Association of tumor location, extent of resection, and neurofibromatosis status with clinical outcomes for 221 spinal nerve sheath tumors

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OBJECT Intradural extramedullary spine tumors represent two-thirds of all primary spine neoplasms. Approximately half of these are peripheral nerve sheath tumors, mainly neurofibromas and schwannomas. Given the rarity of this disease and, thus, the limited analyses of clinical outcomes, the authors examined the association of tumor location, extent of resection, and neurofibromatosis (NF) status with clinical outcomes.

METHODS Patients were identified through a search of the University of California, San Francisco, neuropathology database and a separate review of current procedural terminology codes. Data recorded included patient age, patient sex, clinical presentation, presence of NF, tumor type, tumor location, extent of resection (gross-total resection [GTR] or subtotal resection [STR]), and clinical follow-up.

RESULTS Of 221 tumors in 199 patients (mean age 45 years), 53 were neurofibromas, 163 were schwannomas, and 5 were malignant peripheral nerve sheath tumors. The most common presenting symptom was spinal pain (76%), followed by weakness (36%) and sensory abnormalities (34%). Mean symptom duration was 16 months. In terms of spinal location, neurofibromas were more common in the cervical spine (74% vs 27%, $p < 0.001$), and schwannomas were more common in the thoracic and lumbosacral spine (73% vs 26%, $p < 0.001$). Rates of GTR were lower for neurofibromas than schwannomas (51% vs 83%, $p < 0.001$), regardless of location. Rates of GTR were lower for cervical (54%) than thoracic (90%) and lumbosacral (86%) lesions ($p < 0.001$). NF was associated with lower rates of GTR among all tumors (43% vs 86%, $p < 0.001$). The mean follow-up time was 32 months. Recurrence/progression was more common for neurofibromas than schwannomas (17% vs 7%, $p = 0.03$), although the mean time to recurrence/progression did not differ according to tumor type (45 vs 53 months, $p = 0.63$). As expected, GTR was associated with lower recurrence rates (4% vs 22%, $p < 0.001$). According to multivariate analysis, cervical location (OR 0.239, 95% CI 0.110–0.520) and presence of NF (OR 0.166, 95% CI 0.054–0.507) were associated with lower rates of GTR. In a separate model, only GTR (OR 0.141, 95% CI 0.046–0.429) was associated with tumor recurrence.

CONCLUSIONS Resection is an effective treatment for spinal nerve sheath tumors. Neurofibromas were found more commonly in the cervical spine than in other regions of the spine and were associated with higher rates of recurrence and lower rates of GTR than other tumor types, particularly in patients with NF Types 1 or 2. According to multivariate analysis, both cervical location and presence of NF were associated with lower rates of GTR. According to a second multivariate model, the only variable associated with tumor recurrence was extent of resection. Maximal safe resection remains ideal for these lesions; however, patients with cervical tumors or NF should be counseled about their increased risk for recurrence.

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KEY WORDS spine; nerve sheath tumor; neurofibroma; schwannoma

ABBREVIATIONS GTR = gross-total resection; NF = neurofibromatosis; NF1 = NF Type 1; NF2 = NF Type 2; STR = subtotal resection.

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PRIMARY spinal cord tumors represent approximately 5% of primary CNS tumors in adults; every year in the United States alone, up to 1700 new cases are diagnosed.^{3,8,11} These tumors can be classified according to anatomical location as intramedullary, intradural extramedullary, dumbbell (intradural, both intraspinal and extraspinal), and extradural. Intramedullary tumors are primarily glial tumors (ependymomas and astrocytomas), and extradural lesions consist primarily of metastases, hematopoietic tumors, and primary bony tumors. Intradural extramedullary spinal cord tumors consist primarily of peripheral nerve sheath tumors and meningiomas¹⁶ and less commonly of metastases, lipomas, spinal nerve sheath myxomas, paragangliomas, sarcomas, and vascular tumors.²

Spinal neurofibromas are found in up to 38% of patients with neurofibromatosis Type 1 (NF1).^{10,18,24,25} However, they are estimated to cause symptoms or become clinically significant in only approximately 5% of patients, although this estimate is probably low.^{13,25,27} An alternate form of NF, known as familial spinal NF, is categorized by multiple neurofibromas symmetrically affecting the entire axial spine.^{6,19,26} Histologically, neurofibromas are composed of Schwann cells with abnormal nuclei and scant cytoplasm and of fibroblasts in a matrix of collagen fibers and myxoid material.¹⁷ They grow along the course of nerve fibers and are generally surrounded by a thick epineurium. Schwannomas are composed of neoplastic Schwann cells forming 2 basic patterns: compact, elongated cells with occasional nuclear palisading (Antoni A pattern) or less cellular, loosely textured cells with indistinct processes (Antoni B).¹⁷ Approximately 90% of schwannomas are solitary and sporadic; 4% arise in patients with NF Type 2 (NF2), and another 5% are multiple but unassociated with NF2.⁵

Spinal neurofibromas and schwannomas are rare, and published studies are limited to single-institution case series.^{4,7,9,12,15,20–22} These contributions are valuable but limited by sample size and age of data sets. We sought to characterize our institutional experience with the management of these lesions, focusing on patient demographics, history of NF, clinical presentation, and factors associated with extent of resection and tumor recurrence.

Methods

Data Collection

Patients were identified through a search of our institutional neuropathology database and a separate review of current procedural terminology codes by two of the authors (N.M.B. and C.P.A.). All research activities were approved by the Committee on Human Research, University of California, San Francisco, institutional review board. Pathology records were reviewed, and the following peripheral nerve sheath tumors were included in the study: neurofibromas, schwannomas, and malignant peripheral nerve sheath tumors. Medical records were reviewed to establish patient age, sex, presence of NF1 or NF2 according to clinical criteria, presenting symptoms and duration, use of radiotherapy, tumor location, extent of resection (defined by postoperative MR images or operative report),

time to last follow-up visit, and date of tumor recurrence. Tumor location was classified by the level of the involved nerve root (cervical, thoracic, or lumbosacral) and relationship with adjacent dura as follows: intradural extramedullary, extradural intraspinal (tumor within the spinal canal), or extradural paraspinal (tumor at the neural foramen or extending outward into adjacent tissues). For the purposes of this article, they are described as intradural, extradural, and paraspinal. Extent of resection was defined as gross-total resection (GTR) if there was no evidence of residual disease on postoperative MR images and as subtotal resection (STR) if residual tumor was present. Use of radiotherapy was limited to a small number of patients in this study. All patients who received radiation received stereotactic radiosurgery; however, for some, it was received at an outside institution and treatment regimens were unavailable for review. Patients with malignant peripheral nerve sheath tumors almost exclusively received treatment with fractionated radiotherapy at outside facilities. One patient received intensity-modulated radiation therapy in addition to proton-beam therapy.

Statistical Analysis

Univariate analysis of continuous variables was performed by using the Student t-test, and categorical variables were compared by using the chi-square test or Fisher exact test. Multivariate analysis was performed by using binary logistic regression. Variables were included in the multivariate model if univariate analysis demonstrated a statistically significant relationship, defined as $p < 0.05$. To assess recurrence-free survival times (the likelihood of a recurrence event over time), we generated Kaplan-Meier plots and used the log-rank test. All analyses were performed by using SPSS version 22 (IBM).

Results

Patient Demographics

A total of 221 tumors in 199 patients were identified. Patient demographics are summarized in Table 1. The mean patient age was 45 years (range 1–88 years). Tumor type (pathology) was classified as neurofibroma in 53 cases, schwannoma in 163 cases, and malignant peripheral nerve sheath tumor in 5 cases. The mean age was 36 years among patients with neurofibroma and 48 years among those with schwannoma ($p < 0.001$). Of the 221 tumors, 98 (44%) were in female and 123 (56%) in male patients. Tumors were slightly more common among males: 28 (53%) of 53 neurofibromas and 92 (56%) of 163 schwannomas were in males; however, the difference was not significant ($p = 0.646$). Tumors were associated with NF in 53 patients (24%); 42 tumors (19%) occurred in patients with NF1 and 11 (5%) in patients with NF2. NF was strongly associated with neurofibromas; NF was present in 40 of 53 neurofibroma and 12 of 163 schwannoma ($p < 0.001$) patients. Among neurofibromas, 39 of 40 occurred in patients with NF1 and the other in a patient with NF2; among the 12 schwannomas with NF, 10 were in patients with NF2 and 2 were in patients with NF1.

Clinical Presentation

Among all patients, the most common presenting symp-

tom was spinal pain (76%), followed by weakness (36%), sensory symptoms (34%), gait disturbances (5%), and bowel or bladder incontinence (5%). Only 2% of tumors were asymptomatic and found incidentally. Demographics

TABLE 1. Characteristics, treatments, and outcomes for 221 tumors in 199 patients

Characteristic	No. (%) [*]
Patient age (yrs)	
Mean	45
Median	46
Range	1–87
Patient sex	
M	123 (56)
F	98 (44)
Neurofibromatosis	
Type 1	42 (19)
Type 2	11 (5)
None	168 (76)
Symptom duration (mos)	
Mean	16
Median	6
Range	0–120
Clinical presentation	
Spinal pain	168 (76)
Weakness	79 (36)
Numbness/paresthesias	76 (34)
Gait disturbance	12 (5)
Bowel/bladder incontinence	12 (5)
Incidental finding	4 (2)
Tumor type	
Neurofibroma	53 (24)
Schwannoma	163 (74)
Malignant peripheral nerve sheath	5 (2)
Tumor spinal level	
Cervical	85 (38)
Thoracic	62 (28)
Lumbosacral	74 (34)
Location	
Intradural	160 (73)
Extradural	47 (21)
Paraspinal	14 (6)
Extent of resection	
GTR	166 (75)
STR	54 (24)
Biopsy	1 (0.5)
Postop radiotherapy	14 (6)
Recurrence	20 (9)
Time to recurrence (mos)	
Mean	49
Median	39
Range	4.5–119
Follow-up duration (mos)	
Mean	32
Median	16
Range	0–162

* Unless otherwise indicated, data reflect the number (%) of tumors, not the number (%) of patients.

of patients with neurofibroma and schwannoma are compared in Table 2. Pain at presentation was described by 58% of patients with neurofibroma and by 81% of those with schwannoma ($p = 0.003$). Weakness was present for 43% with neurofibroma and 34% with schwannoma ($p = 0.141$). Sensory symptoms were present in 26% of patients with neurofibromas and 38% with schwannomas ($p =$

TABLE 2. Comparison of tumor types

Characteristic	Neurofibroma (n = 53), No. (%) [*]	Schwannoma (n = 163), No. (%) [*]	p Value
Patient age (yrs)			<0.001
Mean	36	48	
Median	35	49	
Range	1–76	14–88	
Patient sex			0.646
M	28 (53)	92 (56)	
F	25 (47)	71 (44)	
Neurofibromatosis			
Type 1	39 (74)	2 (1)	<0.001
Type 2	1 (1)	10 (6)	0.222
None	13 (25)	151 (93)	<0.001
Symptom duration (mos)			0.560
Mean	19	15	
Median	6	6	
Range	0.5–120	0–120	
Clinical presentation			
Spinal pain	31 (58)	132 (81)	0.003
Weakness	23 (43)	55 (34)	0.141
Numbness/paresthesias	14 (26)	62 (38)	0.168
Gait disturbance	2 (4)	10 (6)	0.549
Bowel/bladder incontinence	5 (9)	7 (4)	0.146
Incidental finding	0 (0)	4 (2)	0.250
Location			
Cervical	39 (74)	44 (27)	<0.001
Thoracic	7 (13)	55 (34)	0.004
Lumbosacral	7 (13)	64 (39)	<0.001
Location			
Intradural	35 (66)	123 (75)	0.179
Extradural	13 (25)	31 (19)	0.387
Paraspinal	5 (9)	9 (6)	0.315
Extent of resection			
GTR	27 (51)	135 (83)	<0.001
STR	26 (49)	27 (17)	<0.001
Biopsy	0 (0)	1 (0.1)	0.568
Postop radiotherapy	4 (8)	6 (4)	0.245
Time to recurrence (mos)			0.640
Mean	45	53	
Median	37	53	
Range	10–118	5–119	
Follow-up duration (mos)			0.300
Mean	38	31	
Median	17	16	
Range	0–163	0–157	

* Unless otherwise indicated, data reflect the number (%) of tumors, not the number (%) of patients.

0.168). Gait disturbances were less common and occurred only in 4% of patients with neurofibromas and 6% with schwannomas ($p = 0.549$); bowel and bladder incontinence were present in 9% of patients with neurofibromas and 4% with schwannomas ($p = 0.146$). No neurofibromas and 2% of schwannomas were found incidentally ($p = 0.250$). The mean symptom duration was 16 months and did not differ significantly between patients with neurofibromas (19 months) and schwannomas (15 months) ($p = 0.560$).

Tumor Locations

Among all tumors, 38% were localized to the cervical spine, 28% to the thoracic spine, and 34% to the lumbosacral spine. Overall classification was intradural (73%), intraspinal extradural (21%), and paraspinal (6%). Specifically, neurofibromas were 66% intradural, 25% extradural, and 9% paraspinal. Schwannomas were 76% intradural, 19% extradural, and 5% paraspinal. The proportion of intradural, extradural, and paraspinal lesions did not differ between tumor types. Among neurofibromas, an intradural location was associated with an increased rate of STR.

Tumor types were compared by location. Overall, 74% of neurofibromas and 27% of schwannomas were localized to the cervical spine ($p < 0.0001$). However, in this study, schwannomas were more prevalent, and of the 85 cervical tumors included, 39 (46%) were neurofibromas, 44 (52%) were schwannomas, and 2 (2%) were malignant peripheral nerve sheath tumors. The proportion of thoracic tumors was 13% for neurofibromas and 34% for schwannomas ($p = 0.004$); the proportion of lumbosacral tumors was 13% for neurofibromas and 39% for schwannomas ($p < 0.001$). Of 62 thoracic tumors included in this study, 55 were schwannomas; of 74 lumbosacral tumors, 64 were schwannomas.

Extent of Resection

All patients received treatment for their tumors at the time of diagnosis. Among 216 neurofibromas and schwannomas, the extent of resection was GTR in 162 lesions, STR in 53, and biopsy in 1. Of the patients for whom tumor resection was subtotal, 10 received postoperative radiotherapy; 8 had previously undergone STR, 1 had undergone biopsy only, and 1 had 2 adjacent lesions (1 of which underwent GTR, and the other was asymptomatic and treated by radiotherapy alone). Of the 5 malignant peripheral nerve sheath tumors included in this study, 4 received GTR, 1 STR, and all postoperative radiotherapy.

Rates of GTR differed according to tumor pathology and location. The rate of GTR was 51% among neurofibromas and 83% among schwannomas ($p < 0.001$). Rates of GTR based on location were 54% for cervical, 90% for thoracic, and 86% for lumbosacral tumors ($p < 0.001$). NF status was also associated with extent of resection. Rates of GTR were 44% among patients with NF1 or NF2 and 85% among those without NF ($p < 0.001$). A multivariate model was generated to identify factors associated with GTR and used variables found to be significant on univariate analysis. A complete comparison of factors associated with GTR and STR for neurofibromas and schwannomas is presented in Tables 3 and 4, respectively. Only cervi-

TABLE 3. Neurofibroma analysis

Characteristic	GTR (n = 27), No. (%) [*]	STR (n = 26), No. (%) [*]	p Value
Patient age (yrs)			0.174
Mean	39	33	
Median	37	33	
Range	5–64	1–76	
Patient sex			0.884
M	14 (52)	14 (54)	
F	13 (48)	12 (46)	
Neurofibromatosis			
Type 1	15 (56)	24 (92)	0.002
Type 2	0 (0)	1 (4)	0.491
None	12 (44)	1 (4)	0.001
Symptom duration (mos)			0.349
Mean	24	13	
Median	11	6	
Range	0.5–120	1–108	
Clinical presentation			
Spinal pain	19 (70)	12 (46)	0.067
Weakness	10 (37)	13 (50)	0.331
Numbness/paresthesias	7 (26)	7 (27)	0.931
Gait disturbance	2 (7)	0 (0)	0.490
Bowel/bladder incontinence	1 (4)	4 (15)	0.183
Incidental finding	0 (0)	0 (0)	—
Location			
Cervical	16 (59)	23 (88)	0.016
Thoracic	6 (22)	1 (4)	0.100
Lumbosacral	5 (19)	2 (8)	0.420
Dural location			
Intradural	14 (52)	21 (81)	0.026
Extradural	9 (33)	4 (15)	0.202
Paraspinal	4 (15)	1 (4)	0.351
Postop radiotherapy	0	4 (15)	0.051
Recurrence	2 (7)	7 (27)	0.076
Time to recurrence (mos)			0.233
Mean	17	53	
Median	17	40	
Range	10–24	17–117	
Follow-up duration (mos)			0.022
Mean	24	52	
Median	9	55	
Range	0–160	0–162	

^{*} Unless otherwise indicated, data reflect the number (%) of tumors, not the number (%) of patients.

cal location (OR 0.231, 95% CI 0.109–0.488) and presence of NF mutation (OR 0.199, 95% CI 0.073–0.541) were associated with an effect on GTR; tumor pathology and intradural location were not (Table 5).

Tumor Control

The mean time to last follow-up visit was 32 months; 60% of patients were followed up for at least 1 year. The mean follow-up time was slightly longer for patients with neurofibroma (38 months) than for patients with schwannoma (31 months), but the difference was not significant ($p = 0.300$). Among neurofibromas and schwannomas, 20

TABLE 4. Schwannoma analysis

Characteristic	GTR (n = 135), No. (%) [*]	STR (n = 27), No. (%) [*]	p Value
Patient age (yrs)			0.960
Mean	48	48	
Median	49	50	
Range	16–79	14–88	
Patient sex			0.321
M	79 (59)	13 (48)	
F	56 (41)	14 (52)	
Neurofibromatosis			
Type 1	2 (1)	0 (0)	1.000
Type 2	6 (4)	4 (15)	0.064
None	127 (95)	23 (85)	0.117
Symptom duration (mos)			0.240
Mean	14	19	
Median	6	12	
Range	0.1–120	1–72	
Clinical presentation			
Spinal pain	108 (80)	23 (85)	0.789
Weakness	42 (31)	12 (44)	0.180
Numbness/paresthesias	48 (36)	13 (48)	0.218
Gait disturbance	8 (6)	2 (7)	0.673
Bowel/bladder incontinence	7 (5)	0 (0)	0.602
Incidental finding	4 (3)	0 (0)	1.000
Location			
Cervical	29 (21)	15 (56)	<0.001
Thoracic	50 (37)	5 (18)	0.064
Lumbosacral	56 (42)	7 (26)	0.130
Dural location			
Intradural	105 (78)	18 (67)	0.218
Extradural	24 (18)	7 (26)	0.326
Paraspinal	6 (4)	2 (7)	0.621
Postop radiotherapy	1 (1)	4 (15)	0.003
Recurrence	5 (4)	5 (19)	0.004
Time to recurrence (mos)			0.262
Mean	64	34	
Median	58	36	
Range	5–119	4–58	
Follow-up duration (mos)			0.136
Mean	28	42	
Median	15	24	
Range	0–156	0–139	

* Unless otherwise indicated, data reflect the number (%) of tumors, not the number (%) of patients.

recurred (total recurrence rate 9%). Among patients with at least 1 year of follow-up, the rate was 15% (20 of 130), and for those with at least 2 years of follow-up the rate was 20% (18 of 91). For those with at least 3 years of follow-up, the rate was 23% (17 of 73). Recurrence was more common for neurofibromas (17%) than for schwannomas (7%) ($p = 0.026$). The recurrence-free period was significantly shorter for patients with neurofibromas than for those with schwannomas (Fig. 1) ($p = 0.018$). Recurrences were more common among patients with NF (17%) than without NF (7%) ($p = 0.022$). Time to recurrence was also shorter among patients with NF mutations (Fig. 2). The rate of re-

TABLE 5. Multivariate analysis of factors associated with GTR

Variable	Odds Ratio	95% CI	p Value
Cervical location	0.231	0.109–0.488	<0.001
NF mutation	0.199	0.073–0.541	0.002
Tumor pathology	0.880	0.310–2.500	0.811
Intradural location	1.259	0.572–2.768	0.567

currence was highest for cervical tumors (16%), compared with 2% for thoracic tumors and 8% for lumbosacral tumors ($p = 0.015$). In addition to differences in recurrence rates, the times to recurrence also differed among tumors at different locations and were highest for thoracic tumors (Fig. 3). Recurrence rates for intradural, extradural, and paraspinal lesions did not differ.

Extent of resection was significantly associated with tumor recurrence. The rate of recurrence was 4% for patients who underwent GTR and 24% for those who did not ($p < 0.001$). When tumor recurrence over time was assessed by use of Kaplan-Meier plots, this difference remained significant (Fig. 4). The number of patients receiving radiotherapy was limited; however, rates of recurrence were 27% (12 of 45) among patients who underwent STR and 0 (0 of 8) among those who underwent STR plus radiotherapy ($p = 0.097$). According to a multivariate model, only extent of resection was associated with tumor recurrence (OR = 0.160, 95% CI 0.051–0.503) (Table 6).

Malignant Peripheral Nerve Sheath Tumors

Small sample size precluded a detailed analysis of this cohort. Among 5 patients with malignant peripheral nerve sheath tumors, the mean age at presentation was 42 years; 2 patients were female and 3 male. Only 1 patient had a history of NF1, and none had a history of NF2. Tumor location was cervical spine for 2 and lumbosacral region for 3. Follow-up in this cohort was limited to 0, 4, 6, 10, and 52 months. All but 1 patient underwent GTR of the tumor. Only 1 patient received radiotherapy before surgery (20 months before STR); unfortunately, disease recurred and

FIG. 1. Tumor pathology was associated with recurrence-free survival (time to tumor recurrence). Time to recurrence was longer for schwannomas than neurofibromas (log-rank, $p = 0.018$).

FIG. 2. Neurofibromatosis mutation status was associated with recurrence-free survival. Time to recurrence was significantly shorter among patients with NF1 or NF2 than among those without known NF mutations (log-rank, $p = 0.012$).

the patient died 10 months after surgery. The remaining 3 patients all received postoperative radiotherapy, all at outside facilities. For 2 of these patients, therapy consisted of fractionated radiotherapy; these patients had no evidence of recurrent disease at 4 and 6 months, respectively. The third patient received intensity-modulated radiotherapy with proton-beam therapy; he remained alive without evidence of recurrent tumor at 52 months.

Discussion

This study characterized the clinical presentation of spinal nerve sheath tumors and identified factors associated with extent of resection and tumor recurrence. Among the 199 patients with 221 tumors, the mean age at diagnosis was 45 years, and the mean age differed significantly between patients with neurofibromas and those

FIG. 3. Tumor location was associated with recurrence-free survival. Time to recurrence was shorter among patients with tumors in the cervical spine than among those with tumors in the lumbosacral or thoracic spine. Recurrence-free survival time was longest among patients with tumors in the thoracic spine (log-rank, $p = 0.038$).

FIG. 4. Extent of resection was associated with recurrence-free survival. Time to recurrence was significantly longer among tumors that underwent GTR than among those that underwent STR (log-rank, $p = 0.011$).

with schwannomas (36 vs 48 years, respectively). Given the high number of NF1 patients with neurofibromas included in this study (40 of 53) the younger age at presentation is not unexpected on the basis of the underlying tumor biology and is consistent with other reports in the literature.^{9,21} Among all NF patients included in this study, the majority (39 of 40) of neurofibromas were in patients with NF1 and the majority (10 of 12) of schwannomas were in patients with NF2. The associations between NF1 and neurofibromas and NF2 and schwannomas, as well as the underlying molecular mechanisms driving tumorigenesis, have been well described.^{1,14} There was no significant association between these tumors and patient sex, although neurofibromas (53%) and schwannomas (56%) were both slightly more commonly found in men.

Neurofibromas demonstrated a predilection for the cervical spine, which is consistent with other reports.^{7,21} However, among all cervical tumors in our cohort, approximately half (47%) were neurofibromas and the rest were schwannomas. Unlike neurofibromas, schwannomas are more evenly distributed throughout the spine and their prevalence is higher. Because these tumors share similar radiographic features, the presence of a cervical lesion does not make the diagnosis of neurofibroma more likely, and it is difficult to make any inference about nerve sheath tumor pathology based on clinical presentation or radiographic features unless there is a known history of NF1.

Although neurofibromas are often more challenging lesions for obtaining GTR and their biology is distinct from

TABLE 6. Multivariate analysis of factors associated with tumor recurrence

Variable	Odds Ratio	95% CI	p Value
GTR	0.160	0.051–0.503	0.002
Tumor pathology	0.716	0.149–4.387	0.677
Cervical location	1.646	0.517–5.241	0.399
NF mutation	0.890	0.181–4.387	0.886
Radiotherapy	0.326	0.037–2.910	0.316

that of sporadic schwannomas, our multivariate analysis found that only cervical location and the presence of NF, and not tumor type, were associated with lower rates of GTR. The association with cervical location is not unexpected, given the anatomical constraints of the spinal cord and nerve roots compared with those of lesions in the thoracic (where the nerve roots can be sacrificed) or lumbosacral spine (where the nerve roots can be moved). The association with NF mutations was surprising but not completely unexpected. We believe that this association was identified because of the effect of the NF mutations on the invasive potential of the tumor as well as the presence of nerve fascicles within tumor tissue, making these lesions more challenging for complete resection because the planes are less distinct. Indeed, there is a biological rationale based on pathology and laboratory data that supports this notion.²³ Among schwannomas included in this study, the rate of GTR was 66% (8 of 12) among patients with NF and 84% (127 of 151) among those without NF, although the difference was not statistically significant ($p = 0.261$), probably because of small numbers.

The rate of tumor recurrence among all nerve sheath tumors was 9% and significantly higher among neurofibromas (17%) compared with schwannomas (7%). The mean follow-up times between these groups was slightly higher among those with neurofibroma (38 months) than with schwannoma (31 months); however, this difference was not significant ($p = 0.300$). The recurrence rate was higher among patients with at least 1 year or at least 3 years of follow-up (20% and 23%, respectively). For previous surgical series, recurrence rates of 1.9%–5.8% and GTR rates of 85%–97% have been reported.^{4,7,9,12,15,20–22} However, many of these studies are characterized by higher numbers of schwannomas than neurofibromas. The likely explanation for the higher recurrence rates in our study is the higher number of spinal neurofibromas (53) and higher percentage of cervical nerve sheath tumors (38%) than are typically reported in the literature. Our multivariate analysis found that cervical location and the presence of NF mutations were associated with lower rates of GTR, factors that certainly contributed to the results.

The only variable found to correlate with tumor recurrence was extent of resection; not correlated were presence of NF, tumor pathology, tumor location, and use of postoperative radiotherapy. Although the presence of NF and cervical location can contribute to extent of resection, they are not independently associated with an increased risk for tumor recurrence, making surgical resection the most effective factor associated with disease control in these patients.

Limitations of this study include its retrospective nature and limited follow-up times, which hindered our ability to assess tumor control in this cohort. The rarity of these lesions makes prospective studies challenging. Limited follow-up time is an inevitable consequence of our clinical practice, in which complex patients from a large catchment area are referred to our center for surgical treatment and then choose to follow up with local providers. Another limitation is the lack of pathologic markers, for example MIB-1, to stratify tumors by their mitotic index because these markers would probably help predict which patients

are more likely to experience tumor recurrence. Postoperative MR images were obtained for 67% of patients; however, future prospective studies should rely solely on postoperative imaging to determine extent of resection.

Conclusions

Resection is an effective treatment for spinal nerve sheath tumors. Neurofibromas were found more commonly in the cervical spine and are associated with higher rates of recurrence and lower rates of GTR. Multivariate analysis found that cervical location and NF were associated with lower rates of GTR. A second multivariate model to assess factors associated with tumor recurrence found that only extent of resection was significant. Maximal safe resection remains the ideal therapy for these lesions; however, patients with cervical tumors or NF should be counseled on their increased risk for recurrence.

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