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ORIGINAL ARTICLE

Outcome predictors in the management of spinal cord ependymoma

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Abstract The aim of this study was to determine predictors of functional outcome and survival in a retrospective cohort of spinal cord ependymomas treated at a single institution. Twenty-six patients who underwent treatment of spinal cord ependymoma at a single institution were retrospectively analysed. The clinicopathological features were reviewed and correlated with functional outcome (measured using the Frankel grade), recurrence (clinical or radiological), progression-free survival (PFS) and overall survival (OS). Seventy-nine percent of patients with complete excision had maintained or improved functional outcome, compared to 75% in the incomplete resection plus radiotherapy group. Patients with a good preoperative Frankel grade tended to maintain their functional status, though this did not reach statistical significance (Fisher's Exact test, $P = 0.090$). Univariate analysis revealed that longer symptom duration prior to treatment was associated with poorer functional outcome ($P = 0.006$). Extent of resection and the use of adjuvant radiotherapy did not influence PFS or OS; however, early diagnosis and treatment are paramount in the management of spinal ependymoma if a good functional outcome is to be achieved.

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Introduction

In the spinal cord, ependymomas are the most common neuroepithelial tumour, accounting for 50–60% of adult spinal tumours [18]. The benign pathological nature of these tumours poses great difficulty in their early diagnoses and management [15]. However, their compressive rather than infiltrative nature makes them amenable to surgical resection [14], but the role of adjuvant radiotherapy and chemotherapy is still debated [3, 10, 23]. The ultimate goal in spinal ependymoma treatment is progression-free survival (PFS) with good functional outcome. The aim of this study was to determine functional outcome and survival predictors in a retrospective cohort of spinal ependymomas treated at a single institution.

Materials and methods

Study population

Patients with intramedullary spinal cord tumours were identified retrospectively from theatre log books and cross-checked with pathology records. Adult intramedullary spinal cord ependymomas as defined by the latest WHO guidelines [11], treated between April 1994 and October 2004 at the Walton Centre for Neurology and Neurosurgery, were chosen for the study. Ependymomas arising from the cauda equine were excluded. Clinicopathological data was obtained

by retrospective case note review, and follow-up was by clinical examination and interval magnetic resonance imaging (MRI).

Functional outcome

Functional outcome was assessed using the Frankel scale [7]. Post-operative functional status was defined as the last recorded clinical examination in the case notes prior to either discharge, loss to follow-up or deterioration due to disease progression. Since complete tumour excision was not possible in all cases, tumour recurrence was defined as new symptoms related to tumour growth or tumour re-growth on follow-up MRI.

Statistical analysis

The relationship between pre- and post-operative Frankel grade was assessed using Fisher's Exact test. For logistic regression analysis functional outcome was converted to a binary outcome of ambulatory (Frankel grade D–E) and non-ambulatory (Frankel grade A–C). Univariate and logistic regression analysis was used to identify factors that could significantly affect the binary outcomes: tumour recurrence, death and ambulation. Multiple linear regression was used to investigate ambulatory status at the last clinical assessment. Correlation was used to identify and remove correlated explanatory variables before performing regression analysis. Stepwise regression was used to simplify any resulting models. The following explanatory variables were investigated: subject age (years), duration of symptoms (months), complete tumour resection, histological subtype, use of adjuvant therapy, recurrent tumour (excluded when used as an outcome), pre- and post-operative ambulatory status (excluded when used as an outcome).

Progression-free survival and overall survival (OS) were calculated from the date of surgery. Kaplan–Meier survival curves were obtained and differences in OS or PFS were tested for statistical significance using the LogRank test. Probability (P) values less than 0.05 were considered significant. Data analysis was performed using SPSS (SPSS, UK)

Results

Twenty-six patients underwent surgery for spinal cord ependymoma. The median age at the time of surgery was 47 years (range 21–72) and median symptom duration was 13 months (range 3–61). The tumours were located in the cervical ($n = 9$), thoracic ($n = 5$), thoracolumbar ($n = 7$) and lumbar ($n = 5$) regions of the spinal cord (Table 1). Median follow-up was 49 months (range 7–106 months). Two patients relocated to a different part of the country and were followed-up at different institutions, but remain included in this series. A further two patients had significant neurological deficits and declined further follow-up. The median follow-up for these four patients was 36 months (range 20–70 months).

Surgical outcome

The surgical aim in all cases in this series was to attempt complete macroscopic tumour excision; this was achieved in 15 patients. Ten patients had subtotal resection and one underwent biopsy, and all received adjuvant radiotherapy. The technical problems encountered preventing complete resection were either involvement of multiple nerve roots in cervical or conus tumours, or lesions with a poorly defined plane between the tumour and cord preventing total excision. The overall complication rate was 42%. Cerebrospinal fluid leak occurred post-operatively in six patients, leading to culture positive meningitis in two cases. In one patient methacillin-resistant *Staphylococcus aureus* was cultured, resulting in brain stem infarction and death. Two patients had superficial wound infections. Seven patients developed dysaesthetic pain that required treatment from a pain specialist.

Four patients had evidence of disease progression and the median time to recurrence was 21 months (range 12–84 months). Three out of 11 cases (27%) from the incomplete excision group and 1 out of 15 cases (7%) from the complete excision group had clinical and radiological recurrence. Two of these patients had extensive cauda equina recurrence after

Table 1 Clinicopathological characteristics of study population

	Mtyxopapillary ependymoma	Grade II ependymoma
Age at surgery (median: range)	45 (21–76)	48 (24–72)
Symptom duration (median: range)	9 (2–29)	15 (2–61)
Tumour location (cervical:thoracic: thoracolumbar:lumbar)	0:0:4:4	9:5:4:3
Extent of resection (complete:subtotal:biopsy)	5:3:0	13:7:1
Adjuvant therapy	3	8
Recurrence	1	3

incomplete resection of conus tumours and radiotherapy. Further surgery was performed in both cases; however complete resection was not possible due to extensive involvement of multiple nerve roots. Despite concerns that repeat surgery would more difficult this was not the case, and no significant problems were encountered intraoperatively.

Mean PFS was 75 months for myxopapillary tumours, and 90 months for grade II ependymomas. There were no deaths in patient with myxopapillary tumours; therefore mean OS could not be calculated. In the grade II ependymoma group, mean OS was 90 months. Mean PFS of tumours treated with incomplete excision and adjuvant radiotherapy was 85 months, compared to 80 months in those treated by complete excision alone. Mean OS was 98 months in the complete excision group compared to 75 months in those treated with incomplete excision and radiotherapy. Kaplan–Meier survival curves did not demonstrate a statistically significant difference in PFS or OS, between histopathology subtypes and treatment groups (Fig. 1).

Functional outcome

Patients with a good pre-operative Frankel grade tended to maintain functional status post-operatively (Tables 2, 3), though this did not reach statistical significance (Fisher's Exact test, $P = 0.090$). In the series, 88% were ambulant pre-operatively, and 12% were non-ambulant. Following treatment, 78% of patients who were ambulant pre-operatively, maintained or improved their functional status. In the non-ambulant group, 66% became ambulant. In the complete excision group, 79% maintained or improved their functional status, compared to 75% in the incomplete excision and radiotherapy group. Univariate analysis identified favourable post-operative ambulatory status in those patients with a shorter duration of symptoms prior to surgery (Tables 4, 5). No factors were identified predicting tumour recurrence or survival. Multivariate analysis revealed that a shorter duration of symptoms prior to surgery predicted good post-operative ambulatory status, but no other predictive factors were identified.

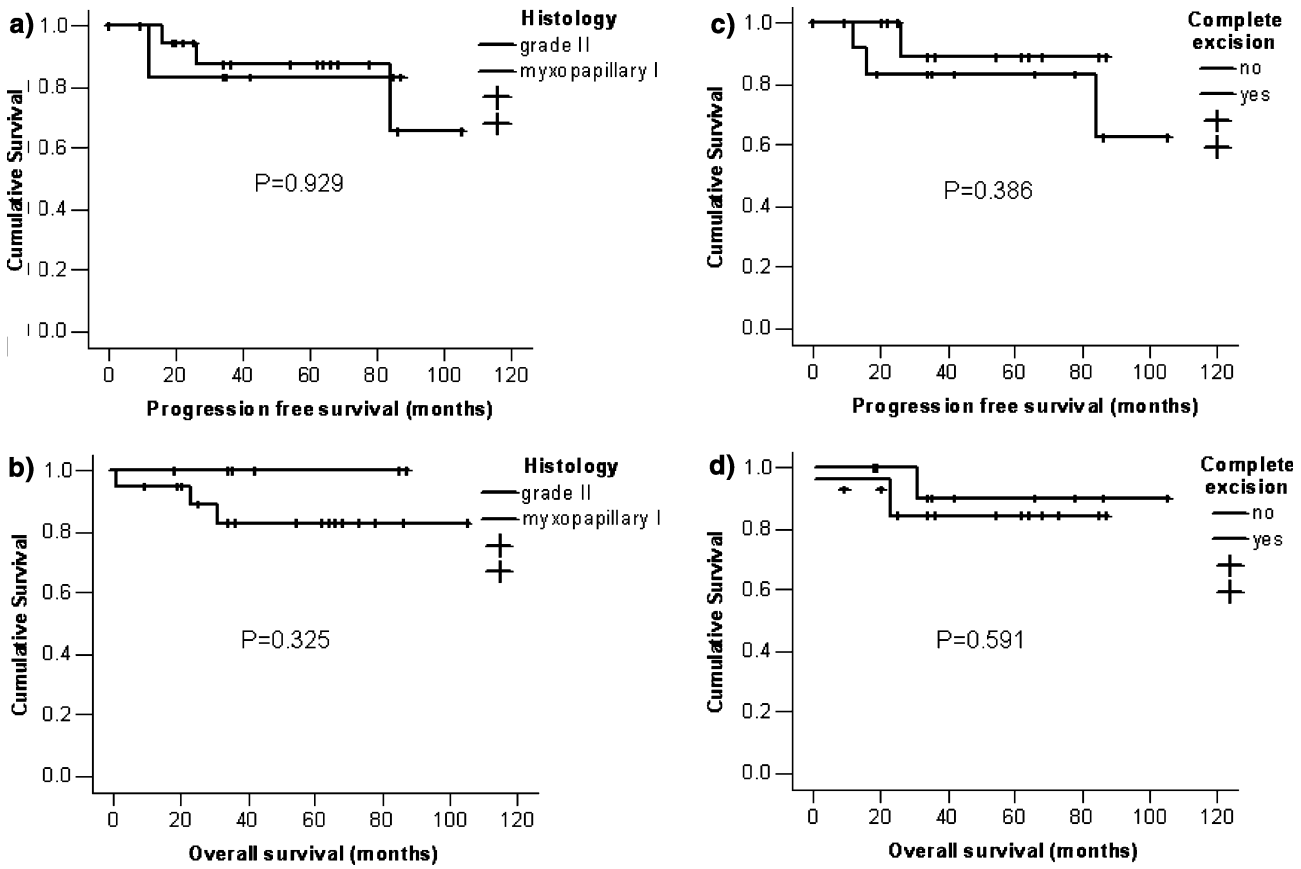

Fig. 1 Kaplan–Meier survival curves showing differences in outcome depending on tumour histology and extent of surgical excision: **a**, **c** progression-free survival and **b**, **d** overall survival. There was no statistically significant difference between histology subtypes and extent of resection (complete vs. incomplete)

Table 2 Functional outcome in spinal cord ependymomas for complete excision

Pre-operative Frankel grade	Post-operative Frankel grade				
	A	B	C	D	E
A					
B					
C					
D	*1*	*0*	*2*	**8**	$\underline{\mathbf{1}}$
E					$\underline{\mathbf{3}}$

Deteriorated (italics); unchanged (bold); improved (underlined)

Table 3 Functional outcome in spinal cord ependymomas for incomplete excision and adjuvant radiotherapy

Pre-operative Frankel grade	Post-operative Frankel grade				
	A	B	C	D	E
A					
B				$\underline{1}$	
C			**1**	$\underline{\mathbf{1}}$	
D		*1*	*1*	$\underline{\mathbf{3}}$	
E					$\underline{\mathbf{2}}$

Deteriorated (italics); unchanged (bold); improved (underlined)

Discussion

In this retrospective analysis of spinal cord ependymomas treated at a single institution we have shown that post-operative ambulatory status is better in those patients with a shorter duration of symptoms, and that patients with good functional status prior to treatment have good post-treatment function. Neither histopathological subtype, extent of resection nor the use of adjuvant radiotherapy influenced PFS or OS.

The treatment of spinal ependymomas remains centre dependant without universal agreement. Historically, complete macroscopic excision of these tumours resulted in significant post-operative morbidity and mortality [9], therefore subtotal resection with adjuvant radiotherapy was advocated as optimal treatment [12, 17, 20]. Advances in surgical technique and the routine use of corticosteroids has lead to reduced morbidity and mortality, however, the role of adjuvant radiotherapy after spinal ependymoma surgery remains unclear. Some authors have suggested post-operative radiotherapy following complete excision [13, 19, 21], whilst many feel that adjuvant therapy is unnecessary after complete excision [1, 2, 6]. When technical reasons prevent complete excision or in cases with metastatic spread, radiotherapy is advocated [4, 8], however, concerns that radiotherapy may cause reactive gliosis and fibrosis making re-operation for recurrence technically difficult [10], and concern about long-term radiation myelopathy leading to severe neurological dysfunction [16, 22] have limited its use in some centres.

In our centre the goal of spinal ependymoma treatment is complete surgical excision with good long-term functional outcome. In cases where subtotal resection is only possible, patients receive adjuvant fractionated, conformal radiotherapy to the residual tumour. Adopting this treatment approach, 78% of patients with complete excision had maintained or improved functional outcome, compared to 82% in the incomplete resection plus radiotherapy group. However, univariate analysis did not identify completeness of excision or use of adjuvant radiotherapy as predictors of survival or ambulatory status. As with other studies [4, 10] shorter duration of pre-operative symptoms predicted good functional outcome, and the level of pre-operative functional status was associated with a similar level of post-operative function. Of the three pre-operatively non-ambulant patients, two gained useful function following treatment, therefore, early diagnosis is importance in disease management.

Previous studies have demonstrated that patients with complete tumour excision have a significantly longer PFS compared to those who receive incomplete

Table 4 Univariate analysis for the three outcomes; recurrence, death and ambulatory status for categorical variables

Variable	Outcome					
	Recurrence		Death		Ambulatory status	
	Odds ratio	*P* value	Odds ratio	*P* value	Odds ratio	*P* value
Histology	0.88	0.921	NC	0.313	0.60	0.671
Extent of resection	NC	0.259	1.83	0.636	1.22	0.829
Adjuvant therapy	5.25	0.150	0.65	0.783	0.67	0.664
Recurrence	–	–	3.33	0.360	0.88	0.921
Pre-op ambulation	0.30	0.360	NC	0.506	1.80	0.654
Post-op ambulation	0.88	0.921	0.56	0.654	–	–

Table 5 Univariate analysis for the three outcomes; recurrence, death and ambulatory status for continuous variables

Variable	Outcome								
	Recurrence			Death			Ambulatory		
	Yes	No	*P* value	Yes	No	*P* value	Yes	No	*P* value
Age (years) Mean (SD)	49.4 (21.7)	43.7 (14.6)	0.640	55.1 (27.0)	43.2 (13.8)	0.218	41.2 (14.5)	55.9 (14.2)	0.056
Symptom duration (months) Mean (SD)	21.4 (26.9)	19.9 (16.5)	0.874	33.5 (29.4)	18.4 (15.9)	0.466	15.1 (11.5)	36.9 (25.3)	**0.006**

Bold face represents the only value which approaches statistical significance

excision and adjuvant radiotherapy, though radiotherapy was not an independent prognostic factor [4]. Similar findings were not evident in our study, though median survival times were not reached. The role and indications for adjuvant radiotherapy are still unclear, and several retrospective studies [5, 10], have failed to demonstrate any benefit to functional outcome, PFS or OS. A different pattern of disease progression has been described depending on post-operative radiotherapy: longer PFS in the radiotherapy group compared to those without, though this did not reach statistical significance [4]. In our study, since adjuvant radiotherapy was administered to all patients with incomplete resection, it was not possible to determine whether radiotherapy influenced functional outcome, PFS or OS. Larger prospective studies are needed to resolve this issue. However, there appears to be a consensus in the published literature that early diagnosis and treatment, and good pre-operative functional status are important factors for producing good long-term, post-operative functional results.

The relatively benign nature of spinal ependymoma, and the limited follow-up time in our study means that the survival data should be interpreted with caution. Additionally, and in keeping with the published literature on spinal ependymomas, the conclusions of this study are drawn from a retrospective, non-randomised series of patients with limited long-term follow-up.

Conclusions

(1) Univariate analysis revealed that longer symptom duration prior to treatment is associated with poorer functional outcome; therefore early diagnosis and treatment are important in this disease.
(2) Long-term survival was similar in the surgery alone and subtotal excision plus radiotherapy groups.
(3) Complete macroscopic excision should be the aim of surgery.

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