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Overview

An Overview of the Management of Adult Ependymomas with Emphasis on Relapsed Disease

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Abstract

Ependymomas are rare neoplasms of the central nervous system. Disease-free survival after relapse is poor and approaches to treatment in recurrent disease often palliative. This overview summarises the management of primary disease for which broad consensus exists. We also extensively review treatment options in relapsed disease for which approaches to treatment are varied due to the paucity of literature evidence. Incorporated in this overview is a survey of UK neuro-oncology units to form a snapshot of current UK practise with respect to preferred systemic therapy regimens for patients with recurrent ependymoma. The outcome reflects a preference for mainly oral-based regimens.

Universal guidance is lacking in the management of non-operable irradiated recurrent ependymoma and there are worthy therapeutic avenues for further investigation, in particular the role of radical re-irradiation and also the potential of bevacizumab in advanced disease. It is hoped that advances can be achieved by multicentre collaboration in future studies to overcome the difficulties posed by achieving meaningful data in such a rare tumour with extensive natural history.

Key words: Chemotherapy; ependymoma; radiotherapy; re-irradiation

Statement of Search Strategies Used and Sources of Information

The aim of the overview was to analyse the available published evidence related to relapsed adult ependymoma. Pubmed was searched for articles containing the words 'adult ependymoma', 'recurrent ependymoma', 'relapsed ependymoma chemotherapy and radiotherapy' and 're-irradiation in ependymoma'. All literature to 1 April 2012 was considered.

Introduction

Ependymomas are slow-growing tumours of the central nervous system (CNS) that arise from the ependymal cells lining the cerebral ventricles, the central canal of the spinal cord and filum terminale [1]. Ependymal cells are also present in the brain parenchyma as a result of migration in the embryonic stage from periventricular areas to the cortex. Therefore, ependymomas can be found in the brain parenchyma [2]. About 60% of the ependymomas are infratentorial and 40% are supratentorial [3]. The single most common location is in the region of the fourth ventricle. In about 3–15% of all intracranial ependymomas, cerebrospinal fluid (CSF) dissemination may develop and is more frequent in infratentorial and anaplastic tumours [4,5]. Extraneural metastases are extremely rare and only a few cases have been reported [6–9].

Ependymomas are rare, accounting for about 5% of all CNS malignancies [10]. They are more common in children; about 60% of ependymomas occur in children younger than 16 years and 25% occur in children younger than 4 years [11–13]. Among primary CNS cancers, it is estimated that the ependymomas constitute 8–10% of all paediatric tumours, whereas in adults they account for fewer than 4% of adult nervous system tumours, combining both brain and spinal cord tumours [14].

In England and Wales, there were 9156 registered cases of brain tumour in 2010 and it was estimated that ependymomas constituted around 2%; no further subclassification details were available (personal communication,

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David Greenberg/National Brain Tumour Registry, 6 March 2013). Metellus *et al.* [15] quoted 46 (30.3%) supratentorial and 106 (69.7%) infratentorial; 109 (71.7%) were grade II and 43 (28.3%) were grade III in a cohort of 152 cases.

Pathological Classification

The World Health Organization classifies ependymal tumours as follows [16]:

Grade I: Subependymomas and myxopapillary ependymomas
Subependymomas are slow growing; benign neoplasms and myxopapillary ependymomas are slow-growing ependymal gliomas mainly in the region of conus medullaris, cauda equina and filum terminale of spinal cords in young adults.
Grade II: Ependymomas
Generally slow-growing tumours of neoplastic ependymal cells.
Grade III: Anaplastic ependymomas
Malignant gliomas of ependymal differentiation.

Ependymoma grading is based on the recognition of a number of characteristics. The most important features are necrosis, mitotic activity, vascular proliferation, cytological atypia and degree of cellularity. Tumour grading is particularly influenced by the measurement of mitotic activity and endothelial proliferation. Low-grade tumours are more common than high-grade tumours [17].

Immunohistochemistry shows that ependymomas tend to show vascular endothelial growth factor expression, which is relevant when considering treatment options [18].

Data regarding the studies of genetic changes in ependymomas of adults are sparse. Recently, efforts have been made to understand the exact molecular abnormalities in ependymomas, and despite extensive analysis, the genetic pathology is not well characterised in ependymomas as compared with that in other primary brain tumours [19]. Various studies have revealed that loss of heterozygosity on chromosome arm 22q is common in ependymomas and NF2 gene mutations are associated with this loss of heterozygosity in spinal ependymomas [20]. Genomic losses have also been reported on the chromosomes arms 2q, 4q, 5q, 6q, 7q, 15q, 16q, 17p, and 19p [14,21]. TP53 gene mutations, although common in other malignancies, are rare in ependymomas [22].

It has been reported that epigenetic changes may play a significant role in the pathogenesis. It was found that the tumour suppressor gene RASSF1A was methylated in a high percentage of ependymomas, but the MGMT gene was rarely methylated [23,24].

Diagnosis and Staging

Clinical presentation is variable depending upon the location, size and presenting grade of the tumour. The range of symptoms varies from non-specific symptoms of lethargy and backache to specific symptoms of raised intracranial pressure. The most probable presenting symptoms depending on the location of the tumour can be described as [25]:

Intraventricular ependymomas – often presents with signs and symptoms of raised intracranial pressure secondary to either a tumour mass effect or obstruction in the CSF pathway. These patients may present with nausea, vomiting, headaches, vertigo ataxia and/or papilloedema.

Brain parenchyma – behavioural changes, memory loss and/or focal neurological signs and symptoms.

Posterior fossa involvement – visual disturbances, dizziness, ataxia, hydrocephalus.

Spinal cord ependymomas – backache, focal neurological deficit of upper or lower limbs.

The work up plan for diagnosis and staging of ependymomas constitute a comprehensive clinical history, a detailed physical examination, radiological imaging of neuroaxis and a CSF examination. As a diagnostic technique, magnetic resonance imaging (MRI) has a superior role than computed tomography in diagnosing the location and extent of the tumour. Usually they appear as well-circumscribed lesions. The degree of contrast enhancement varies according to the grade of the tumour, less likely in low-grade subependymomas and more pronounced in anaplastic ependymomas [25]. It is difficult to distinguish the brain parenchymal tumours from other forms of brain tumours radiologically. Therefore, surgical resection is warranted for diagnostic and therapeutic purposes. For staging of ependymomas, MRI of brain and spine is required and for high-grade tumours CSF examination is essential (Figure 1).

Treatment

There are a significant number of studies that support a more favourable prognosis with a greater extent of surgical resection of primary tumour [5,15,26–28]. Hence, maximum possible surgical resection is the mainstay of treatment. In localised cases where postoperative imaging has shown residual tumour, 'second look' surgery is recommended if not contraindicated by proximity to eloquent structures [5].

If complete resection is not possible, maximal debulking is advantageous to aid local control, provide histological diagnosis and in some cases re-establish CSF flow in those presenting with obstructive lesions.

Radiotherapy is commonly used in adjuvant settings after complete surgical resection of localised high-grade ependymomas, although there has been no randomised, clinical trial providing a clear benefit. The retrospective studies to date have suggested that grade is one of the recognised risk factors for recurrence of ependymomas and that the pattern of recurrence is predominantly local, hence the rationale of local radiotherapy [5,17].

In completely resected low-grade ependymomas, there is a lack of consensus as to whether adjuvant radiotherapy is required. It is preferable until definitive evidence exists for each case to be decided on individual merit, considering factors such as spectrum of histological characteri