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CLINICAL STUDY

Spinal ependymomas in NF2: a surgical disease?

M. Kalamarides[1,2,3] · W. Essayed[1] · J. P. Lejeune[3,4] · R. Aboukais[3,4] · O. Sterkers[2,3,5] · D. Bernardeschi[3,5] · M. Peyre[1,2,3] · S. K. Lloyd[6,10] · S. Freeman[6,10] · C. Hammerbeck-Ward[7,10] · M. Kellett[8,10] · S. A. Rutherford[7,10] · D. G. Evans[9,10] · O. Pathmanaban[7,10] · A. T. King[8,10]

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Abstract
The management of spinal cord ependymomas in Neurofibromatosis Type 2 (NF2) has traditionally been conservative, in contrast to the management of sporadic cases; the assumption being that, in the context of NF2, they did not cause morbidity. With modern management and improved outcome of other NF2 tumours, this assumption, and therefore the lack of role for surgery, has been questioned. To compare the outcome of conservative treatment of spinal ependymomas in NF2 with surgical intervention in selected patients. Retrospective review at two NF2 centers, Manchester, UK and Paris/Lille, France. In Manchester patients were managed conservatively. In France surgery was a treatment option. Inclusion in the study was based on tumor length of greater than 1.5 cm. The primary parameter assessed was acquired neurological deficit measured by the Modified McCormick Outcome Score. 24 patients from Manchester and 46 patients from France were analyzed. From Manchester, 27% of these patients deteriorated during the course of follow-up. This effectively represents the natural history of ependymomas in NF2. Of the surgical cases, 23% deteriorated postoperatively, but only 2/18 (11%) of those operated on in the NF2 specialist centers. Comparison of the two specialist centers Manchester/France showed a significantly improved outcome ($P = 0.012$, χ^2 test) in the actively surgical center. Spinal ependymomas produce morbidity. Surgery can prevent or improve this in selected cases but can itself can produce morbidity. Surgery should be considered in growing/symptomatic ependymomas, particularly in the absence of overwhelming tumor load where bevacizumab is the preferred option.

Keywords Neurofibromatosis type 2 · NF2 · Ependymoma · Spinal cord · McCormick grading system

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic condition characterized by the development of multiple tumors of the central nervous system, the hallmark feature being bilateral vestibular schwannomas. Other tumors that may develop include cranial and spinal meningiomas, and spinal cord ependymomas [1].

The management of spinal ependymomas in NF2 has traditionally been conservative, or more accurately, to avoid surgery at all costs and therefore not offer treatment. This contrasts to the management of sporadic spinal ependymoma, in which surgical resection is at the center of management decisions. The reasons for this non-operative approach are multifactorial. Whilst spinal ependymomas are a common feature of NF2 (present in up to 65% of patients), it has been felt that they did not cause significant morbidity, even when growing [2–4]. However, a recent series of 19 NF2 patients with 42 ependymomas showed that 71% of the tumors grew over the course of a median follow-up of 4.5 years and could cause severe symptoms [5]. The problem of identifying ependymoma-related morbidity is complicated by other NF2-related pathology. A patient with deteriorating gait might have a number of causes such as vestibular schwannoma with loss of vestibular function, other spinal tumors and a peripheral neuropathy. Moreover, there has been reluctance by surgeons to operate on these lesions in the context of NF2 based on the concern of producing increased post-operative morbidity. Given the multiple other causes of neurological deficit in NF2, to add even a small deficit from the surgery could be argued would produce a disproportionate neurological deficit and therefore poor outcome, particularly when compared to the excellent outcome in sporadic ependymoma surgery.

✉ M. Kalamarides
michel.kalamarides@aphp.fr

Extended author information available on the last page of the article

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Table 1 Modified McCormick functional scale [9]

Grade	Definition
1	Neurologically normal; mild focal deficit not significantly affecting limb function; mild spasticity or reflex abnormality; normal gait
2	Presence of sensorimotor deficit affecting function of involved limb; still functions and ambulates independently; mild gait difficulty; mild pain or dysesthesia, slightly impairing QOL
3	Presence of sensorimotor deficit affecting function of involved limb; still functions and ambulates independently; moderate gait difficulty; moderate pain or dysesthesia, fairly impairing QOL
4	More severe neurological deficit; requires cane/brace for ambulation or significant bilateral upper extremity impairment; may or may not function independently
5	Severe deficit; requires wheelchair or cane/brace w/bilateral upper-extremity impairment; usually not independent

However, the increasingly improved care and reduced morbidity for non-ependymoma tumors, including the option of bevacizumab for NF2 schwannomas, has meant that the potential for ependymomas to produce morbidity and, therefore, the possibility that surgery should be considered as a treatment option, has been brought recently into sharper focus [6]. Based on our concern that perhaps surgery should be considered in current NF2-management, we reviewed the outcome of ependymomas at our two NF2 reference centers. In Manchester, the management of spinal ependymomas was almost exclusively to avoid surgery and therefore not to treat them [4]. In France, a more interventional approach has been taken. This paper describes the largest NF2 ependymoma series ever published, comparing the outcomes of a non-interventional approach (what might be termed the natural history) and of an interventional approach (surgery for selected patients) to help clinicians in the management of these tumors in NF2.

Methods

We retrospectively reviewed the cases of spinal ependymomas in our NF2 centers, Manchester and Paris/Lille. In France, all living patients provided written consent. In the UK, patient consent was not required as there was no patient identifiable information. We selected for inclusion on the study only those patients with clinical history and imaging available. The genetic severity was rated following published criteria [7, 8].

In terms of inclusion criteria, given that the study was designed to assess the role of surgery, we only included those ependymomas, which we considered a potential surgical target selecting tumors larger than 1.5 cm in long axis at some point during their clinical course. We, of course, recognized the somewhat arbitrary nature of this selection. However, we would argue that the study was designed, not to look at the natural history of ependymomas in NF2, nor still to identify tumours that might become symptomatic with time, but rather as a pragmatic examination, in a retrospective study, as to whether the long held belief in those physicians managing NF2, that (i) ependymomas in NF2 left untreated did no harm, and (ii) that surgery would inevitably add morbidity that could be completely avoiding by not operating.

Ependymoma size and radiological progression was calculated by measuring the maximum longitudinal extent on sequential sagittal MRI scans of the spinal cord on T1-post contrast and T2 weighted-images, tumor cyst being included in the measurement.

Neurological function was assessed using the modified McCormick (MCC) scale (Table 1) assessed on first consultation, on pre-op admission, at discharge, and at last follow-up [9]. This scale takes into consideration motor function and remains the most used scale to assess neurological function in patients with intra-medullary tumors. Near-total resection and partial resection were respectively defined as >95 and $>70\%$ resection on post-operative imaging [10]. Recurrence was diagnosed when imaging reported a development of a 3 mm tumor after total resection or a growth of more than 3 mm in not-totally resected tumors.

Results

Manchester series: description of population and ependymomas

Among 64 individuals with ependymomas in the database, 47 had relevant clinical and radiological data with 24 having ependymomas of minimum length 1.5 cm or greater at some point in their history. The clinical course of these 24 patients essentially represents the outcome of choosing a non-operative course in patients in whom the size of the tumour meant that it was a potential surgical target. At presentation, the age range of these 24 patients was 20–65 years (median 32.5 years). The majority of spinal ependymomas were located in the cervical cord (23/24) extending to brainstem in three and to the thoracic region in six with only 1/24 located exclusively in the thoracic region. Clinical follow up was for 0.15–8.2 years (median 3.8 years). For these 24 patients, 18 had serial imaging available and, therefore, data

on tumor progression over time. The initial size range from 6 to 160 mm (median 40.5 mm). Growth over the follow up period was 1–252 mm (median 7 mm and an interquartile range of 3–16.75). In terms of genetic severity, of the 24 patients seven were mild, eight were moderate, and nine were severe.

French NF2-center series: description of population and ependymomas

Among 95 patients harboring ependymomas in the database, we identified 46 patients (33 in Paris and 13 in Lille) with ependymomas greater than 1.5 cm. Eight patients exhibited two or more lesions. The clinical course of these 46 patients represents the outcome of potentially considering the option of surgery in the same tumour group as was managed non-operatively in Manchester. Twenty-two patients underwent surgery at some point in their clinical course.

The overall median age at the first referral was of 23 years (range 4–58). The cervical spinal cord was the most frequent location of the ependymoma with 67% of the patients having a cervical component. 24% of the cervical lesions had an extension to the cervico-medullary junction (CMJ), while the thoracic spine was involved in 33% of the patients. CMJ extension was correlated to a deceased initial MMC score (P = 0.049). An exact size of the tumor at the beginning of the follow-up was available for 33 patients (42 tumors). The tumor size ranged from 6 to 73 mm (median 20.5 mm).

Of those that underwent surgery to their ependymoma, the ependymoma itself was the presenting feature in two patients (9%), and operated on immediately, before the NF2 diagnosis. For the remaining 20 patients who eventually underwent surgery, the median follow-up before surgery was 30 months (range 3 months–10.5 years). Motor deterioration or radiological progression represented the most frequent indication of surgery, in respectively seven patients (32%) and seven patients (32%). Eight patients (36%) suffered from both motor deterioration and radiological progression at the time. Sensory symptoms were present in nine patients (45%) but did not motivate surgery when isolated. Concerning the extent of resection, gross total resection was attained in 50% of the patients while 36% had near-total resection. Two patients (9%) had only a partial resection and one (5%) had a biopsy with a large bony and dura-mater decompression. All tumors were WHO Grade II ependymomas [11]. In the non-surgical group, 14 patients (58%) had stable images throughout follow-up while ten patients (42%) had slow progressive radiological evolution of the tumor with an average speed of increase of 0.8 mm/year (0.2–1.8 mm/year). The growth was faster in the surgical group, with an average growth/year that reached 4.5 mm/year (0.11–20.8 mm/year). Of note, four patients were operated in other institutions before getting transferred to our NF2 center for follow-up. The range of postoperative follow-up was for 3 months–15 years with a median of 4 years. In terms of genetic severity, of the 46 patients 12 were mild, 15 were moderate, and 19 were severe.

Clinical course-Manchester (Table 2)

Table 2 shows the clinical course of the 24 patients: eight deteriorated because of ependymoma disease. Of these eight, one deteriorated after a surgical biopsy carried out elsewhere and one deteriorated because of inoperable cranial and spinal tumor load. Therefore, six patients deteriorated because of what might be described as the natural history of ependymoma in the context of NF2. This represents 27% (6/22, 2 being excluded for the reasons described above) of ependymoma related deterioration in patients with tumors greater than 1.5 cm. Of the 24 patients, two died because of ependymoma disease, one of these is referred to above with inoperable cranial and spinal tumor load but one patient died specifically as a result of extension of an upper cervical spinal cord ependymoma. This patient at the age of 29 was known to have a cervical cord ependymoma and was clinically McCormick Grade 2. The lesion was not felt to be a surgical target and 4 years later, he developed a rapidly progressive quadraparesis progressing to respiratory failure and death. Imaging showed a dramatic expansion in the ependymoma with extension in to the brainstem.

Clinical course-France (Table 3)

For the sake of clarity, we have divided the clinical course of the 46 patients in the French group into those who had been "selected" into the non-operative group and those into the operative group.

Table 2 Manchester patients clinical course: start versus end of follow-up MMC scores (n = 24)

	End of follow-up MMC scores				
	1	2	3	4	5
Start of follow-up MMC scores					
1	12	–	2	–	–
2	–	1	1	1	2[b]
3	–	–	–	–	1
4	–	–	1[a]	2	1
5	–	–	–	–	–

[a]Improvement due to Bevacizumab

[b]Eventually improved with surgery

Table 3 French NF2-centers patients clinical course: start versus end of follow-up MMC scores (n = 42)

	End of follow-up MMC scores				
	1	2	3	4	5
Start of follow-up MMC scores					
1	22	–	–	1	–
2	–	7	1	2[a]	1[a]
3	1	2[b]	5	–	–
4	–	–	–	–	–
5	–	–	–	–	–

[a]One patient refusing surgery for spinal schwannoma

[b]One patient improved by Bevacizumab

Table 4 NF2 center surgical subgroup clinical course: start versus end of follow-up MMC scores (n = 18)

	End of follow-up MMC scores				
	1	2	3	4	5
Start of follow-up MMC scores					
1	4	–	–	1	–
2	–	5	1	2[a]	1[a]
3	1	1	2	–	–
4	–	–	–	–	–
5	–	–	–	–	–

[a]One patient refusing surgery for spinal schwannoma

Non-operated group (24 patients)

At the first referral, only four (16%) had a decreased MMC that could be linked to their ependymoma. After a median follow-up of 9.6 years, 21 patients (87.5%) had stable MMC scores and one exhibited slight improvement under Bevacizumab. Two patients (8%) deteriorated due to pathology unrelated to their spinal ependymoma. Since clinical deterioration represented the major indication for surgery, the non-operated patients displayed a favorable clinical and radiological spinal ependymoma natural history.

Operated group (22 patients)

Patients were operated with an attempt to totally resect the tumor. As observed for vestibular schwannomas in NF2, ependymomas are frequently composed of multiple nodules and cysts and are difficult to be removed compared to sporadic spinal ependymomas.

Four of the 22 patients have been operated on in non-NF2 centers: three of them worsened badly after surgery. Therefore, when considering only the 18 patients operated in our NF2-center with expert neurosurgeons, nine patients (50%) presented temporary immediate postoperative deterioration, with an average increase of 2 points in the MMC score, while seven patients (39%) were post-operatively stable, and two patients (11%) improved. Postoperative complications were limited to two cases of meningocele and one case of kyphosis.

After a median follow-up of 4 years, the MMC score deterioration persisted or increased (in comparison to preoperative scores) in five patients. In only two of these patients, the ependymoma surgery can be linked to the persisting deterioration. In the remaining three patients, the deterioration was long after ependymoma surgery and due to multiple spinal schwannomas surgeries in two patients while the third deteriorated after refusing surgery for a large T9 schwannoma.

Therefore, from the 18 relevant patients from NF2 centers, post-operative deterioration was responsible of decreasing the MMC in only two patients (11%). No statistical correlations between initial size and location, extent of resection, postoperative deterioration and long-term progression were found. Two patients developed radiologically documented slow recurrences (with an average regrowth speed was 1 mm/year). Both were symptomatic. Repeat surgery was performed in one with major peri-operative difficulties because of previous surgery. The patient worsened from MMC 2–5.

Overall clinical course (Table 4)

The clinical course over the median 7 years (0.4–21 years) follow-up of 42 patients (18 operated in NF2 centers and 24 non-operated) was favorable, with 34 (81%) stable patients and 3 (7%) clinically improved patients (two after surgery and one under Bevacizumab). Five patients (12%) clinically worsened their initial MMC score, with only 2 (5%) actually linked to the ependymoma. It should be noted that, a total six patients received Bevacizumab (five for vestibular schwannoma and one for ependymoma), resulting in a MMC score improvement in two patients.

In this time period, a total of six patients died after a median follow up of 5.5 years (1.6–8 years). Three patients died after meningioma surgery and three succumbed to a heavy intracranial tumor load. Consequently, no mortality could be linked to the spinal ependymoma.

Comparison between Manchester and Paris series

Overall, at the first referral, the two series were statistically similar. When considering the cases where the motor deterioration was directly linked to ependymoma progression or surgery, we found that 27% (6/22) deteriorated during the course of the Manchester study. In the French series, 23% of surgical group (5/22) deteriorated while, during the

course of follow-up for those patients managed non-operatively, there was no evidence of neurological deterioration. However only 11% (2/18) of those operated on in the NF2-specialised institutions deteriorated from their surgery. Whilst there was no statistical outcome difference between the overall Manchester and France series, we report a clear improvement of the motor outcome between the Manchester patients and the patients treated in the French NF2 specialist center, with respectively 27% (6/22) and 5% (2/42) of deterioration related to the ependymoma ($P=0.012$, χ^2 test).

The mortality related to the ependymoma natural history was 4% (1/24), in the Manchester patients while no death occurred in the French series.

Discussion

It will be clear that in this two center series, we have studied only those tumours, which at some point during the clinical course, reached a maximum long axis size of 1.5 cm. We appreciate the somewhat arbitrary nature of this size. Given that we cannot imagine that anyone would consider surgery to the, often multiple, smaller lesions that one commonly sees in NF2, we would argue that this figure represents a reasonable minimum size of ependymoma to study in order to attempt to answer the question we have addressed. It is important to understand the nature of this specific question: should surgery be considered for NF2 ependymomas? The paper was not designed to look at the natural history of these tumours in NF2, nor their growth rate, nor the relationship between size, rate of growth and any potential predictive link between these or any other factors. Rather, it was designed to attempt to answer the essentially pragmatic question that faces all of those clinicians who manage NF2. With the outcome of other NF2 tumours improving with modern management, including bevacizumab, the dilemma of whether to consider surgery to spinal cord ependymomas has never been in such sharp focus. It is this dilemma that we have attempted to address.

In this paper, the Manchester series effectively describes the consequences in terms of morbidity and indeed mortality of pursuing an aggressively non-operative course in NF2 ependymomas, which are of size whereby the tumour might represent a surgical target. 27% of patients in the Manchester series with tumors of this size deteriorated neurologically over the course of follow up because of their ependymoma and indeed one patient died exclusively of their ependymoma.

In terms of surgical outcome, from the French series, not unsurprisingly, it does depend upon the technical skills of the surgical team. In the French series, a number of patients (4/46) were operated on outside of the NF2 center: three patients deteriorated badly. However, when looking at those managed in the specialized NF2 centers, only 9% (2/22) deteriorated from the ependymoma surgery. When focusing on these patients, the surgical intervention made a statistically significant improvement ($P=0.012$, χ^2 test) compared with the natural history corresponding to the Manchester series.

In the same French series, 0% of conservatively managed tumors deteriorated neurologically. This clearly describes the selection bias by transferring into the surgical series those cases, which during the course of their natural history, would have produced neurological deficit. By operating on some of the surgically amenable tumours, the French series removes the morbidity associated with the natural history, and replaces it with the morbidity associated with surgery. We believe that this represents the main strength of this study, namely that the comparison of two independent series, managed in very different ways, avoids the inevitable selection bias related to transfer from the non-surgical to the surgical group that would be a feature of a single center study.

It is not the purpose of this paper to send a message that surgery must be undertaken for every growing spinal ependymomas in the context of NF2. Rather, this retrospective study attempts to throw some light on the uncertainty that exists as to the "best" treatment option for spinal ependymomas.

We believe that the paper does show that timely surgery in good hands and in appropriate cases can produce an improvement over the natural history, a natural history that does involve progressive neurological deficit. The case for surgery needs to be tempered by the fact that there is morbidity related to the surgery. Also, at the time of writing this paper, there is a recurrence rate in the surgical series that has not yet manifested itself with clinical deterioration. It is possible that with longer follow up, the seemingly better outcome of surgery over the natural history may be less striking.

Two other potential weaknesses should be described. It is well recognized that ependymomas can be multifocal in the context of NF2. It has been necessary to describe both in the surgical and conservatively managed groups what we considered the primary symptomatic lesion. This selection of a single lesion in the context of multifocal disease involves a degree of subjective judgement. The second weakness of the study is in classifying the patients accordingly to the modified MMC score. In NF2, neurological deterioration can be multifactorial. In order to try and describe ependymoma-related morbidity, a degree of subjective judgement as to the McCormick classification was required.

Conclusions

The natural history of spinal cord ependymomas in NF2 is that they can produce significant morbidity. Surgery can prevent or improve this natural history in selected cases but can in itself produce morbidity. We believe surgery should be considered in growing and/or symptomatic ependymomas, particularly in the absence of overwhelming tumor load where bevacizumab is likely to be the preferred option [12–14].

Compliance with ethical standards

Conflict of interest The authors declare that they have no personal conflicts of interest and no institutional financial interest in any drugs, materials, or devices described in this manuscript.

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Affiliations

M. Kalamarides[1,2,3] · W. Essayed[1] · J. P. Lejeune[3,4] · R. Aboukais[3,4] · O. Sterkers[2,3,5] · D. Bernardeschi[3,5] · M. Peyre[1,2,3] · S. K. Lloyd[6,10] · S. Freeman[6,10] · C. Hammerbeck-Ward[7,10] · M. Kellett[8,10] · S. A. Rutherford[7,10] · D. G. Evans[9,10] · O. Pathmanaban[7,10] · A. T. King[8,10]

1 Department of Neurosurgery, Groupe Hospitalier Pitié -Salpêtrière, 47-83 boulevard de l'Hôpital 75013 Paris, France

2 UPMC, Sorbonne Universités, Paris, France

3 NF2 Clinic, Paris and Lille, France

4 Department of Neurosurgery, CHU Lille, Lille, France

5 Department of ENT, Hopital Pitie-Salpetriere, AP-HP, Paris, France

6 Department of ENT, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

7 Department of Neurosurgery, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

8 Department of Neurology, Salford Royal NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

[9] Manchester Centre for Genomic Medicine, Manchester Academic Health Science Centre, Central Manchester NHS Foundation Trust, Manchester, UK

[10] NF2 Clinic, Manchester, UK