Surgical strategies for managing foraminal nerve sheath tumors: the emerging role of CyberKnife ablation

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Received: 20 October 2008 / Revised: 18 July 2009 / Accepted: 30 August 2009 / Published online: 2 October 2009
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Abstract Sixteen Stanford University Medical Center (SUMC) patients with foraminal nerve sheath tumors had charts reviewed. CyberKnife radiosurgery was innovative in management. Parameters were evaluated for 16 foraminal nerve sheath tumors undergoing surgery, some with CyberKnife. Three neurofibromas had associated neurofibromatosis type 1 (NF1). Eleven patients had one resection; others had CyberKnife after one (two) and two (three) operations. The malignant peripheral nerve sheath tumor (MPNST) had prior field-radiation and adds another case. Approaches included laminotomy and laminectomies with partial (three) or total (two) facetectomies/fusions. Two cases each had supraclavicular, lateral extracavitary, retroperitoneal and Wiltze and costotransversectomy/thoracotomy procedures. Two underwent a laminectomy/partial facetectomy, then CyberKnife. Pre-CyberKnife, one of two others had a laminectomy/partial facetectomy, then total facetectomy/fusion and the other, two supraclavicular approaches. The MPNST had a hemi-laminotomy then laminectomy/total facetectomy/fusion, followed by CyberKnife. Roots were preserved, except in two. Of 11 single-operation-peripheral nerve sheath tumors, the asymptomatic case remained stable, nine (92%) improved and one (9%) worsened. Examinations remained intact in three (27%) and improved in seven (64%). Two having a single operation

then CyberKnife had improvement after both. Of two undergoing two operations, one had symptom resolution post-operatively, worsened 4 years post-CyberKnife then has remained unchanged after re-operation. The other such patient improved post-operatively, had no change after re-operation and improved post-CyberKnife. The MPNST had presentation improvement after the first operation, worsened and after the second surgery \and CyberKnife, the patient expired from tumor spread. In conclusion, surgery is beneficial for pain relief and function preservation in foraminal nerve sheath tumors. Open surgery with CyberKnife is an innovation in these tumors' management.

Keywords Foraminal tumor · Peripheral nerve sheath tumor · Malignant peripheral nerve sheath tumor · Schwannoma · Neurofibroma

Introduction

Spinal peripheral nerve sheath tumors (PNSTs) typically are found on the dorsal sensory nerve root [59]. These tumors are usually located in an intradural-extramedullary location and intradural growth along the nerve into the spinal canal also occurs [59]. Fifteen percent of nerve sheath tumors extend laterally through the nerve root dural sleeve as dumbbell masses with intra- and extradural components [19, 33, 51, 59]. Concentric growth within the spinal nerve has been observed, as well [33, 59].

Eighty percent of spinal PNSTs are schwannomas, while only 14% were neurofibromas in one series [33, 48]; foraminal tumors exhibit a similar schwannoma preponderance. Thus, of 12 cervical dumbbell tumors evaluated by McCormick [33], the number of schwannomas and neurofibromas was eight and one, respectively, and in

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another McCormick series [32] five of five PNSTs in a foraminal location, with and without dumbbell configurations, were schwannomas.

Spinal tumors are not a regular feature of neurofibromatosis (NF) type 1 (NF1), however, they do occur in approximately 90% of NF type 2 (NF2) patients [14, 22, 29]. Conversely, only 35–45% of spinal PNSTs are NF1- or NF2-associated [14, 48, 59]. For example, of Sepalla et al.'s [48] 17 foraminal neurofibromas, 13 (76%) were NF1-associated, while Klekamp and Samii [22] found an NF2-association in only four (18%) of 22 foraminal dumbbell schwannomas.

In the past, foraminal tumors have been resected using various open surgical approaches. Recently stereotactic radiosurgery has become an important tool in the management of these lesions. Spinal radiosurgery using the CyberKnife radiosurgery (RS) System (Accuray, Inc., Sunnyvale, CA, USA) incorporates image-guidance technology and has been in use since 1999 at Stanford University Medical Center (SUMC). Dodd et al. [8] published the SUMC CyberKnife RS experience with 51 benign spinal intradural extramedullary schwannomas, neurofibroma and meningioma cases. Most patients in the present paper had surgery alone, however, five had additional CyberKnife RS.

Presently, charts of 16 operative SUMC patients with 15 foraminal PNSTs and one MPNST, and in five patients, CyberKnife RS, were reviewed retrospectively, as approved by an institutional review board (IRB) protocol. Presenting symptoms, history of neurofibromatosis (NF), prior radiation, clinical findings and tumor imaging characteristics were documented. The operative approaches, nerve root transection or preservation and outcomes were analyzed.

A 5-year literature review using the Ovid Medline (R) search engine and inputting “spinal neoplasms”, “neurilemmoma” and “foraminal” is presented in the “Discussion”.

Materials and methods

Charts of 16 patients with 15 foraminal benign PNSTs and one MPNST managed at SUMC between 1993 and 2006 were reviewed retrospectively (Table 1). The average age of the PNST patients was 48 years (range 24–87, median 47 years); the MPNST patient was 40. The mean age for 11 patients with benign schwannomas was 54 and for four with benign neurofibromas, 34. There were nine males and seven females. Most patients had surgery alone, while five had additional CyberKnife RS.

Accompanying neurofibromatoses

In patients with spinal foraminal tumors, a diagnosis of associated NF1 was made using the standard criteria [38]. No patients had NF2, nor schwannomatosis [28].

Tumor classification system

Asazuma et al.'s [3] cervical dumbbell tumor classification system was used to categorize tumors in the cervical, thoracic and lumbosacral areas (Fig. 1). Additional classifications per Asazuma et al. [3] indicated (1) degree of craniocaudal tumor spread, i.e. involvement of one (stage 1) or more (stages 2 and 3) intervertebral foramen/foramina (IF), and in the cervical region, (2) transverse foramen/foramina (TF) transgression. A TF stage 1 tumor showed involvement of one TF, whereas TF stages 2 and 3 involved two and three transverse foramina, respectively.

Symptoms and neurological examination findings

Pre- and post-procedure symptoms and findings were evaluated (Table 1). Pain symptoms were subcategorized as localized, radiculopathic, i.e. radiating with or without dysesthesias or radiculomyelopathic, i.e. radiating pain with weakness. Examinations were subclassified as intact, radiculopathic, radiculomyelopathic or myelopathic. These complaints and findings were graded as improved, stable or worse at each follow-up visit. Patients undergoing surgery alone were presented in operative chronological order in Table 1, with those having additional CyberKnife RS at the end.

Imaging characteristics

Tumor size and pertinent radiological findings are included in Table 1 [15]. Benign schwannomas and neurofibromas had classic magnetic resonance imaging (MRI) and computerized tomography (CT) findings (Table 2). The MPNST in the present series was atypical, since it was uniformly enhancing on post-contrast T1.

Clinical and radiographic follow-up

Post-operative follow-ups were at 1 week, 3-month intervals times two, then yearly (Table 1). Follow-up MRIs were obtained if the patient developed post-operative new or recurrent symptoms or findings. After CyberKnife RS, clinical and radiographic follow-ups were performed at 6-month intervals for 2 years, and then yearly.

Results

Sixteen patients with 15 foraminal benign PNSTs and a foraminal MPNST underwent surgery at SUMC between 1993 and 2006. Of 16 patients, four with benign PNSTs

Table 1 Summary of tumor location and type, CK/Preop clinical presentations and outcomes in 16 open surgery $\pm$ CK cases

Patient no.	Age, sex	Site of lesion/MRI size (cm) $\pm$ findings	Type, NF	OR/CK	Preop presenting Sxs	Initial Pre-op/Pre-CK neuro exam pertinent +s	F/u Post-op/ Post-CK Sxs (mos)	F/u Post-op/ Post-CK NE (mos)	F/u (mos)/ MRI f/u (mos)
1	59, M	rt C3–C4 5.0 $\times$ 2.5 rt cord compr.	S	8/03	rt neck mass; rt anterior shoulder dysesthasias	Intact	impr (4)	Intact (24)	24/no tumor (24)
2	40, M	lt L1–L2/ 2.5 $\times$ 4.8 $\times$ 4.8/ cystic deg./rt cord compr.	S	3/04	Periodic back, rt LE pain, hypesthesia	3 + knee DTRs	impr (1)	impr (1)	24
3	40, M	lt L3–L4/ 0.6 $\times$ 0.8 $\times$ 0.7	S	5/04	Back, lt knee, calf, ankle pain, dysesthasias, foot and 2–3rd toe dysesthasias	1 + lt ankle DTR	impr (1/4)	impr (1/4)	24/enh. scar tissue (18)
4	24, F	lt L1–L2/5.5 $\times$ 3.5/ dumbbell-shaped, retroper.	N, NF1	5/04	Asymptomatic	Intact	None	Intact (24)	24
5	43, M	rt C6–C7/ 3.5 $\times$ 1.7 $\times$ 2.6 into soft tissue; ant lat cord compr. (marked)	S	2/05	rt hand weakness, decreased coordination; rt hand fingertip hyposthesia; LE twitching, spasticity, gait imbalance, lt > rt LE weakness, dysesthasias; lt LE pain, stiffness; inability to walk	mild rt proximal flexion weakness; mod lt LE weakness; lt > rt ankle clonus	impr (4)	impr (1)	6
6	40, F	rt T1–T2/ 4.7 $\times$ 6.0 $\times$ 4.1 ext. into rt lung apex/ central cystic change/ foramen/vb bony remodeling	N	3/05	rt neck, shoulder, medial arm, forearm dull ache; rt anterior chest dysesthasias	Intact	impr (4)	Intact (17)	17/no tumor (12)
7	26, M	rt L3–L4/2.6 $\times$ 2.0 ext into parasp space	N, NF1	12/05	mod back, rt LE pain; rt thigh hyp- and dysesthasias; mild rt LE weakness	mild rt proximal weakness; 3 + rt patellar DTR	impr (1)	impr (1)	18/no enh. mass (1/2)
8	87, F	rt T5–T6/10.5 $\times$ 9.5 rt post. med. mass transv. proc/ped. eros/ lt ant sp cord compr.	S	2/06 and 4/06*	rt > lt LE pain, dysesthasias, weakness	mild bilateral LE weakness; gait spasticity	impr (1)	impr (1)	24
9	50, F	lt C3–C4/ext into prevert. soft tissue/ epid sp/vent lat cord. compr.	S	4/06	lt neck mass, pain; lt UE pain, hypesthesias	Intact	worse (1/2)	Intact (2)	2
10	63, M	lt L4–L5	S	4/06	lt buttock, posterior LE pain, mod distal weakness; rt, lt toe dysesthasias	mod lt ankle flexor, EHL weakness; bilateral 1 + ankle DTRs	impr (2)	impr (2)	14
11	40, F	rt C6–C7/2.7 $\times$ 1.8	S	4/06	Neck, lt occiput, rt shoulder blade pain; rt, lt hand dysesthasias; rt UE weakness	mild rt triceps weakness; absent rt UE DTRs	impr (1/2)	impr (1/2)	9

Table 1 continued

Patient no.	Age, sex	Site of lesion/MRI size (cm) ± findings	Type, NF	OR/CK	Preop presenting Sxs	Initial Pre-op/Pre-CK neuro exam pertinent +s	F/u Post-op/Post-CK Sxs (mos)	F/u Post-op/Post-CK NE (mos)	F/u (mos)/MRI f/u (mos)
12	47, M	lt C4–C5/ 4.8 × 1.0 × 2.0	S	3/02/ 10/03	mild lt shoulder blade pain/mild lt neck pain; lt > rt hand, LE dysesthesias; mild lt UE weakness; bowel, bladder dysfunction	mild lt UE weakness/3 + lt UE, LE DTRs; gait difficulty	impr (6)/impr (48)	impr (6)/impr (48)	54
13	61, M	rt L4–L5/ 2.1 × 1.5 × 2.0 (03)	S	1/03/3/ 04	mod rt back, LE pain, rt ant lat calf hypo-, dys- esthesias/mod back, rt LE pain, rt ant lat thigh hypo-, dysesthesias	Absent rt knee DTR/absent rt knee DTR	impr (1/2)/impr (24)	impr (1/2)/impr (12)	14
14	40, M	lt C7–T1/ 2.3 × 1.2 × 1.3 ext.into adj.soft tissue/ cystic center	M	9/05	lt 4th, 5th finger dysesthesias	lt 4th, 5th finger numbness	impr	impr	
15	61, F	lt C5–C6/lt marked ant lat cord compr.	S	11/05/ 12/05	Neck pain; lt forearm, 3rd, 4th digit dysesthesia mild lt hand weakness/ neck pain; lt forearm, 3rd, 4th digit dysesthesias; mild lt hand weakness	lt C8 hypesthesia; mild lt intrinsic weakness; 3 + lt UE DTRs/lt C8 hypesthesia; mild lt intrinsic weakness; 3 + lt UE DTRs	worse (6)/worse (6)	worse (6)/worse (6)	8 (exp.)/ 0.6 × 0.6x0.6 (1)/diffuse nodular enh.in T-spine/brain leptomeninges
16	45, F	lt C5–C6/sl. lt VA ant. compr./ext into neck soft tissues; lt lat epid sp cord compr.	N, NF1	6/93/5/ 00	Posterior neck, lt shoulder. UE pain/severe lt neck, UE stiffness, pain, dysesthesia	lt UE hyperesthesias/lt UE, LE hyperesthesia; 4 + lt knee DTR	impr (1) worse (48)	impr (1) stable (48)	15
				6/06	Severe lt neck shoulder, UE pain > rt neck, shoulder; lt LE pain	lt 2nd digit hyperesthesia; 3 + lt knee, ankle DTRs	No change (15)	impr (15)	
				00	Neck and lt UE pain; lt UE dysesthesias, weakness	lt UE weakness, numbness	impr (1/4)	impr (1/4)	72/No t. seen (72)
				8/03/9/ 05	Neck and lt UE pain; lt UE dysesthesias, weakness/mod lt UE pain, hypesthesia, weakness, spasticity	lt UE weakness, numbness/lt UE hyperesthesia; mild rt hand, bilateral proximal LE weakness; 4 + DTRs; spastic gait	No change (3)/impr (6)	No change (3)/impr (6)	

CK CyberKnife radiosurgery, preop pre-operative, No number, M male, F female; lt left, rt right, NF neurofibromatosis, S schwannoma, N neurofibroma, M malignant peripheral nerve sheath tumor, NF1 neurofibromatosis type 1, UE upper extremity, > greater than, mod moderate, Sxs symptoms, NE neurological examination, DTR deep tendon reflex, + positive, mos months, F/u follow-up, impr improved, exp expired, * staged procedure for one tumor, deg. degeneration, retroperitoneal, ant lat anterolateral, sp spinal, ext extends, parasp paraspinous, adj. adjacent, T thoracic, compr. compression, sl slight, VA vertebral artery, t tumor, post posterior, med mediastinal, transv transverse, proc process, prevert prevertebral, vent ventral, MRI magnetic resonance imaging, Post-op post-operative, epid epidural, cm centimeter, lat lateral, eros erosion, vent lat ventrolateral

Table 2 PNST and MPNST neuroimaging characteristics

Tumor type	MRI			CT
	T1-weighted	T2-weighted	Gd	
Schwannoma	(↓↑)	(↑↑) or (↓↑)	+	Iso- or hypodense; bone erosion
Neurofibroma	(↓) to (↓↑)	(↑↑) or target sign ^a	+	Hypodense w/ a dumbbell shape; bone erosion
MPNST	(↓)	(↑↑)	+	Hypodense; ill-defined, w/marginal enhancement

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^a *Target sign* central area of low signal intensity surrounded by an area of high signal intensity

PNST peripheral nerve sheath tumor, *MPNST* malignant peripheral nerve sheath tumor, *MRI* magnetic resonance imaging, *CT* computerized tomographic scan, *Gd* gadolinium, *w/* with

and one with a MPNST underwent CyberKnife RS in addition to surgery.

Tumor locations and nerve root involvement

Tumor locations included seven cervical, two thoracic and six lumbosacral PNSTs; the MPNST was in the cervico-thoracic region. One MPNST and eight PNSTs were located on the left and seven PNSTs on the right.

Classification and imaging characteristics

Schwannomas

Eleven foraminal schwannomas were classified using Asazuma et al.'s system (Fig. 1) [3]. Of four cervical schwannomas which involved a single IF (Cases 1, 11–12 and 15), TFs were not involved: two exhibited epidural thecal sac compression (type IIa with cord compression, IF stage 1, TF stage 1 and 2 were without thecal sac compression (type IIa, IF stage 1, TF stage 1). Another cervical tumor (Case 9) abutted the left vertebral artery and extended into the prevertebral soft tissues (type IIb with cord compression, IF stage 1, TF stage 2). One intra- and extradural cervical tumor (Case 5) expanded from the foramen into the lateral soft tissues (type IIIb with cord compression, IF and TF stage 1). A type VI, IF stage 2, TF stage 1 thoracic foraminal schwannoma (Case 8) expanded two adjacent foramina and caused erosion of the superior pedicle and transverse process (Fig. 1). Three lumbar schwannomas (Cases 3, 10 and 13) were each located in a single IF and were type IIa, IF stage 1; Case 13 remained the same type at presentation for CyberKnife RS. Case 2 was located in a single IF with right cord compression and thus was a type IIa with cord compression.

Schwannomas exhibited an intermediate T1-weighted (T1) signal intensity (SI) on MRI and were of intermediate-or-hyperintense SI on T2-weighting (T2). Gadolinium-uptake, common to schwannomas, was homogeneous in nine and heterogeneous in two. On computerized

tomographic (CT) scanning, schwannomas are iso- or hypodense and may show bony erosion.

Neurofibromas

Intraforaminal neurofibromas were categorized using the Asazuma et al. classification [3]. Of neurofibromas, one involved the left C5–C6 foramen (Case 16) and resulted in mild thecal sac compression and vertebral artery displacement (type IIa with cord compression, IF stage 1, TF stage 1) and had the same pattern at presentation at surgery and CyberKnife RS. Two other lumbar dumbbell tumors (Cases 4 and 7) each had retroperitoneal and paraspinal extensions, respectively (type IIc, IF stage 1). Another neurofibroma (Case 6) resulted in bony remodeling of the vertebral bodies (type VI, IF stage 1).

Neurofibromas were found to have a low or intermediate SI on T1 MRI. On T2, signal hyperintensity or a hyperintense rim with an intermediate SI focus (target sign) was seen; gadolinium-enhancement occurred in all neurofibromas in this series. On CT scan, neurofibromas are hypodense and tend to have a dumbbell shape; there is often bony erosion.

MPNST

The pre-operative MPNST MRI (Case 14) revealed a uniformly enhancing, partially cystic left foraminal C7–T1 tumor extending into the adjacent paraspinal soft tissues (type IIb, IF stage 1, TF stage 1). At the second surgery, the tumor was intradural (type IIIa): CyberKnife RS was next used for residual enhanced soft tissues bordering the spinal canal at C6–T1.

On MRI, MPNSTs have been shown to be inhomogeneous with patchy contrast enhancement, which, per Mautner et al. [29] corresponds to areas of necrosis and hemorrhage. Malignant PNSTs characteristically exhibit decreased T1 SI, which is markedly increased on T2 MRI (Table 2). The MPNST on CT is hypodense and ill-defined with contrast enhancement and it enhances marginally.

Fig. 1 Asazume et al.'s cervical dumbbell tumor classification system was used to categorize tumors. Type I represents intraspinal intra- and extradural tumors which constrict the dura and do not involve the foramen. Type IIa, lesions are extradural, show foraminal constriction, but are not extraforaminal. Types IIb and IIc tumors are extradural/paravertebral and foraminal/paravertebral, respectively. Type III tumors have both dural and foraminal constrictions: type IIIa tumors include intra- and extradural foraminal tumors with dural and foraminal constrictions and IIIb are intra- and extradural paravertebral. Type IV tumors are extra- and intravertebral and invade the vertebral body; type V lesions are extradural and extralaminar with laminar invasion and type VI tumors show multi-directional bone erosion (Reprinted with permission from Lippincott, Williams & Wilkins, Spine, vol 49, number 1, 2003, p. e11, Figure 1)

The MPNST in the present series had the atypical presentation of, T1-homogeneity and uniform-enhancement on post-contrast T1. This tumor also had a central non-enhancing cystic component, which extended from the lateral margin of the foramen into the paraspinal soft tissues.

Clinical presentations

Presenting symptoms and findings are included in Table 1. Patients with schwannomas and neurofibromas were evaluated individually for presenting symptoms and findings. Of eight patients with schwannomas who underwent a single open surgery, seven presented with radiculopathic symptoms with intact (2), radiculopathic (3) or myelopathic (2) findings; the eighth patient had been experiencing radiculomyelopathic symptoms with myelopathic findings at the time of presentation. Of three patients with schwannomas who had CyberKnife RS in addition to their original surgery, two patients each had one operation presenting in each instance with radiculopathic symptoms and findings. CyberKnife RS followed at the time of recurrence and one patient had radiculopathic symptoms and findings and the other, radiculomyelopathic

complaints and myelopathic findings. Another patient undergoing additional CyberKnife ablation initially had surgery with radiculopathic symptoms and findings. This surgery was followed by CyberKnife RS and at that time the patient presented with radiculopathic symptoms and radiculomyelopathic findings. Pre-operatively at the second surgery, this patient presented with radiculomyelopathic symptoms and findings.

Of three patients with neurofibromas, each underwent a single operation for tumor resection. Pre-operatively, one was asymptomatic and intact, and two had radiculopathic complaints with an intact examination in one and radiculomyelopathic findings in the other. Another patient with a neurofibroma had two operations for tumor-removal followed by CyberKnife RS. Prior to each of the two operations, the patient experienced radiculopathic complaints and findings and pre-CyberKnife RS, the symptom and finding presentations were radiculomyelopathic.

The patient with a foraminal MPNST (Case 14) presented with radiculopathic symptoms and findings at the time of the first operation. At both the subsequent reoperation and at CyberKnife RS, the patient also presented with radiculopathic symptoms, but had progressed to radiculomyelopathic findings.

Table 3 Surgical approaches for foraminal tumors

Patient no.	
<i>Surgical procedures without CyberKnife RS</i>	
1	rt posterior cervical triangle approach
2	T12–L2 laminectomy/total facetectomy + T12–L2 PLF; T12–L3 TPSF
3	L3, partial L2, L4 laminectomy/partial facetectomy
4	Retroperitoneal approach
5	rt C6–C7 hemilaminectomy/partial facetectomy C6–C7/partial pedicle removal
6	rt T1–T2 lateral extracavitary approach
7	Lateral paraspinous approach L3–L5 with partial vertebrectomy and transverse process removal
8	Costotransversectomy/thoracotomy (staged) T5 laminectomy/total facetectomy + T4–T7 PLF + TPSF
9	C3–C4 laminectomy/partial facetectomy
10	L4 laminotomy
11	rt C6–C7 laminectomy/total facetectomy + C6–C7 LMSF
<i>Surgical procedures with CyberKnife RS</i>	
12	C3–C5 laminectomy/partial facetectomy
13	rt L4 laminectomy/partial facetectomy/partial pedicle removal
14	lt C7 hemilaminectomy, facetectomy and intradural resection of tumor; lt C7, T1 LMSRF Partial C6, T1 total C7 laminectomy/total facetectomy + C5–T2 PLF + C5, C6 LMSF + T1, T2 TPSF
15	C5–C6 laminectomy and partial facetectomy rt C6–C7 laminectomy/total facetectomy + C6–C7 LMSF
16	lt anterior supraclavicular approach lt anterior supraclavicular approach

RS radiosurgery, PLF posterolateral fusion, TPSF transpedicular screw fixation, LMSF lateral mass screw fixation

Potential associated predisposing factors

Neurofibromatosis type I

Of four patients with benign foraminal neurofibromas, three had associated NF1 (Table 1). No patients had NF2, nor schwannomatosis.

Associated radiation history

One patient with a left C7–T1 foraminal MPNST had a history of Hodgkin's disease 14 years earlier, which had been treated with radiation therapy to the mantle field. The radiation consisted of 36–44 Gy to the neck, chest, and under-arm lymph nodes. The disease had been in remission, until the foraminal MPNST developed in the prior radiation field.

Surgical techniques

Surgical approaches

Operative reports documented approaches for removal of 15 foraminal PNSTs and one MPNST (Table 3). The procedures were analyzed with reference to Asazuma's

tumor categorization and are presented in order of number and increasing complexity.

Schwannomas

Two patients with foraminal IIa, IF1, TF1 schwannomas, one at C4–C5 (Case 12), which was followed by CyberKnife RS and the other at C3–C4 (Case 1), underwent a midline posterior laminectomy with partial facetectomy and a posterior cervical triangle approach, respectively. A similar cervical schwannoma (Case 11) without cord compression, was removed using a laminectomy with total facetectomy and fusion. Case 16 presented with cord compression and underwent a laminectomy and partial facetectomy. A recurrence was treated with CyberKnife RS and the patient remained stable for 72 months. The tumor increased in volume and the patient underwent a re-do laminectomy, facetectomy and fusion. For IIb, IF1, TF1 (Case 9) and IIIb, IF1, TF1 (Case 5) schwannomas both with cord compression, a laminectomy with partial facetectomy and hemilaminectomy with partial facetectomy and partial pedicle removal were used, respectively.

A right posterior mediastinal tumor, 9.5 × 10.5 cm type VI with cord compression (Case 8), was an IF 2 thoracic tumor with retromediastinal and spinal extensions and was

Fig. 2 An 87-year-old female (Case 8) presented initially with shortness of breath (SOB), back and right lower extremity (LE) pain and bilateral LE weakness. Five years earlier, a 2.0×3.0 cm right posterior mediastinal mass had been found on chest X-ray, however, the patient did not wish to have surgery. At a subsequent admission, a chest X-ray revealed the tumor to be 9.5×10.5 cm (a). On MRI, the tumor extended through the right T5–T6 foramen into the T5 vertebral body and resulted in T5 extradural cord compression. Due to

increasing SOB and worsening of her other symptoms, the tumor was removed in two separate stages. A T5 laminectomy with costotransversectomy and an extracavitary approach with a partial T5 vertebrectomy and T4–T7 instrumentation and fusion were performed (b, c). Two months later, a right thoracotomy and resection of her posterior mediastinal mass was carried out (d). The patient's SOB, back and right LE pain and bilateral LE weakness were markedly improved 2 months after the second-stage of the two operations

removed in two stages (Fig. 2). Three IIa, IF1 lumbar schwannomas (Cases 10, 3 and 13) underwent (1) an L4 laminotomy, (2) a partial L2, L4 and complete L3 laminectomy and (3) a laminectomy with partial facetectomy and partial pedicle removal, followed at recurrence by CyberKnife RS, respectively. Case 2, a IIa, IF1 lumbar schwannoma with cord compression was removed via a laminectomy, total facetectomy and fusion.

Neurofibromas

An anterior supraclavicular approach for Case 16 to resect a C5–C6 tumor (IIa with cord compression, IF1, TF2) was used twice followed by CyberKnife RS. A lateral extracavitary approach (LECA) was used for a type VI, IF1 thoracic tumor (Case 6) and an L3–L5 IIc, IF1 (Case 7) was removed via a lateral paraspinal approach. A retroperitoneal approach was carried out in Case 4, a type IIc, IF1.

MPNST

The foraminal C7–T1 MPNST (type IIb, IF stage 1, TF stage 1) underwent a gross total resection (GTR) via a C7 hemilaminectomy and total facetectomy with fusion. A recurrence was removed via a partial C6, T1, total C7 laminectomy and total facetectomy with fusion then CyberKnife RS.

Nerve root preservation versus transection

Information regarding preservation or resection of the involved nerve root was available for nine patients with benign foraminal schwannomas and four with

neurofibromas. The dorsal nerve root from which the tumor originated was preserved in each of six schwannomas and transected in two. In another schwannoma, both the dorsal and ventral nerve roots were involved and both were transected after intraoperative ventral root stimulation revealed a lack of motor function; the ventral root in the latter case was described as being dysplastic. Of four neurofibromas, two had the dorsal nerve roots preserved. Another two neurofibromas had their dorsal nerve roots transected to enable tumor removal.

Intraoperative electrophysiological monitoring

Somatosensory-evoked potentials (SSEPs) and motor evoked potentials (MEPs) were monitored during surgery. A handheld monopolar stimulation electrode was used to elicit evoked electromyographic (EMG) responses to identify and to trace the course of nerves in relation to the tumor.

In the case of motor nerve roots, all fascicles involved by tumor which failed to evoke motor impulses were removed. Conversely, all motor fibers that evoke either muscle contraction or EMG response were left intact.

Symptom outcomes

Schwannomas

Of eight patients with schwannomas, who underwent a single operation, symptoms improved in seven (88%) and one worsened. Two patients undergoing a single surgery followed by CyberKnife RS experienced symptom improvement in all instances. Another patient had surgery

followed by CyberKnife RS then further surgery and had symptom improvement. She then became worse and remained unchanged.

Neurofibromas

Three patients with neurofibromas underwent a single operation: one patient without complaints remained unchanged and the other two patients had improvement of symptoms. The fourth patient with a neurofibroma who underwent two operations followed by CyberKnife RS experienced either no change or improvement in symptoms after all procedures.

MPNST

The patient with an MPNST had an improvement in symptoms postoperatively after the initial surgery. The symptoms recurred and after the second surgery followed by CyberKnife RS, the patient expired from tumor spread.

Neurological examination outcomes

Schwannomas

Eight patients with schwannomas who underwent a single operation either remained intact (2) or improved (6). Two patients with schwannomas undergoing a single surgery followed by CyberKnife RS had improvement in their examinations after both procedures. One patient with a schwannoma who had surgery, improved then underwent CyberKnife RS and worsened after 48 months. After further surgery, the patient became remained unchanged.

Neurofibromas

Three patients with neurofibromas underwent a single operation: two patients who were intact preoperatively, remained unchanged, another had improvement of findings. Another patient underwent two operations followed by CyberKnife RS and experienced improvement, no change then improvement in findings.

MPNST

The patient with an MPNST had an improvement in his examination after the first operation. The presentation again worsened and after the second surgery followed by CyberKnife RS, he expired as described above.

Discussion

Literature review

NF-associated foraminal tumors

A review of recent English language publications regarding the association of foraminal tumors with NF1 was performed. Thakkar et al. [56] evaluated the spinal MRIs of 54 NF1 patients. Thirty-five cases had spinal tumors, of which 31 were intraforaminal. A histological confirmation of neurofibroma was documented in nine patients with these foraminal tumors who had undergone eventual surgery. In the present paper, of 16 patients with foraminal tumors, three had NF1 and each of the latter patients had an intraforaminal neurofibroma, which concurs with Thakkar et al.'s results.

Regarding NF2, in a review of 22 patients with spinal dumbbell schwannomas, Klekamp and Samii [22] found only four (18%) who had co-existing NF2. George and Lot [10] evaluated 42 nerve sheath tumors of the C1 and C2 nerves and found only one of 27 schwannomas in their series was associated with NF2. There were no NF-2-associated schwannomas in the present paper.

Foraminal tumor series and case reports

Recent series presenting PNSTs specifically described as foraminal include that of Seppala et al. [49] who evaluated the long-term outcomes after surgical removal of 38 foraminal schwannomas. Another paper by Seppala et al. [48] presented a similar evaluation of 17 foraminal neurofibromas.

Asazuma et al. [3] analyzed 42 cervical foraminal tumors: 23 were upper cervical and 19, middle or lower cervical; there were 38 schwannomas, three neurofibromas and one MPNST. The authors used a similar classification described in the present paper to categorize tumors, and they presented each tumor categories' optimal surgical approach.

In George and Lot's cervical foraminal tumor series [10] 42 nerve sheath tumors of the first two cervical nerve roots were reviewed; seven were intradural, 16 were exclusively extradural and 19 had an hour-glass configuration. The same authors also presented 57 cervical neuromas, including 30 neurofibromas, 23 schwannomas and four neurofibrosarcomas [26].

Krishnan et al. [23] evaluated six C1 and 15 C2 nerve sheath tumors of unspecified type, of which 20 (95%) of 21 tumors were dumbbell-shaped. McCormick [33] published a series of 9 cervical dumbbell PNSTs and also authored a series of 12 thoracic and lumbar dumbbell and paraspinal tumors [32]: three thoracic and two lumbar

schwannomas were described as foraminal or dumbbell-shaped. The number of patients with benign PNSTs in our present series, i.e. 15, is similar to the total of 14 foraminal or dumbbell PNSTs published in the above two McCormick papers. Smaller foraminal neuroma series included Celli et al.'s [5] who described 16 patients with intradicular schwannomas or neurofibromas, of which seven were foraminal and intraspinal; the remainder included two which were intraspinal and seven intraspinal and/or foraminal tumors with an extraforaminal component. Of 143 intrathoracic neurogenic tumors presented by Liu et al. [25], four were dumbbell tumors, whose removal required combined approaches by neurosurgical and thoracic teams via microscopy and thoracoscopy. Vallieres et al. [58] outlined a similar surgical approach to three dumbbell schwannomas, each with mediastinal extensions. Mazel et al. [30] demonstrated their surgical management of three thoracic dumbbell tumors which were foraminal and intraspinal with anterior paraspinal components. They used combined anterior and posterior trajectories for removal of two neurofibrosarcomas and a malignant schwannoma.

Regarding case reports, Dickman and Apfelbaum depicted the thoracoscopic microsurgical removal of a thoracic foraminal schwannoma [6]. Nakano et al. [36] performed a paramedian transmuscular access to a cervical dumbbell type neurofibroma without the need for paravertebral muscle dissection from the spinous process or facetectomy. Aaron et al. [1] presented a case of an intraforaminal sacral schwannoma.

Foraminal surgical anatomy

Using cadaveric studies, the cervical foraminal region has been defined anteriorly, by the posterolateral aspect of the uncovertebral joint, the intervertebral disc and the inferior part of the suprajacent vertebra, posteriorly, by the medial aspect of the facet joint and the adjacent part of the articular column and laterally, by the foramen transversarium. Its superior and inferior margins are the pedicles of the superior and inferior vertebrae, respectively [54, 62]. In tumors located at the occipito-cervical and atlanto-axial levels, the facet pillars lie anterior to the nerve roots exiting through the intervertebral foramina [23].

A knowledge of the spinal nerve root anatomy is important, since foraminal spinal nerve sheath tumors often occur on dorsal nerve roots [14]. Spinal nerve roots are nerve bundles consisting of dorsal sensory and ventral motor roots inside a sleeve of dura. These respective roots are in turn composed of root filaments. The dorsal root and ventral root each extends from the point of

emergence from the spinal cord to the dorsal ganglion's distal pole where they merge. Each root has two segments: the first intrathecal segment include the point of the roots' emergence from the cord to the thecal sac exit orifices [5]. As these roots cross the subarachnoid space they do not have epineurium, nor do the roots have interstitial connective tissue [5, 31]. Both roots are ensheathed by a fenestrated arachnoid membrane per McCormick [31] and Parke [5, 41] or per Nicholas and Weller, an intermediate fenestrated arachnoid and pial layer, i.e. leptomeningeal layer [5, 39].

The second segment, which is extrathecal, encompasses the dural sac exit of the anterior and posterior roots to the point at which these nerve roots merge at the ganglion's distal pole [5]. At the location just beyond the ganglion where the two roots join, they become a typical mixed peripheral nerve. The dural sleeve here adheres to the nerve and becomes epineurial tissue from this point forward [9].

Regarding other means of deriving anatomical information, the radiological aspects of the cervical neural foramina and its contents were evaluated in 19 cervical spine specimens using CT and cryomicrotomy by Pech et al. [43]. They found that both the ventral and dorsal nerve roots were seen in a lower position within the foramen at or below the level of the disc. The dorsal nerve roots and ganglion contacted the superior facet, while the ventral nerve roots abutted the uncinat process and bottom of the neural foramen [43].

Pathogenesis of foraminal nerve sheath tumors

The anatomy specific to this region may be involved in the pathogenesis of neurofibromas. The etiology of neurofibromas is postulated to include the disruption of perineurium, which allows Schwann cell escape from the endoneurial space and subsequent proliferation outside the blood–nerve barrier [44]. Thus, it is possible that foraminal tumors arise from beyond the ganglion, where this perineurial tissue occurs [44, 46].

Per Pummi et al. [46] in NF1 gene-mutated mice, neurofibroma development required (1) mutations in both NF1 alleles of Schwann cells and (2) heterozygosity in the NF1 alleles of the other cell types [63]. The latter heterozygosity may result in altered stability of cell–cell junctions, including tight junctions in perineurial cells and in subsequent loss of cohesion of perineurium. As described in the preceding paragraph, the perineurial loss of cohesion may predispose to neurofibroma growth. Mast cells may have an additional role in the disruption of perineurium, since mast cell protease has been shown to affect the permeability of tight junctions by changing the localization of occludin [47].

Age at tumor presentation and age versus tumor location, histology

Age at tumor presentation

The mean age for 118 foraminal PNSTs in a study by Ozawa et al. [40] was 43 years. The average age for foraminal PNST patients in the present series was 48 years.

Age versus tumor location

Cervical schwannomas in the present series had a mean age of 50, while patients with lumbar schwannomas averaged 51; the cervical number is slightly older than those presented in the literature. Thus, the mean age of symptom-onset in Krishnan et al.'s [23] 21 patients with C1–C2 dumbbell-shaped PNSTs was 35. McCormick [33] presented eight cervical dumbbell schwannomas with a mean age at presentation of 42. McCormick [32], also, presented three thoracic and three lumbar foraminal schwannomas who were slightly older at 47 and 57, respectively.

Per Ghani et al. [11] the reason for cervical dumbbell tumors presenting at a younger age is possibly due to the larger size of the upper cervical roots, as compared with those at other levels. The resulting higher nerve cell density here may allow for tumors to occur more readily and to appear at a younger age.

Age versus histology

The mean age for 11 benign schwannomas in the present series was 54 and for four benign neurofibromas, 34. This younger age of presentation for neurofibromas may be due to the fact that the majority occurred in NF1 patients. Puumi et al.'s proposal that the NF1 $\pm$ genotype in NF possibly resulted in altered perineurial cell tight junction stability and predisposed to neurofibroma formation may predispose neurofibromas to occur more readily and at an earlier age than schwannomas.

For MPNSTs, the average age was 43 for three of Mazel et al.'s [30] cases. For the MPNST in the present series the age was 40.

Tumor location

Forty-three to fifty-eight percent of foraminal tumors occur in the cervical spine. [24, 27, 60] which agrees with the current series' prevalence of cervical tumors. Cervical tumor predominance may also be related to the theory posed by Ghani et al. [11] above.

Tumor classification system

More than half of all spinal PNST lesions are found in an extramedullary intradural location. Approximately 25% are completely extradural, 15% are both intra-extradural and in <1% they are found to be intramedullary in location. Many classification systems utilize this location stratification to categorize spinal PNSTs [59].

Our paper utilized one such three-dimensional classification system by Asazuma et al. [3]. Type I was omitted, since this was a non-foraminal categorization and the terms "epidural cord compression" were added, if present. In the present series of six patients, who presented with cord compression on MRI, four had evidence of more severe radiculomyelopathic or myelopathic presentations and many such patients required more complex procedures than a laminectomy to remove their tumors.

Neurofibromatosis-related neurofibromas

In the current series, three- of four foraminal neurofibromas were NF1-associated tumors. Neurofibromatosis type 1 (NF1) is a common autosomal dominant disorder, occurring in 1 in 3,000 births [13, 16, 56]. It is linked to a genetic defect on chromosome 17 [22, 35, 37, 45, 55], which results in a mutation in the gene encoding neurofibromin, a GTP-ase activating protein (GAP) for Ras [7, 57]. Functional loss of neurofibromin compromises Ras inactivation, which results in the aberrant growth of neural crest derivatives and ultimately tumor formation [7].

Sporadic schwannomas

All schwannomas in the present series were sporadic, i.e. the patients harboring these tumors did not have NF2 or schwannomatosis. While schwannomas may occur sporadically, they can also develop in association with NF2, an autosomal dominant disorder which predisposes to multiple schwannomas, meningiomas and spinal ependymomas, with bilateral vestibular schwannomas as the classic hallmark. In a study of genetic aberrations by Antinheimo et al. [2] the most common alteration was loss on 22q, found in eight of their studies' 25 schwannomas, of which 12 were NF2-related and 13 were sporadic. Thus, the overall number of genetic aberrations was similar in patients with NF2 and in those with sporadic schwannomas. The loss of chromosome 22q harboring the NF2 gene thus plays a universal role in the pathogenesis of both sporadic and NF2-related schwannomas.

Radiation-related MPNST

One patient with an MPNST in our series had a history of radiation for Hodgkin's disease. A paper by Isler et al. [17] similarly presented another such case of radiation-induced malignant schwannoma, which arose in the site at which a neurofibroma had been resected. Our case thus adds another case to the literature of such radiation-associated nerve sheath tumors.

Surgical approaches

Celli et al. [5] analyzed 16 patients with extrathecal intradiscal nerve sheath tumors in cervical, thoracic and lumbar locations. In their series, two intraspinal tumors were each cervical and lumbar in location; one cervical and six lumbosacral lesions were located in intraspinal/foraminal locations, while seven lumbosacral tumors were "intraspinal and/or foraminal with a not-too-large extra-foraminal component".

These authors used a posterior midline approach with a unilateral laminectomy to remove two tumors; the laminectomy was extended to include a facetectomy, which was "limited" in six and "more or less complete" in eight cases [50]. Per the authors, extended facetectomies underwent pedicle screw lumbosacral posterior fixation in the later stage of the study.

The majority of cervical, thoracic and lumbar tumors in our series were also removed via either a laminectomy alone or a laminectomy accompanied by a partial facetectomy; if a laminectomy plus total facetectomy was carried out, then a fusion was performed.

The results of a current literature review regarding techniques used to remove foraminal tumors have been grouped into approaches used for specific regions of the spine; a summary of procedures used for each region in the present series is included.

Cervical region

For removal of cervical dumbbell tumors, McCormick [33] used a partial laminectomy with complete unilateral facetectomy in his 12 patients. He recommended fusion depending on the degree of tumor erosion of the lateral vertebral body and uncovertebral joint. Lot and George advocated lateral techniques, i.e. postero- or anterolateral approaches, both with vertebral artery control, to remove cervical dumbbell neuromas [18, 26].

For cervical benign tumors in the present series, in patients undergoing a single operation for tumor removal, three patients' tumors were removed via a laminectomy and medial, i.e. partial facetectomy and one each had, a laminectomy and total facetectomy with fusion and

posterior cervical triangle approach. In patients having two operations, one patient had a laminectomy followed by a laminectomy, total facetectomy and fusion. Another patients had the tumor removed on two occasions via an anterior supraclavicular approach.

Cervicothoracic region

To expose a cervicothoracic lesion, Sundaresan et al. [52] recommended an anterior approach to the upper thoracic spine in which the medial clavicle and part of the manubrium were excised. Birch et al. [4] elevated the medial manubrium, the sternoclavicular joint and the medial half of the clavicle on a pedicle of the sternocleidomastoid muscle to expose the cervicothoracic spine. Micheli and Hood [34] combined an anterolateral cervical and posterior transpleural transthoracic approach to the cervicothoracic spine, while Grillo et al. [12] used a posterolateral thoracotomy extended vertically over the spinous processes of the involved vertebrae and accompanied by a laminectomy [58].

In the C7–T1 MPNST in the present series, a left C7 hemilaminectomy, facetectomy and intradural tumor resection with a left C7, T1 fusion was used for a GTR. The tumor recurred and a partial C6 and T1 and total C7 laminectomy with total facetectomy followed by a C5–T2 posterolateral fusion, C5, C6 lateral mass screw fixation and T1, T2 transpedicular screw fixation were carried out. These procedures were followed by CyberKnife RS.

Mid- and lower-thoracic regions

In the literature, the recommended treatment for mid- and lower-thoracic dumbbell tumors is laminectomy, hemilaminectomy alone [20, 50] or combined with a partial costotransversectomy. A combined posterior and lateral approach has also been described for tumor-removal in this location. Vallieres et al. [58] presented a two-staged approach at the same operation. A posterior laminectomy with foraminotomy was carried out for removal of the adjacent intervertebral facet and transverse process and was used in three patients with thoracic dumbbell schwannomas. The patient was then re-intubated with a double-lumen endotracheal tube, positioned for a full thoracotomy and an anterior video-assisted thoracoscopy technique was then used through a four-port thoracoscopy setup. Jules et al. [20] advocate assessing the foraminal diameter. If an intraspinal component's volume is lower than the diameter of the enlarged foramen, it can be removed by the transforaminal route via a posterolateral thoracotomy.

The costotransversectomy approach can also be used alone for lesions in this region. This approach allows decompression of the posterior and lateral wall of the spinal canal to approximately the midline. There is

insufficient ventral exposure, however, to perform vertebral body reconstruction if the tumor was a type VI in the majority of cases.

In the present series, a combined posterior approach, i.e. laminectomy and costotransversectomy was used for removal of a T5 dumbbell tumor (Case 8) (Fig. 2). A thoracotomy followed with the patient in a lateral decubitus position to remove the retromediastinal portion of the tumor.

Thoracolumbar region

Per Wolfla et al. [61] transthoracic approaches are useful for T4- to T10-located tumors, while the thoraco-abdominal approach is used for those in the T10 to L2 region.

For foraminal tumors in the thoracolumbar region, laminectomy, laminectomy with transpedicular decompression, the lateral extracavitary approach (LECA) and the costotransversectomy approach can be used. In our series, the LECA approach was used for Case six.

Lumbar region

Also per Wolfla et al. the retroperitoneal approach can be used for lesions at L2–L5. This approach was also used in Case four of our series for an L1–L2 foraminal tumor. The Wiltse approach, however, was used for Case seven. The latter approach involves a longitudinal separation between the multifidus and the longissimus muscles. For the other three lumbar lesions, a laminectomy and partial facetectomy was used in two patients and a laminotomy in one patient.

Fig. 3 Foraminal nerve sheath tumor management algorithm

Nerve root resection

The growth of foraminal dumbbell PNSTs tends to begin on dorsal sensory roots. Dumbbell extension through the root sleeve may necessitate resection of the entire spinal nerve. This transection is usually well-tolerated because, per Parsa et al. [42] “adjacent roots can compensate for functional deficits of the involved root”. Substantiating this statement, Kato et al. [21] reported on their operative results involving two intraforaminal lumbosacral neurofibromas and ten schwannomas. In four of their cases, including neurofibromas and large tumors, the nerve root had to be divided, however, no new postoperative deficits occurred. In the current series, the nerve root was preserved whenever possible. Longer-term follow-up is needed to determine if this will result in recurrence and thus the necessity of reoperation.

Conclusions

This series presents the operative SUMC management of 15 benign foraminal PNSTs and one MPNST. Also illustrated is the emerging role of CyberKnife RS in the treatment of these tumors. The majority of cases showed an improvement in symptoms and neurological findings postoperatively using a multi-disciplinary treatment approach used at our institution for these tumors. Various surgical techniques, as well as CyberKnife RS were used.

Most intraforaminal tumors were schwannomas. Three of four foraminal neurofibromas were associated with NF1. The MPNST case had prior radiation in the tumor field and adds another such case to the literature of prior radiation-associated lesions.

An algorithm is presented (Fig. 3) to illustrate the combined use of CyberKnife RS and operative techniques for management of these tumors. Patients exhibiting symptoms and signs of radiculomyelopathy or myelopathy and MRI evidence of spinal cord compression should have their tumors debulked prior to CyberKnife RS administration.

Acknowledgment Thank-you to Elizabeth Hoyte for figure preparation.

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