBB4 receptors, which belong to the RTK I family, are frequently co-expressed in childhood ependymoma and may represent an additional risk factor for ependymoma prognosis: Gilbertson has recently reported a group characterized by a high-molecular risk, *i.e.* Ki-67 labeling index (LI) ≥ 25% or high ERBB2 and ERBB4 coexpression (Gilbertson, et al., 2002).

Diagnostic methods
Like in any other clinical situation when a brain mass is suspected, a cranial computed tomography (CT) and a magnetic resonance (MR) are mandatory. CT scans show infratentorial ependymomas as usually isointense to brain parenchyma, often with calcifications. MRI images depict these tumors as usually isointense with gray-matter on T1-weighted images, hyperintense on proton-density weighting, and isointense on T2-weighted imaging (Tortori-Donati *et al*., 1995). Staging must always include MRI of the spine, including cauda and filum terminale that can be sites of metastatic deposits, and spinal fluid cytologic examination, although metastatic ependymomas at diagnosis are found in less than 10% of patients.

Epidemiology
Ependymoma accounts for 10% of childhood central nervous system tumors, with half the cases presenting in children below 3 years of age, and 10-15% as spinal tumors (Mørk *et al*., 1977; Nazar *et al*., 1990; Robertson *et al*., 1998). These tumors are the third most common type of pediatric brain tumors, after pilocytic astrocytoma and medulloblastoma.
Tumor may occur at any age, with one peak between 0 and 10 years and another between 40 and 50 years. Intracranial ependymomas prevail in young people and spinal ependymomas arise mainly in older patients. Spinal and intracranial ependymomas differ also as to their biology, prognosis and treatment.
Both sexes are equally affected and sex has no prognostic role.
Apart from intracranial location that is subdivided into the supratentorial, infratentorial and spinal regions, ependymomas can also arise in ectopic locations, such as the sacro-coccigeal region.
Intracranial ependymomas in children are more frequently located infratentorially.

Management
Most of our knowledge about ependymoma derives from the reports of single institutional series spanning many years, so it is not surprising that the conclusions of some reports are partially in conflict. There are still uncertainties as to the optimal radiotherapy volumes, doses and techniques, the usefulness of chemotherapy as adjuvant treatment, and the prognostic impact of histological grading, patient's age, tumor site, persistent hydrocephalus (Souweidane *et al*., 1988; Perilongo *et al*., 1997; Grill *et al*., 2001; Schild *et al*., 1998).
The management of intracranial ependymoma is still a controversial topic in pediatric neuro-oncology and, among institutions, may range from surgery alone to a combination of surgery, radiotherapy and chemotherapy (Nazar *et al*., 1990; Robertson *et al*., 1998; Schild *et al*.,1998; McLaughin *et al*., 1998; Vanuystel *et al*., 1992; Timmerman *et al*., 2000). The lack of uniformity is partially justified by the disappointing results reported by most series. The five-year survival for children with ependymoma ranges between 30% and 50% with a worse prognosis for patients with residual disease after surgery. In many series reported so far, the annual accrual rate does not exceed 3-8 patients and this paucity contributes to uncertainties regarding the optimal treatment.
The main challenge in treating ependymoma is local relapses, which account for most failures. Ependymoma has consequently been considered as a "surgical disease" since total excision can only be reached in about half of the cases (Robertson *et al*., 1998; Perilongo, *et al*., 1997; Grill et *al*., 2001; McLaughin *et al*., 1998).
Isolated metastatic relapses have been reported in 3-15% of cases (Robertson *et al*., 1998; McLaughin *et al*., 1998; Duffner *et al*., 1993; Salazar *et* al., 1983) despite the use of cranio-spinal radiotherapy (Vanuystel *et al*., 1992; Timmerman *et al*., 2000), and different total radiotherapy doses and fractionations (Goldwein *et al*., 1990; Kovnar *et al*., 1996, Goldwein *et al*., 1990*b*).

In ependymoma, complete resectability depends not only on the skill of the operator, but also on the characteristics of the tumor itself (Healey *et al*., 1991; Spagnoli *et al*., 2000; Sutton *et al*., 1990-91): in more than 50% of cases, infratentorial ependymoma (Kricheff *et al*., 1964; Ikezaki *et al*., 1993) involves the cerebello-pontine angle intimately related with the cranial nerves. Finally, the resectability of ependymoma may also reflect a favorable tumor biology determining a non-infiltrating growth pattern (Horn *et al*., 1999; Spagnoli *et al*., 2000; Tomita *et al*., 1998). Complete tumor removal may therefore be achieved in several stages, using "second-look" resections, either after an early post-operative scan or later on, after chemotherapy and before radiotherapy. This approach can be wiser than a single "heroic" and probably more harmful surgery that can lead to severe sequelae (Healey *et al*., 1991; Foreman *et al*., 1997; Allen *et al*., 1998).

Adjuvant radiotherapy is mainly used on the basis of historical data that still leaves many questions unanswered (Robertson *et al*., 1998; Schild *et al*., 1998; Horn *et al*., 1999). In view of the results reported by Vanuystel and Brada (1991), which concluded that spinal seeding is not influenced by the extent of radiotherapy volume (local versus craniospinal radiotherapy), the majority of neuro-oncologists use local radiotherapy, which has become a standard post-operative treatment in most institutions (McLaughin *et al*., 1998; Paulino *et al*., 2000; Wallner *et al*., 1986). Hyperfractionation radiotherapy (HFRT) was adopted by the Italian neuro-oncology group (Massimino *et al., in press*) in the attempt to increase the chances of local tumor control, both in patients with residual tumor after surgery and in patients without residual tumor, throughout the delivery of a higher total dose (70.4 Gy) in comparison with conventional treatments (54-56 Gy), without increasing late damages on normal brain tissues. The preliminary results reported by a mono-institutional series of 19 patients were indeed very favorable, with a PFS of 72% at 5 years after systemic chemotherapy using a HFRT at a total dose of 72 Gy (Needle *et al.*, 1997). Results from the Italian study, however, show that local failures have not been prevented by using the hyperfractionated schedule or by delivering a high total dose in most cases. Despite several studies supporting a dose-response relationship in radiation therapy for ependymoma (Paulino *et al*., 2000; Shaw *et al*., 1987; Healey, *et al*., 1991), the schedule adopted has not dramatically improved local control compared to historical series, especially in patients with residual disease and anaplastic histology.

Regarding chemotherapy, the only randomized study published to date, using vincristine and lomustine, concluded that this regimen did not improve survival (Evans *et al*., 1996). Among other drug combinations, the "8 in one" regimen, MOPP and etoposide-carboplatin, gave disappointing results (Robertson *et al*., 1998; Bouffet *et al*., 1999), while the best response rate so far has been reported by Duffner with the POG "baby-brain" protocol (Duffner *et al*., 1993): the combination of vincristine plus cyclophosphamide, alternating with etoposide and cisplatin, resulted in an objective response of 48%. In this study, moreover, delaying radiotherapy until a long chemotherapy schedule (12-24 months) did not seem to interfere with the outcome of radiotherapy. However, the role of chemotherapy in newly-diagnosed ependymoma remains a matter of debate. As Duffner *et al.* (Duffner *et al*., 1993; Duffner *et al.*, 1999; Duffner *et al*., 1998) have already pointed out, the real question is not related to the chemo-sensitivity of this tumor, that we and other authors have identified (Fouladi *et al*., 1998; White *et al*., 1993; Kühl *et al*., 1998), but whether chemotherapy can be curative, bearing in mind that children with ependymoma tend to develop progressive disease after several years, in a striking contrast with other pediatric tumors that usually reoccur earlier. Most studies using chemotherapy, however, have contributed little to our understanding of the activity of the drugs adopted, because these were used shortly after radiotherapy (Timmerman *et al*., 2000; Needle *et al.*, 1997; Salazar *et al*., 1983), or regardless of the presence of measurable disease (Perilongo *et al*., 1997; Evans *et al*., 1996). A recent hypothesis, also stemming from the issue of the "baby"-protocols (Grill *et al*., 2001; Duffner *et al*., 1998) is that chemotherapy could facilitate a subsequent second surgical approach, not only because of reduction or stabilization of tumor volume, but also for the time left to the recovery from post-surgical morbidity (Souweidane *et al*.,1998; Bouffet *et al*., 999; Bouffet *et al*., 1998) and possibly because the residual tumor becomes more circumscribed and amenable to resection (Foreman *et al*., 1997).

Unresolved questions

The different prognostic criteria adopted in the classification of risk categories for intracranial ependymoma have contributed in the past to determine very different treatment approaches. Treatment can be tailored according: 1) to tumor grade, with more aggressive strategies for the anaplastic histotype; 2) to tumor's site of origin or age at diagnosis; 3) or to surgical results, like in the Italian series (Massimino, *et al., in press*). Each of these approaches may determine a

different trend in the natural history of the disease, but it is more likely that we are dealing with different diseases, all grouped under the same name of ependymoma.
We conclude that, to the best of our current knowledge, surgery remains the main treatment for ependymoma, but it should be tailored in a prospective setting to suit the patient's neurological conditions, in one or more operations, to decrease surgical morbidity, thereby increasing chances to implement subsequent treatment. Chemotherapy regimens so far adopted are not the key for the cure of ependymoma, but drugs can enable a further surgery by reducing volume or infiltrating aspects of residual tumor. As far as radiotherapy is concerned, hyperfractionation radiotherapy does not seem to have a significative therapeutic impact in comparison with historical controls. New radiotherapy treatment techniques, such as 3-D conformal radiotherapy, may enable the delivery of high radiation doses focused to small volumes while sparing significantly surrounding normal brain and improving the therapeutic ratio, and patients with poor prognosis should benefit from their application.

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