Clinicopathological variables of sporadic schwannomas of peripheral nerve in 291 patients and expression of biologically relevant markers

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OBJECTIVE While sporadic peripheral schwannomas (SPSs) are generally well treated with surgery, their biology is not well understood. Consequently, treatment options are limited. The aim of this study was to provide a comprehensive description of SPS. The authors describe clinicopathological features and treatment outcomes of patients harboring these tumors, and they assess expression of biomarkers using a clinically annotated tissue microarray. Together, these data give new insight into the biology and management of SPS.

METHODS Patients presenting with a primary SPS between 1993 and 2011 (n = 291) were selected from an institutional registry to construct a clinical database. All patients underwent follow-up, and short- and long-term outcomes were assessed. Expression of relevant biomarkers was assessed using a new tissue microarray (n = 121).

RESULTS SPSs were generally large (mean 5.5 cm) and frequently painful at presentation (55%). Most patients were treated with surgery (80%), the majority of whom experienced complete resolution (52%) or improvement (18%) of their symptoms. Tumors that were completely resected (85%) did not recur. Some patients experienced short-term (16%) and long-term (4%) complications postoperatively. Schwannomas expressed higher levels of platelet-derived growth factor receptor- β (2.1) than malignant peripheral nerve sheath tumors (MPNSTs) (1.5, p = 0.004) and neurofibromas (1.33, p = 0.007). Expression of human epidermal growth factor receptor-2 was greater in SPSs (0.91) than in MPNSTs (0.33, p = 0.002) and neurofibromas (0.33, p = 0.026). Epidermal growth factor receptor was expressed in far fewer SPS cells (10%) than in MPNSTs (58%, p < 0.0001) or neurofibromas (37%, p = 0.007). SPSs more frequently expressed cytoplasmic survivin (66% of tumor cells) than normal nerve (46% of cells), but SPS expressed nuclear survivin in fewer tumor cells than in MPNSTs (24% and 50%, respectively; p = 0.018).

CONCLUSIONS Complete resection is curative for SPS. Left untreated, however, these tumors can cause significant morbidity, and not all patients are candidates for resection. SPSs express a pattern of biomarkers consistent with the dysregulation of the tumor suppressor merlin observed in neurofibromatosis Type 2–associated schwannomas, suggesting a shared etiology. This SPS pattern is distinct from that of other tumors of the peripheral nerve sheath.

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KEY WORDS sporadic schwannoma; peripheral nerve; clinical variables; tissue microarray; biomarker expression; oncology

ABBREVIATIONS EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor-2; MPST = malignant peripheral nerve sheath tumor; NF2 = neurofibromatosis Type 2; PDGFR- β = platelet-derived growth factor receptor- β ; RTK = receptor tyrosine kinase; SPS = sporadic peripheral schwannoma; TMA = tissue microarray.

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THE intricate histological features of schwannomas were first described more than 100 years ago²⁶ and were later found to arise from Schwann cells of the peripheral nerve sheath.¹⁸ Schwannomas occur most frequently as a single, sporadic lesion.¹³ They are considered benign tumors as demonstrated by their generally low proliferative potential,¹ their frequently well-circumscribed gross appearance,²⁹ and the fact that malignant transformation is exceedingly rare.³² However, deep-seated tumors and those intimately associated with critical vascular, neural, and other anatomical structures can cause significant morbidity due to mass effect or erosion of adjacent bone.³⁰ Such situations present challenges in resection,²⁴ which is currently the best therapeutic option.¹⁷ The slow growth rate of sporadic peripheral schwannomas (SPSs) renders them generally unresponsive to conventional chemotherapy,¹⁴ suggesting a need for new treatment options, particularly for patients who are not surgical candidates.

Given these challenges, we sought to elucidate the biology of SPS. Loss or dysfunction of the known tumor suppressor gene *NF2* on 22q12.2²⁵ drives tumorigenesis of schwannomas arising in the hereditary cancer syndrome neurofibromatosis Type 2 (NF2). *NF2* encodes the protein merlin, which mediates contact inhibition⁷ by linking a cell's physical surroundings and its mitotic activity.³³ Merlin also restrains cell proliferation by negatively regulating several receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptor- β (PDGFR- β), human epidermal growth factor receptor-2 (HER-2), and epidermal growth factor receptor (EGFR).⁴ Interestingly, loss of heterozygosity in chromosome 22 where merlin is located has been demonstrated in SPS,¹¹ providing evidence for similar pathogenesis in sporadic tumors and their congenital counterparts. Thus, we hypothesized that if similar mechanisms drive sporadic schwannoma growth, we might be able to detect these expression patterns in tumor samples obtained in humans.

To characterize the biology of these tumors, we constructed a clinically annotated tissue microarray (TMA) and used it to assess biomarker expression. We also constructed a clinical database of patients with primary SPS and gathered their clinical presentation, treatment, and outcome information. Together, these new resources provide an informative vignette characterizing the morbidity of SPS both in situ and as sequelae to their resection.

Methods

Review of the Literature

We reviewed tissue-based studies of SPS from the literature containing at least 10 patients with follow-up. From these, only tumors that met the following conditions were included: 1) The sample was diagnosed definitively by histological analysis as a schwannoma (vs malignant schwannoma, malignant peripheral nerve sheath tumor [MPNST], neurofibroma, or other peripheral nerve sheath tumor). 2) The sample was sporadic and did not occur in the context of a congenital neurocutaneous syndrome (e.g., NF2, schwannomatosis). 3) The tumor was peripherally located (vs intracranial, or associated with cranial nerves). The clinicopathological features of these tumors were compared with those in the present series (Table 1).

Clinical Database

Clinical data were collected and analyzed with the approval of the institutional review board at the University of Texas MD Anderson Cancer Center. Patients treated for SPS at University of Texas MD Anderson Cancer Center from January 1, 1993, through December 31, 2011, were selected from the pathology archives and institutional tumor registry databases. Patients with a diagnosis of a single schwannoma (neurilemmoma) arising from a peripheral nerve (including spinal nerve roots) were included in the database, as were histological variants such as cellular schwannoma, plexiform schwannoma, and ancient

TABLE 1. Literature review of clinicopathological data for patients with sporadic schwannomas arising in the peripheral nerves

Authors & Year	No. of Pts	Sex	Age Range, Yrs*	Tumor Size, cm*	No. w/ FU	FU Range, Yrs*	Recurrence (%)
Stout, 1935	46	26 F, 20 M	19–68 (39.3)	1–7.5 (3.2)	23	0.25–14 (2.9)	0 (0.0)
Ackerman & Taylor, 1951	19	13 F, 6 M	19–66 (44.6)	3.5–20 (9.3)	16	0.3–8 (3.3)	0 (0.0)†
Woodruff et al., 1981	13	6 F, 7 M	25–71 (49.1)	2.7–11 (5.7)	8	0.167–10 (2.58)	0 (0.0)‡
Fletcher et al., 1987	16	9 F, 7 M	17–73 (41.9)	NA	13	2–32 (15.1)	0 (0.0)§
Lodding et al., 1990	29	21 F, 8 M	15–79 (median 55)	2–12 (median 6.0)	28	0.25–19.5 (median 7)	0 (0.0)
White et al., 1990	57¶	35 F, 22 M	1.3–81 (44.0)	1–19.5 (6.2)	49	1–24 (6)	3 (6.1)
Agaram et al., 2005	23	14 F, 9 M	0.4–67 (28.8)	NA	6	1.1–10.0 (median 2.0)	3 (50.0)
Strauss et al., 2011	28	21 F, 7 M	NA (median 47)	5–23 (median 9)	28	NA (median 3.25)	0 (0.0)**
Voltaggio et al., 2012	51	40 F, 11 M	29–90 (58)	1–10.5 (5.1)	41	1–34.9 (11.5)	0 (0.0)
Current study	291	153 F, 138 M	7–89 (49.7)	0.3–26 (5.5)	291	0.1–18.9 (4.0)	0 (0.0)

FU = follow-up; NA = not available, Pts = patients.

* Values in parentheses are means unless stated otherwise.

† There was progression of residual disease after incomplete excision in 1 patient (5.3%).

‡ Residual tumor was observed in 2 patients who received subtotal resection.

§ There was progression of residual disease after incomplete excision with need for repeated excisions in 1 patient (6.25%).

¶ Series includes 15 patients from Woodruff et al., 1981 and 1983.

** No progression of residual disease in 3 subtotally resected tumors.

schwannoma. Patients with other benign (e.g., neurofibroma and neuroma) and malignant (e.g., MPNST, malignant schwannoma, and psammomatous melanotic schwannoma) nerve sheath tumors were excluded. Schwannomas arising from the cranial nerves were not included in the data set in order to exclude potential cases of NF2. Only patients with at least 30 days of follow-up were included. Demographic, disease-specific, tumor-specific, and follow-up variables were analyzed. Progression of disease was defined as an increase in tumor size as detected by MRI, with both T1-weighted postcontrast and T2-weighted images reviewed in all 3 standard planes.

Tissue Microarray Construction

From tumor registry databases, patients with formalin-fixed, paraffin-embedded schwannoma and control tissues were selected. A total of 188 blocks were selected from 169 patients. Slides were reviewed, and viable areas of tumor were delineated by a soft-tissue sarcoma pathologist (F.L.L.). These areas were manually punched in duplicate with a 1.0-mm core and placed into the recipient TMA block; 121 samples from patients with primary SPSs were included. Control tissues included adjacent histologically normal nerves from patients with schwannoma ($n = 11$). Other control tissues included tumor from patients with NF Type 1 ($n = 7$); schwannoma ($n = 1$); glandular malignant schwannoma ($n = 1$); neurofibroma ($n = 2$); MPNST ($n = 3$); sporadic MPNST ($n = 2$); NF2 ($n = 6$); schwannomatosis ($n = 5$); sporadic schwannomas from cranial nerves ($n = 8$); *INI1*-negative epithelioid sarcomas ($n = 6$); *INI1*-positive, unclassified sarcoma with epithelioid features ($n = 1$); pigmented psammomatous schwannoma ($n = 1$); melanoma from a patient treated for schwannoma ($n = 1$); and other benign nerve tumors (neuroma [$n = 1$], spindle cell tumor with schwannian differentiation [$n = 1$], and benign nerve sheath tumor [$n = 2$]). Tumors were recurrent at presentation in 7 patients, and tumor status was not available for 1 sample. No tissue sample was included from any tumor that had been irradiated prior to surgery.

Immunohistochemistry

Unstained slides were de-paraffinized using standard procedures, and antigen retrieval was achieved using Envision FLEX target retrieval solution (PDGFR- β), citrate buffer (HER-2, survivin), and proteinase K (EGFR). Antibodies were obtained from Santa Cruz (PDGFR- β , sc-339, 1:50), Thermo Scientific (HER-2, clone e2-4001, 1:300), and Invitrogen (EGFR, clone 31G7, 1:50). Expression of biomarkers was scored by 2 independent observers (A.J.F.L. and G.A.S.). The percentage of tumor cells showing staining and the intensity of staining in the tumor cells on a scale of 0–3, where 0 represents no staining; 1, low staining; 2, moderate staining; and 3, intense staining (see Fig. 2 for results of TMA biomarker expression). Specimens that did not contain sufficient material for scoring were excluded from further analysis.

Statistical Analysis

The Student 2-tailed t-test was performed to determine the differences in expression of biomarkers as determined

using immunohistochemistry. Graphs were constructed using R statistical software.

Results

Clinical Database

Patient Variables

Clinicopathological variables of 291 patients presenting with SPS are summarized in Table 2. Of these, 215 patients were Caucasian (74%), 38 were Hispanic (13%), 19 were Asian or Pacific Islander (7%), 17 were African American (6%), 1 was Native American (0.3%), and race was not specified for 1 patient (0.3%). Diagnosis was made by histological examination of the tumor after resection, biopsy, or fine needle aspiration. Diagnosis was made based on findings from presurgical biopsy in 150 samples (51%), fine needle aspiration in 11 samples (4%), incisional biopsy in 1 (0.3%), frozen section in 3 (1%), and postexcision paraffin section in 126 (43%). The chief complaint was not available for 6 patients.

Tumor Variables

Tumor size was available for 271 patients and was defined as the maximum dimension reported at radiological or pathological assessment, as measurements by both methods were unavailable for all patients. Nonvestibular (noncranial nerve) schwannomas located in the head and neck (10% of the total) arose from the cervical nerve roots, sympathetic chain, or subcutaneously. A more detailed description of where tumors arose in these locations and the spinal levels affected by schwannoma are described in Table 3 and Fig. 1, respectively. Erosion of adjacent bone was noted in 17 tumors (6%). Histologically, SPSs were divided into the following subclasses: 247 (85%) were identified as conventional schwannomas, 37 (13%) were cellular schwannomas, 6 (2%) showed ancient or degenerative changes, and 1 (0.3%) was a plexiform schwannoma. Of the cellular schwannomas, 12 (32%) occurred in the thorax, 11 (30%) in the abdomen/retroperitoneum, 7 (19%) in the extremities, and 7 (17%) in the pelvis.

Treatment Variables

Surgery was the mainstay of treatment, with 232 patients (80%) undergoing resection. Of these patients, 214 underwent 1 operation (92%), 14 underwent 2 (6%), 2 underwent 3 (0.9%), and 2 patients underwent 4 surgeries (0.9%). Blood loss reported as “not significant” or “negligible” was recorded as 0. Notably, tumors smaller than or equal to the median of 4.7 cm had a mean blood loss of 251 ml, whereas tumors larger than the median had a mean blood loss of 733 ml; the difference between the 2 groups was statistically significant ($p = 0.00096$). As most schwannomas are histologically benign tumors, the extent of resection was reported for 164 (71%) of the 232 patients undergoing surgical extirpation. After resection, surgical margins were either free from tumor (R0) or had tumor present (R1, microscopic tumor present; R2, gross tumor present), as previously defined.²⁰ Tumor removal was done en bloc when the tumor arose from a nonfunctional nerve or one with trivial function, and in a subcapsular fashion when nerve sparing was required for functional preservation.

FIG. 1. Distribution of the 241 nerves affected by schwannoma for which the spinal level where the tumor occurred was available (n = 128), graphed according to spinal level.

Of the 59 patients (20%) who did not undergo surgery for their disease, justification for this course was provided for 48 of these patients. The decision to delay or forgo surgery was most commonly made because the patient's symptoms were considered tolerable (n = 22, 46%). In 8 patients (17%) a watch-and-wait approach was chosen. In 8 patients (17%) the tumor was in an anatomical location for which surgical exposure was problematic (pelvis, sacrum, tail of pancreas, or rectum) or was abutting or encasing critical vasculature (common iliac artery, aorta, jugular vein, or vena cava). Four patients were considered to have stable disease (8%), 3 patients declined the recommended procedure (6%), 2 patients delayed surgery because they did not have insurance (4%), and 1 patient (2%) was too sick to undergo surgery. Of patients who did not undergo surgery, nonsurgical therapy was administered to 3 patients (1%): 2 patients (0.7%) received radiation, and 1 patient (0.3%) received chemotherapy (vincristine, dactinomycin, and cyclophosphamide).

Complications

Surgical complications (Table 4) were defined as any deviation from the normal postoperative course,⁸ including asymptomatic complications such as arrhythmia and atelectasis. Data regarding intraoperative complications or complications occurring within 24 hours of surgery were available for 225 patients, of whom 5 (2.2%) experienced one of the following: injury to the bronchus with chylothorax and pleural effusion, renal vein laceration with hypotension, spleen laceration requiring reoperation, persis-

tent venous bleeding delaying closure, and persistent iliac bleeding (n = 1 each).

Short-term postoperative (1–29 days postoperatively) complication data (Table 4) were available for 231 patients, of whom 36 (16%) experienced one or more of the following: hemorrhage, arrhythmia, urinary retention, CSF leakage, and respiratory insufficiency (n = 4 each); ileus (n = 3); thrombosis, chylothorax, seroma, pneumonia, and dehiscence leading to reoperation (n = 2 each); and anemia requiring transfusion, pseudomeningocele, abscess requiring drainage, and pneumothorax (n = 1 each). Follow-up data on long-term complications (more than 30 days postoperatively) were available for 199 patients, of whom 7 (3.5%) suffered from complications including one or more of the following: incisional hernia and pneumonia (n = 2 each); and peritonitis with diverticulum rupture, pleural effusion, vertebral compression fractures requiring kyphoplasty, respiratory insufficiency, DVT, and urinary retention (n = 1 each). Notably, all patients who experienced long-term complications had tumors ranging from 7 to 19 cm with a mean size of 11.1 ± 4.2 cm. These tumors occurred in the pelvis (n = 3, 43%); abdomen (n = 2, 29%); and thoracic spine and the thigh (n = 1 each, 14%). Death as a result of treatment occurred in only 1 patient (0.7%), who died of respiratory distress due to pneumonia 1 month after surgery.

Follow-Up

Follow-up data were collected to the most recent date available and are summarized in Table 4. Significantly, tu-

TABLE 2. Demographic, tumor, and treatment variables of patients with SPSs

Variable	Value
Age, yrs	
Median $\pm$ SD	50
SD	16.8
Range	7–89
Sex	
F	153 (52.6)
M	138 (47.4)
Chief complaint	
Pain	161 (55.3)
Paresthesia	14 (4.8)
Palpated painless mass	14 (4.8)
Dysesthesia	10 (3.4)
Weakness/nerve dysfunction	10 (3.4)
Cough	8 (2.7)
Respiratory symptoms	4 (1.4)
Other*	21 (7.2)
Asymptomatic, incidental finding	49 (16.8)
Tumor size†	
Mean $\pm$ SD	5.5 $\pm$ 4.0
Range	0.3–26
Tumor location	
Head & neck	28 (9.6)
Extremities	69 (23.7)
Thorax	63 (21.6)
Paraspinal	33 (11.3)
Abdomen/retroperitoneum	64 (22.0)
Pelvis	34 (11.7)
Surgery	
Yes	232 (79.7)
No	59 (20.3)
Complete resection‡	
Yes	139 (84.8)
No	25 (15.2)
Margin status	
R0	125 (89.9)
R1	14 (10.1)
Mean op duration $\pm$ SD, hrs§	3.4 $\pm$ 3.1
Blood loss by vol, ml¶	
≤ 500	139 (75.1)
> 500	46 (24.9)
Blood loss per op, ml¶	
Mean $\pm$ SD	533.5 $\pm$ 983.7
Median	125.0
Intraop complications**	
Yes	5 (2.2)
No	220 (97.8)

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TABLE 2. Demographic, tumor, and treatment variables of patients with SPSs

R0 = gross-total resection with microscopically negative margins; R1 = gross-total resection with microscopically positive margins.

Values are presented as the number of patients (%) unless stated otherwise.

* Unknown (n = 4); constipation (n = 3); hematuria (n = 3); ataxia (n = 2); and headache, bloody diarrhea, chronic dyspepsia, tonsillitis, weight loss, hemoptysis, fatigue, flu symptoms, fever (n = 1 each).

† Available for 271 patients.

‡ Available for 164 patients.

§ Available for 155 patients.

¶ Available for 185 patients.

** Available for 225 patients.

mors did not recur in any of the 139 patients who underwent complete, gross-total resection (R0, 125 patients; and R1, 14 patients). Progression of disease occurred in 21 (84%) of 25 patients who received an incomplete (R2, residual gross tumor or debulking) resection. Symptoms were reported at presentation in 184 (79%) of the 232 patients who underwent surgery for schwannoma and in 41 (69%) of the 59 patients who did not undergo surgery. Symptoms persisted without change in 40 patients (98%) without surgery. No patient who forwent surgery experienced complete resolution of their symptoms, although one of these patients (2.4%) did report improvement in symptoms.

In symptomatic patients who underwent resection of the schwannoma, the chance and degree of recovery depended on the symptom in question. In those with dysesthesia prior to surgery (n = 10), full absence of dysesthesia was achieved in 4 (40%) and partial improvement in 4 (40%), and 3 patients (30%) experienced a change in their symptoms from dysesthesia to pain. For those with paresthesia before undergoing surgery for their disease (n = 12), the symptoms cleared completely in 5 (42%), partially in 4 (33%), and 3 patients (25%) experienced an increase in pain from either progression of disease or as sequelae of surgery. The time to recovery varied from 10 days to 5 months and occurred more quickly in the paresthesia group than in patients with dysesthesias. Weakness before surgery (n = 9) improved less readily, with 5 patients (56%) reaching normal strength over recovery periods ranging from 1 to 9 months, and 4 (44%) not showing meaningful recovery of strength. Pain was the most common symptom (n = 161) and it cleared completely in 76% of patients for whom follow-up data were available more than 6 months after surgery. In those with incomplete improvement in pain (14%) a plateau was typically reached no later than 6 months after surgery, and the majority who improved did so within 3 months of surgery. No improvement in pain was seen in 8%, and 5% of patients were worse. No significant differences in outcome were noted by the most common histological variants (Table 5).

Tissue Microarray

Clinical characteristics of the 121 patients with primary SPS in the TMA (Table 6) are similar to those in our clinical cohort. Again, the most common site of tumor was the extremities (28%), although in the TMA more tumors

TABLE 3. Sites of origin of SPS

Site	Location					
	Head & Neck	Extremities	Thorax	Paraspinal	Abdomen/Retroperitoneum	Pelvis
Paratracheal	3	0	0	0	0	0
Spinal nerve root*	14	0	25	31	19	21
Perivisceral	1	0	0	0	10	4
Lung	0	0	9	0	0	0
Peripheral nerve†	3	56	14‡	0	4	2
Autonomic chain	3	0	6	1	3	0
Adrenal gland	0	0	0	0	4	0
Pancreas	0	0	0	0	5	0
Other/NOS	4	13	9	1	19	7

NOS = not otherwise specified.

* Arising intra- or extradurally: head and neck (n = 6), thorax (n = 2), paraspinal (n = 16), abdomen/retroperitoneum (n = 4), and pelvis (n = 1).

† Arising subcutaneously: head and neck (n = 2), extremities (n = 7), thorax (n = 1), and abdomen/retroperitoneum (n = 1). Arising intramuscularly: extremities (n = 3), thorax (n = 5), abdomen/retroperitoneum (n = 3), and pelvis (n = 1).

‡ Within the thorax, 5 tumors were extrapleural.

originated from the thorax (27%) than the abdomen or retroperitoneum (18%); the reverse was true in the clinical cohort.

Tissue microarray results are presented in Fig. 2. PDGFR- β was expressed in the cytoplasm of 69% of tumor cells at an average intensity of 2.1, which was higher than in MPNSTs and neurofibromas (1.50, $p = 0.0039$; and 1.33, $p = 0.0070$, respectively). In nerve, 60% of cells demonstrated cytoplasmic staining with an average intensity of 1.8. HER-2 was moderately expressed with an average of

31% of SPS cells staining and an average intensity of 0.91. By comparison, an average of 20% of nerve cells showed HER-2 expression with an intensity of 0.8. HER-2 was expressed at higher levels (0.91) in the cytoplasm of SPS than in MPNSTs and neurofibromas (0.33, $p = 0.002$; and 0.33, $p = 0.026$, respectively). EGFR was expressed at low levels, with an average of 10% of tumor cells showing cytoplasmic staining with an average intensity of 0.68. This was strikingly lower than the percentage of MPNST and neurofibroma cells showing cytoplasmic EGFR expression (58%, $p < 0.0001$; and 37%, $p = 0.007$, respectively). Nerve had stronger EGFR staining than schwannomas, with an average of 25% of cells showing cytoplasmic staining and an average intensity of 0.75. Survivin was expressed more highly in SPS than in nerve, with an average of 66% showing cytoplasmic staining compared with 46% in nerve ($p = 0.057$). Nuclear survivin was expressed in fewer sporadic schwannoma cells than in MPNST cells (24% and 50% respectively, $p = 0.018$).

TABLE 4. Clinical follow-up

Variable	Value
FU, yrs	
Mean $\pm$ SD	4.2 $\pm$ 4.0
Range	0.1–18.9
Local recurrence*	
Yes	0 (0)
No	139 (100)
Symptom change†	
Complete resolution	96/0 (52.2/0.0)
Improvement	33/1 (17.9/2.4)
No change	45/40 (24.5/97.6)
Worsened	10/0 (5.4/0.0)
Short-term complications‡	
Yes	36 (15.6)
No	195 (84.4)
Long-term complications§	
Yes	7 (3.5)
No	192 (96.5)

Values are presented as the number of patients (%) unless stated otherwise.

* In patients receiving complete (R1/R0) resection.

† Presented as the number of patients who underwent surgery (n = 184)/patients who did not undergo surgery (n = 41).

‡ From 1 to 29 days post-operatively; available for 231 patients.

§ At ≥ 30 days postoperatively; available for 199 patients.

Discussion

While SPSs do not pose the same risks to a patient as malignant tumors, they can enlarge, with pain being the most common reason for patients to seek treatment. Complete resection of SPS prevents tumor recurrence, but symptoms will not improve if the tumor is left untreated. As difficulty of resection increases with tumor size, delaying treatment may lead to excess morbidity. We observed that patients with larger tumors experienced more blood loss during surgery than those with smaller tumors. In addition, the mean tumor size for patients experiencing long-term complications was more than 2 times greater than the overall mean. However, we recognize that a patient's disease may remain stable indefinitely and that surgery itself presents the risk of lasting complications, which must be prudently weighed against potential benefits of resection.

Remarkably, 70% of patients undergoing gross-total resection reported complete resolution (52%) or improve-

TABLE 5. Patient outcomes and tumor size stratified by schwannoma histological variant

Variable	Conventional Schwannoma	Cellular Schwannoma	Schwannoma w/ Ancient/Degenerative Changes	Plexiform Schwannoma
No. of pts	247	37	6	1
Op				
Yes	190 (76.9)	35 (94.6)	6 (100)	1 (100)
No	57 (23.1)	2 (5.4)	0 (0)	0 (0)
Symptomatic				
Yes	150 (78.9)	29 (78.4)	5 (83.3)	1 (100)
No	40 (21.1)	8 (21.6)	1 (16.7)	0 (0)
Symptom change*				
Improved	103 (68.7)	21 (72.4)	4 (80.0)	1 (100)
No change	38 (25.3)	7 (24.1)	1 (20.0)	0 (0)
Worsened	9 (6)	1 (3.4)	0 (0)	0 (0)
Mean size $\pm$ SD, cm	5.1 $\pm$ 3.8†	7.8 $\pm$ 4.0‡	6.7 $\pm$ 3.4	6.3

Values are presented as the number of patients (%) unless stated otherwise.

* Change in symptoms from patients who were symptomatic and received surgery.

† Available for 230 patients.

‡ Available for 34 patients.

FIG. 2. A: H & E stain of the tissue microarray. **B:** Photomicrographs of representative H & E–stained sections. Bar = 40 μm.

C: Expression of biomarkers in schwannomas, normal nerve, neurofibroma, and MPNST. Bar = 40 μm.

TABLE 6. Tissue microarray

Variable	Value
Age, yrs	
Median	48.5
SD	16.2
Range	8.6–84.2
Sex	
F	64 (52.9)
M	57 (47.1)
Tumor size, cm*	
Mean $\pm$ SD	6.0 $\pm$ 3.8
Range	0.6–19.0
Tumor location	
Head & neck	9 (7.4)
Extremities	34 (28.1)
Thorax	33 (27.3)
Paraspinal	7 (5.8)
Abdomen/retroperitoneum	22 (18.2)
Pelvis	16 (13.2)

Values are presented as the number of patients (%) unless stated otherwise.

Data were available for 121 patients except where indicated.

* Tumor size was available for 113 samples.

ment (18%) in their symptoms, whereas 98% of patients who did not undergo surgery reported no improvement during follow-up. This efficacy in reducing symptoms accounts in part for the modest follow-up time in our study (mean 4.2 years), as patients frequently do not return for subsequent appointments. This limitation notwithstanding, studies with fewer patients and longer follow-up times have also shown that gross-total resection prevents tumor recurrence.¹⁰ Agaram et al.³ reported local recurrence in 3 of 6 patients for whom follow-up was available, but they do not comment on the extent of resection, concluding that resection is usually curative for plexiform schwannomas.

Pathology or radiology reports provided measurements of tumor size, as both sources were not available for all patients (e.g., the patient did not undergo surgery). We acknowledge potential discordance between radiological and pathological measurements, but such differences are relatively small (millimeters) in tumors measuring several centimeters. Although we could not detect a worsening of symptoms in patients who did not undergo surgery for their disease, our assessment of the degree of their pain was imperfect because a quantitative assessment of pain at presentation (e.g., “5 out of 10 on a 1 to 10 scale”) was rarely recorded. While this limitation is unlikely to affect conclusions regarding dramatic improvement or worsening of symptoms, incremental changes in pain intensity might have gone undetected.

The clinical and biological features of SPSs reported here are in agreement with previous clinical series,^{2,3,10,16,22,23,27,31} demonstrating that SPSs present as painful tumors that most frequently arise in the extremities, abdomen/retroperitoneum, and thorax. Our series corroborates previous observations in which the proclivity of the cellular

schwannoma variant has been described to occur within the thorax and abdomen/retroperitoneum.³⁰ SPSs show no significant sex predilection, affect patients across a wide age range, and typically present between the 4th and 6th decades of life. Neither the age at presentation nor the clinical course varies significantly between histological subtypes (i.e., cellular, plexiform, or ancient).

Schwannomas arising in the retroperitoneum and pelvis present challenges to resection, especially considering the degree of exposure required to perform a subcapsular dissection without interrupting functional nerve fibers. Patients in whom resection is especially difficult (e.g., when the tumor is large, hard to reach safely, or close to critical anatomical structures) could benefit from targeted therapy. Inactivation of the *NF2* gene has been demonstrated in *NF2*-associated,^{21,25} sporadic vestibular,²⁸ and sporadic spinal¹¹ schwannomas. To assess such potential targets, we constructed a TMA of patients with SPSs and show that their clinicopathological features resemble our clinical cohort.

SPSs display a pattern of biomarker expression distinct from that of other peripheral nerve sheath tumors. HER-2 and PDGFR- β were increased in SPS compared with nerve, and both RTKs are negatively regulated by the *NF2* gene product merlin. While expression of HER-2 was primarily cytoplasmic, differing from the classic membranous pattern, others have observed cytoplasmic expression of HER-2 in cancer and speculated as to its role in tumorigenesis.¹⁵ Nerve samples showed moderate expression of PDGFR- β , but this result was not entirely unexpected as the peripheral nerve has previously been shown to express PDGFR- β .⁹ Consistent with the biology of a benign tumor, SPSs express the antiapoptotic protein survivin at levels intermediate between nerve and MPNSTs, which are known to express high levels of this protein.¹² In agreement with previous analysis of EGFR expression in vestibular schwannomas,¹⁹ expression of EGFR was low in our cohort of SPS. However, neurofibromas and MPNSTs expressed high levels of EGFR and lower levels of HER-2 and PDGFR- β than SPSs, suggesting markedly different signaling mechanisms driving the tumorigenesis of these tumors. These results are consistent with previous data, albeit our observations in other non-SPS tissues are based on a small sample.

While surgery will remain a mainstay in treatment of SPS, small molecule inhibitors of RTKs and other targeted therapies may soon enter the SPS treatment armamentarium. For example, RTKs targeting PDGFR- β , such as nilotinib and selumetinib, have been shown to inhibit growth of schwannomas in vitro;⁵ and targeting HER-2 with the monoclonal antibody trastuzumab reduces the growth of schwannoma xenografts from patients with *NF2*.⁶ Pre-clinical models are required to assess in vivo efficacy of targeted therapy for SPS, and, given the similar PDGFR- β expression we observed between SPS and nerve, potential sensitivity to these agents.

Conclusions

At present, our data provide a clinicopathological portrait of bona fide SPSs and insights into their biology. Ad-

vancing our understanding of the unique pathogenesis of SPS will help establish new treatment options for patients, which could alleviate morbidity, especially in those with locally advanced or unresectable disease.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Conception and design: McCutcheon, Young, Lazar, Torres, Lev, Pollock. Acquisition of data: McCutcheon, Young, Ingram, Metcalf-Doetsch, Khan, Al Sannaa, Le Loarer, Lazar. Analysis and interpretation of data: McCutcheon, Young, Metcalf-Doetsch,

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