

Ependymomas of the adult: molecular biology and treatment

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Purpose of review

To review state of art and relevant advances in the molecular biology and management of ependymomas of the adult.

Recent findings

Ependymomas of the adult are uncommon neoplasms of the central nervous system, and may occur either in the brain or the spinal cord. Compared with intracranial ependymomas, spinal ependymomas are less frequent and exhibit a better prognosis. Studies performed on genetic changes in ependymoma provide some insight into the pathogenesis and prognostic markers and yield new therapeutic targets, particularly focused on signal transduction modulators. The majority of studies have shown a major impact of extent of resection; thus, a complete resection must be performed, whenever possible, at first surgery or at reoperation. Involved field radiotherapy is recommended for anaplastic or incompletely resected grade II tumors. Craniospinal irradiation is reserved for metastatic disease. Chemotherapy is not advocated as primary treatment, and is best utilized as salvage treatment for patients failing surgery and radiotherapy.

Summary

Owing to the rarity of the disease, the literature regarding ependymomas in adults is scarce and limited to retrospective series. Thus, the level of evidence regarding therapeutic strategies is low and universally accepted guidelines are lacking. Molecular biology studies suggest some potential new therapeutic targets.

Keywords

ependymomas, molecular biology, prognostic factors, treatment

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Introduction

Ependymomas are rare neuroepithelial tumors that arise from the ependymal cells of the cerebral ventricles, the central canal of the spinal cord and cortical rests. Ependymomas constitute 8–10% of brain tumors in children and up to 4% of brain tumors in adults [1]. Ependymomas represent 15% of spinal cord tumors and up to 60% of spinal cord gliomas [1,2*]. Compared with intracranial ependymomas, spinal ependymomas are less prevalent and exhibit a better prognosis [3].

The WHO classification (2000, 2007) separates ependymomas into subependymomas (WHO grade 1), myxopapillary ependymomas (WHO grade 1), ependymomas (WHO grade 2), and anaplastic ependymomas (WHO grade 3).

Given the low incidence, the literature regarding ependymomas in adults is sparse [1,4*]. Most series combine pediatric and adult ependymomas, grade II and grade III tumors, are retrospective, include limited numbers of patients and span several decades in which diagnostic

and therapeutic modalities have changed. As a consequence, the level of evidence regarding therapeutic strategies is low and universally accepted guidelines are lacking.

Recently, the genetic changes in ependymoma have undergone extensive analysis, but despite these efforts, ependymomas are not as well characterized as other primary brain tumors such as the malignant gliomas or medulloblastomas [5,6]. The studies that have been performed do provide some potential insight into the pathogenesis of the disease, possibly helping to define the origin of the ependymoma stem cell, may generate prognostic markers and, most importantly, may yield therapeutic targets, particularly focused on signal transduction modulators.

Tumor biology and outcome seem more closely related to tumor location. Patient age and WHO classification have less bearing on genetic profile than tumor location, with the distinction of brain versus spinal cord having the greatest impact on molecular characteristics and, in adults, prognosis. In this review we focus on state of

art and relevant advances in the molecular biology and management of adult ependymomas of the adult.

Molecular biology

Data concerning the molecular abnormalities of ependymomas of the adult are sparse.

Chromosomal changes

Early studies of molecular genetic alterations in ependymomas revealed a high incidence of loss of heterozygosity (LOH) on chromosome arm 22q, often with accompanying NF2 mutations [7,8]. These changes were found at a much higher frequency in intramedullary spinal cord tumors. An inverse association with 11q LOH was also noted as the 11q LOH was found most commonly in tumors that do not demonstrate the 22q LOH. Along with the 11q LOH, mutations in the *MEN1* gene (located at 11q 13) were occasionally found. Interestingly, in a few cases, the *MEN1* gene was intact when the tumor was low grade (WHO grade II), but the mutation was found at tumor recurrence with malignant transformation to a grade III neoplasm. This finding suggests that the *MEN1* gene mutation is associated with the malignant change. Chromosome 10q LOH, a common finding in malignant gliomas, was uncommon in a wide variety of ependymomas including spinal cord, cerebral and myxopapillary. Genomic losses have also been reported on 2q, 4q, 5q, 6q, 7q, 15q, 16q, 17p and 19p, although these are much less common [9–11]. Chromosome gains, as determined by comparative genomic hybridization (CGH), were detected in a high percentage of ependymomas, but there was a high degree of variability. These included both arms of chromosome 17, 9q, 12p, 13q, 20q and 22q. Additionally, gain of 1q has been reported in a moderate percentage of ependymoma samples [12–15]. However, although this chromosomal change was more common in pediatric and anaplastic ependymoma samples, the prognostic significance was not seen in all studies.

Distinct patterns of chromosomal changes based on tumor location could exist, with distinct changes associated with spinal, infratentorial and supratentorial locations [10]. However, with the exception of a few prominent examples, such as the coincident loss of *NF2* or *MEN1*, most of the chromosomal abnormalities have not been clearly associated with genetic changes that contribute to tumorigenesis or biology.

Molecular pathway abnormalities

In ependymoma several molecular pathways abnormalities have been identified. Overexpression of the ErbB2 and ErbB4 receptors was found in over 75% of pediatric ependymomas and correlated with tumor proliferative index and prognosis [16]. Similar findings have been reported in adult supratentorial ependymomas (Gilbertson

R, personal communication). A variety of other molecular pathway targets have been reported. These include increased expression of the integrin $\alpha v \beta 3$ in a high percentage of intracranial ependymomas, and expression of annexin A1 and cyclo-oxygenase-2 [17,18,19^{*}]. The study by De Bustos *et al.* [20] reports a single nucleotide polymorphism in the platelet derived growth factor receptor α (*PDGFR α*) gene promoter region in ependymomas, suggesting that the PDGF pathway may have a functional role in tumor biology.

Gene array based profiles

Several studies have examined gene expression in a variety of ependymomas using microarray technology [21,22,23^{*}]. The study by Korshunov *et al.* [21] analyzed 39 newly diagnosed ependymomas and discovered patterns that could distinguish grade II from grade III supratentorial ependymomas, but could not find a similar pattern for infratentorial tumors. Similarly, they found a unique gene expression pattern for spinal cord tumors that distinguished these from cranial tumors. Furthermore, separate gene expression profiles were associated with typical spinal cord ependymomas and myxopapillary tumors. Suarez–Merino *et al.* [22] examined 19 pediatric ependymomas and found 112 genes that were abnormally expressed compared with normal brain. These included genes involved in cell cycle, cell adhesion and proliferation, notably the oncogene *WNT5A* and the *p53* homologue *p63*. The *NF2* associated gene *SCHIP-1* was underexpressed, a potential alternative to *NF2* loss as described earlier. The study by Lukashova-v Zangen *et al.* [23^{*}] examined 47 ependymomas and was able to identify a gene profile with 27 genes associated with a good prognosis (defined as survival of >10 years). Similar to previous studies, they found distinct genes that differentiated spinal cord from cranial ependymomas but not patterns associated with tumor grade or age.

Overall, no uniform set of prognostic, or ‘location’, or age specific genes were identified. However, each study was able to generate specific patterns of gene expression that were highly correlated with tumor location and prognosis.

Epigenetic studies

The methylation status of the gene promoter region of several known tumor suppressor and related genes has been examined in ependymomas [24–26]. The tumor suppressor gene *RASSF1A* was methylated in a high percentage of ependymomas in two separate studies [25,26]. Interestingly, the *MGMT* gene was rarely methylated in ependymomas. Additionally, some apoptosis-associated tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathway genes were also hypermethylated [26]. The putative tumor suppressor gene *HIC-1* was hypermethylated exclusively in intracranial ependymomas, but not in spinal cord tumors,

providing further evidence of the likely different pathogenesis of these tumors [24].

Ependymoma stem cells

Recent studies support the concept of self-renewing and multipotent stem like cells in cancers that generate the heterogeneous cell types that populate the malignancies. Cancer stem cells provide an opportunity to study fundamental aspects of tumorigenesis and may be a critical target of treatment as a successful eradication of these cells is necessary for cure. Radial-glia cells have been proposed as the stem cells for ependymomas. Work in the Gilbertson laboratory provides compelling evidence, using molecular profile comparisons, that ependymoma stem cells from cranial and spinal cord tumors recapitulate the molecular profiles of the location-specific radial glial cells found during development [27,28^{*}]. Studies of the radial glial cells may provide insights into the pathogenesis of ependymomas and potential therapeutic targets. For example, loss of the adherens gene αE -catenin or dysregulation of the notch cell signal pathway have been found to alter the behavior of radial glial cells, emulating ependymoma activity.

Implications for prognosis and treatment

The studies summarized in the earlier section suggest several potential therapeutic targets. The prominent finding of over-expression of ErbB2 (Her2) and, in some cases, ErbB1 (EGFR) suggests that therapies that target these receptors or pathways may have activity. A polymorphism of the *PDGFR α* gene promoter, that causes dysregulation of this pathway, suggests that blocking this receptor may be a potential treatment strategy. Similarly, overexpression of the $\alpha v\beta 3$ integrin was found in a high percentage of ependymomas, and agents are being tested that specifically target this integrin. The epigenetic analyses may also provide insight into the overall poor response of ependymomas to conventional cytotoxic chemotherapy. Several studies have reported that in most cranial ependymomas the promoter region of the *MGMT* gene is unmethylated, and thus gene expression is likely. Unmethylated *MGMT* promoter has been associated with a poorer prognosis in glioblastoma and a lower response to alkylating agent chemotherapy [29]. Therefore, as is proposed and undergoing evaluation in malignant gliomas, strategies to modulate *MGMT* activity may have benefit in ependymomas [30]. The development of ependymoma models, using a cancer stem cell system, should facilitate testing of new treatment regimens prior to implementation in clinical trials.

Intracranial ependymomas

Intracranial ependymomas are most common in children, whereas they do rarely arise in adults. Regarding natural

history and management, much of what is known about pediatric patients likely holds true for adults.

Location and patterns of failure

Intracranial ependymomas may occur in either the supratentorial or infratentorial compartment. Tumors arising in the supratentorial compartment (50–60% of adult ependymomas) most often are hemispheric or occur in relationship to the third ventricle. Tumors arising in the posterior fossa (40% of adult ependymomas) are found either in a midline (fourth ventricle) or lateral (cerebellopontine angle) location, and may invade the brainstem or extend below the foramen magnum. Up to 30% of intracranial ependymomas are anaplastic.

Cerebrospinal fluid (CSF) dissemination develops in 3–15% of all intracranial ependymomas, and is more frequent in infratentorial and anaplastic tumors [31–34]. The occurrence of this complication at the time of presentation is less than 5%. Extraneural metastases are extremely rare. The vast majority of tumor recurrences occur as a result of lack of local tumor control, and there are a significant number of late failures [35].

Prognostic factors

The 5-year and 10-year overall survival rates for adults with intracranial ependymoma range from 62–84.8% and from 43–76.5 respectively [36,37,38^{**}]. In the same series the 5-year and 10-year progression-free survival rates range from 43–65.3% and from 24–52.8% respectively.

Generally, accepted prognostic factors are lacking. The prognostic value of tumor grade remains a controversial issue, likely due to variability in the definition of anaplasia, pathological misdiagnoses (central neurocytomas, medulloblastomas, metastatic carcinomas, papillary meningiomas) and inclusion in some series of ependymoblastomas and subependymomas, which exhibit a different biological behavior. Some authors did not find any correlation between survival and histologic grade [37,39], whereas most series have demonstrated a significant longer overall and progression-free survival for low-grade ependymomas [36,40–43]. A large multiinstitutional retrospective analysis performed in France on 152 adult patients diagnosed with ependymoma has recently reported that after multivariate analysis histological grade is the most powerful prognostic factor [38^{**}]. The assessment of proliferative potential of tumors (by means of Ki-67 immunolabeling) has been suggested to be of some usefulness in outcome prediction [38^{**},42].

The prognostic value of tumor location is probably confounded by histological grade and to a lesser extent patient age. Studies on adult ependymomas [36,37,38^{**}] show a trend towards a more favorable prognosis for patients with

infratentorial tumors. Supratentorial tumors could have a worse prognosis, because more often they exhibit peripheral infiltrative growth and anaplastic histology [38^{••},40,41,44]. Among supratentorial ependymomas, tumor grade is significantly associated with either risk of recurrence [45] or survival [46[•]].

Younger age (<40 or <55 years) is associated with better prognosis in the series of Reni *et al.* [37] and Metellus *et al.* [38^{••}], but not in that of Guyotat *et al.* [36]. Last, Karnofsky Performance Status could be associated with longer survival [38^{••}].

Therapeutic management

Surgery represents the most important treatment modality for ependymomas, and the goals of surgery are to make a histologic diagnosis, remove obstacles to CSF flow and achieve a complete tumor resection. The majority of series report that completeness of surgical resection is significantly associated with better overall and progression-free survival [32,38^{••},45,46[•],47–49]. In some reports, the extent of surgery also correlates with CSF dissemination and metastatic rate [32,41,50]. The frequency of a complete resection is higher in surgical series than in radiotherapy series; overall, image-verified (MRI) gross total resection is achieved in 50–75% of patients. It can be hindered by anatomical factors, such as adherence of the tumor to the floor of the fourth ventricle, brain stem, lower cranial nerves or major vascular structures. Reoperation following initial incomplete surgery or at tumor recurrence is increasingly advocated, assuming that a complete resection is achievable [38^{••},47,51]. There are a number of reasons why gross total resection cannot be accomplished at first surgery: patient *in extremis* immediately prior surgery, imaging not matching with findings at operation, and expertise of the neurosurgeon. Currently, there is controversy regarding the optimal time of second surgery after initial incomplete surgery: should it be as soon as possible or after a brief course of chemotherapy?

Because a risk for CSF dissemination exists for all patients with newly diagnosed ependymoma, a disease staging, including both craniospinal MRI and CSF cytology, is mandatory following surgery. Regular surveillance with MRI could discover asymptomatic recurrences (in up to 43% of patients who recur), and impact survival and subsequent treatment, in particular the ability to perform a reoperation with complete resection [52]. Several open questions related to follow-up remain: how often and for how long must the surveillance with MRI be performed? When CSF cytology is needed?

Radiotherapy is well established in the management of intracranial ependymomas, despite the lack of randomized clinical trials showing benefit and the general

opinion that ependymomas are relatively radioresistant, without a clear dose–response relationship [34,53,54]. There is general consensus that postoperative radiotherapy is part of standard of care for patients with anaplastic ependymomas. In the past whole-brain radiotherapy (WBRT) or craniospinal radiotherapy (CSI) have been largely employed, but many recent papers have reported no improvement in outcome and/or reduction in frequency of CSF spread when larger treatment volumes have been used [44,49,55–60]. Thus, localized ependymomas are generally treated with limited-field radiotherapy to deliver doses up to 60 Gy, whereas CSI is reserved in the setting of CSF dissemination.

The role of radiotherapy in patients with grade II ependymomas is more controversial [37,38^{••},61]. A number of retrospective series have reported an advantage in terms of survival for patients (mostly after incomplete resection) receiving adjuvant radiotherapy over those receiving surgery alone [38^{••},57,58,62,63], and a better local tumor control with doses greater than 50 Gy [64]. Moreover, a paper on posterior fossa ependymomas [49] has reported that even after gross total resection, confirmed by a postoperative imaging, adjuvant radiotherapy significantly improves local control. Conversely, other authors are in favor of deferring radiotherapy until tumor progression for totally resected intracranial ependymomas (especially for supratentorial tumors) [65,66]. In the absence of data from randomized clinical trials, reserving radiotherapy for recurrent disease can be an option in patients with intracranial grade II ependymoma after either total or subtotal resection, provided there is careful clinical and MRI monitoring.

Stereotactic radiotherapy, by increasing the dose to the tumor ('boost'), could overcome the radioresistance [67–70], but the superiority over conventional techniques remains to be proven by clinical trials.

Few data are available regarding the role of chemotherapy. Chemotherapy has been employed at the time of relapse, and platinum-based regimens are considered the best available option, with response rates (31–67%) higher than that after nonplatinum-based regimens (11–13%) or nitrosourea-based regimens (25%) [71,72]. Moreover, no significant differences regarding time to progression or overall survival have emerged among the various regimens. Anecdotal responses have been reported with irinotecan/topotecan, ifosfamide, diaziquone, idarubicin and tamoxifen plus isotretinoin [73,74].

Temozolomide may have some role because xenograft models have documented activity of temozolomide against ependymoma [75], and a patient with recurrent intracranial ependymoma, treated with temozolomide and in remission 10 years after completing chemotherapy, has been

reported [76]. A phase II study with temozolomide in recurrent ependymoma is ongoing at the University of Torino, and preliminary results are promising [77].

Spinal cord ependymomas

Spinal cord ependymomas may arise at any age, but present most frequently in adults (20–40 years of age).

Location and patterns of failure

There are two distinct categories of spinal cord ependymomas. The myxopapillary type accounts for up to 50% of cases, and is located in the cauda equina with occasional extension into the conus medullaris. The second type is the classic (cellular) ependymoma, which accounts for up to 50% of cases, and is located in the cervical (more frequently) or thoracic spinal cord. Approximately, 50% of tumors span three or more vertebral levels. Overall, about 90% of spinal cord ependymomas have a benign pathology, are slow growing and tend to compress rather than infiltrate the adjacent normal tissue.

The risk of CSF seeding is low, with Peschel *et al.* [78] reporting a rate of 7%. Although rare, recurrences could involve the brain [79,80]. Recently, a case of an early (six weeks of initial surgery) multifocal dissemination of a myxopapillary ependymoma has been reported [81[•]]. Extraneural metastases are extremely rare [82].

Prognostic factors

Recent studies indicate long survival and low recurrence rate in patients with spinal ependymomas. The 5-year, 10-year and 15-year survival rates range from 83 to 97%, 74 to 97% and 61 to 75% respectively [80,83,84]. In the same series the 5-year, 10-year and 15-year progression-free survival rates range from 70 to 75%, 50 to 62% and 35 to 46% respectively.

Regarding prognostic factors, younger age [80,84], smaller tumor size [84], distant spinal disease [85], and myxopapillary histology [86] have been variably associated with prolonged overall or progression-free survival. Conversely, tumor location and type, duration of symptoms prior to diagnosis and Karnofsky Performance Status has not emerged as prognostically relevant.

Therapeutic management

A general consensus, based on institutional experiences, exists regarding management of spinal ependymomas. Extent of surgery is the strongest covariant predicting survival, and local control rates after gross total resection of 90–100% have been reported [87–89,90[•]]. Owing to earlier diagnosis through MRI and modern microsurgical techniques, gross total resection is achieved in 50–65% of patients [90[•],91,92].

Radiation therapy is not generally prescribed following gross total resection, except for the rare anaplastic variants [93]. However, some authors have reported that adjuvant radiotherapy may reduce the rate of tumor progression even after gross total resection [80].

Subtotally resected ependymomas have a predilection for recurrence (up to 50–70%) without any adjuvant therapy [87,94], and thus most institutions use adjuvant conformal radiotherapy, with a range of local control rates of 66–100% [79,80,84,95–98,99[•]]. Some investigators have observed a trend towards an improvement in local control with doses of 50 Gy or higher, and advocated treatment to 55 Gy with the last 5 Gy given to a boost volume [100]. Current models of spinal cord tolerance suggest that up to 55 Gy in conventional fractions (1.8–2 Gy) can be delivered safely with a less than 2% risk of radiation myelopathy [101–103]. Nevertheless, in the absence of strong evidence for a dose–response relationship, most institutions continue to recommend doses in the range of 40–50 Gy (more commonly 45 Gy). CSI should be reserved for patients with diffuse disease.

Multimodality salvage treatments (reoperation, reirradiation with standard techniques or cyberknife) can yield excellent results in terms of local control and extended survivals [90[•]].

Few data are available regarding the benefit of chemotherapy for spinal cord ependymomas, and all deal with recurrent disease. Begemann and De Angelis [104] suggested some activity of single-agent carboplatin. Chamberlain [105] reported two partial responses and five patients with stable disease among 10 consecutive patients receiving chronic oral etoposide. Fakhrai *et al.* [106] reported a slight tumor regression and improvement in neurological symptoms with imatinib in a spinal ependymoma, where the tumor expressed PDGF receptors.

Conclusion

The studies published to date suggest that the histologic diagnosis of ependymoma encompasses a variety of neoplasms that have a similar appearance using conventional microscopy, but vary widely in the genetic alterations that likely led to tumorigenesis and subsequent tumor biology.

The majority of studies on ependymomas have shown a major impact of extent of resection on outcome, even if patient numbers have been inadequate to perform reliable multivariate analyses. Complete resection can achieve excellent local control and survival, especially in spinal ependymomas. For incompletely resected intracranial tumors, postoperative radiotherapy is recommended. Salvage treatments (including CSI) can improve

quality of life and duration of survival of patients with local recurrence or leptomeningeal seeding. The predominant pattern of relapse is local, thus the priority for future studies is to maximize the probability of local tumor control by increasing the proportion of patients undergoing complete resection and 'second surgery' for those with initial incomplete resection, possibly with combined use of chemotherapy. Moreover, the benefit of radiotherapy could be enhanced by dose escalation using modern techniques. A better knowledge of molecular pathways of tumor progression is needed to identify predictive factors and novel targeted agents. In conclusion, multiinstitutional and international studies are necessary to improve understanding of the clinical behavior, biology and management of patients with ependymomas.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 769–770).

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