Tumors of the peripheral nervous system: analysis of prognostic factors in a series with long-term follow-up and review of the literature

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OBJECTIVE Only a few published studies of the surgical treatment of benign peripheral nerve sheath tumors (BPNSTs), malignant peripheral nerve sheath tumors (MPNSTs), and peripheral non-neural sheath tumors (PNNSTs) have analyzed the results and possible prognostic factors using multivariate analysis. The authors report on their surgical series of cases of BPNSTs, MPNSTs, and PNNSTs with long-term follow-up and analyze the role of selected factors with respect to the prognosis and risk of recurrence of these tumors using multivariate analysis. They also review the pertinent literature and discuss their results in its context.

METHODS The authors retrospectively reviewed data from cases involving patients who underwent resection of a peripheral nerve tumor between January 1983 and December 2013 at their institution. Of a total of 200 patients, 150 patients (with 173 surgically treated tumors) had adequate follow-up data available for analysis. Pain was assessed using a visual analog scale (VAS), and motor and sensory function were assessed by means of the Louisiana State University grading system. They also analyzed the relationship between tumor recurrence and patient sex, patient age, diagnosis of neurofibromatosis (NF), tumor histopathology, tumor size, tumor location, and extent of resection (subtotal vs gross-total resection), using univariate and multivariate analyses.

RESULTS There was a statistically significant improvement in the mean VAS pain score (preoperative 3.96 ± 2.41 vs postoperative 0.95 ± 1.6 , $p = 0.0001$). Motor strength and sensory function were significantly improved after resection of tumors involving the brachial plexus ($p = 0.0457$ and $p = 0.0043$, respectively), tumors involving the upper limb ($p = 0.0016$ and $p = 0.0016$, respectively), BPNSTs ($p = 0.0011$ and $p < 0.0001$, respectively), and tumors with dimensions less than 5 cm (motor strength: $p = 0.0187$ and $p = 0.0021$ for ≤ 3 cm and 3–5 cm tumors, respectively; sensory function: $p = 0.0003$ and $p = 0.0001$ for ≤ 3 cm and 3–5 cm tumors, respectively). Sensory function showed a statistically significant improvement also in patients who had undergone resection of tumors involving the lower limb ($p = 0.0118$). Total resection was associated with statistically significant improvement of motor strength ($p = 0.0251$) and sensory function ($p < 0.0001$). In univariate analysis, a history of NF ($p = 0.0034$), a diagnosis of MPNST or PNNST ($p < 0.0001$), and subtotal resection ($p = 0.0042$) were associated with higher risk of tumor recurrence. In multivariate analysis (logistic regression analysis), a history of NF (OR 9.28%, 95% CI 1.62–52.94, $p = 0.0121$) and a diagnosis of MPNST (OR 0.03%, 95% CI 0.002–0.429, $p = 0.0098$) or PNNST (OR 0.081%, 95% CI 0.013–0.509, $p = 0.0077$) emerged as independent prognostic factors for tumor recurrence.

CONCLUSIONS A total resection should be attempted in all cases of peripheral nervous system tumors (irrespective of the supposed diagnosis and tumor dimensions) because it is associated with better prognosis in term of functional outcome and overall survival. Moreover, a total resection predicts a lower risk of tumor recurrence. Patients with a history of NF and tumors with malignant histology remain a challenge both for neurosurgeons and oncologists due to higher recurrence rates and the lack of standardized adjuvant therapies.

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KEY WORDS peripheral nerve sheath tumors; prognostic factors; surgery

ABBREVIATIONS BPNST = benign PNST; MPNST = malignant PNST; NF = neurofibromatosis; OS = overall survival; PFS = progression-free survival; PNNST = peripheral non-neural sheath tumor; PNST = peripheral nerve sheath tumor; VAS = visual analog scale.

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TUMORS involving the peripheral nervous system can be intrinsic (peripheral nerve sheath tumors [PNSTs]) or extrinsic (peripheral non-neural sheath tumors [PNNSTs]), and both can be either benign or malignant. Benign peripheral nerve sheath tumors (BPNSTs) include schwannomas (also called neurilemmomas or neurinomas), the most common tumors arising from peripheral nerves, and neurofibromas.⁴³ These lesions are usually well circumscribed, especially the schwannomas, and grow between the fascicles of peripheral nerves; schwannomas often undergo cystic and degenerative changes.²⁸ Most cases are sporadic; however, some are associated with neurofibromatosis (NF) Type 1 and Type 2,³³ schwannomatosis, or Carney's complex,²⁸ and they may rarely occur following radiation.^{45,50}

Malignant peripheral nerve sheath tumors (MPNSTs) show variable differentiation toward one of the cellular components of nerve sheaths (Schwann cells, fibroblasts, and perineurial cells).⁵¹ MPNSTs account for 5% to 10% of soft tissue sarcomas⁴⁹ and have an incidence of 0.001% in the general population.⁴ Like BPNSTs, they can occur sporadically as well as in patients with NF (affecting 4% to 10% of patients with this condition)^{4,22} and arise either de novo or from a preexisting neurofibroma or, rarely, schwannoma.⁵¹

PNNSTs are rare. As previously reported,³⁴ benign PNNSTs include a number of lesions such as ganglion cysts of the peripheral nerve, localized hypertrophic neuropathy, lipomas, venous angiomas, hemangiopericytomas, glomus tumors, and hemangioblastomas. Myositis ossificans, osteochondromas, ganglioneuromas, meningiomas, cystic hygromas, myoblastomas or granular cell tumors, and epidermoid cysts are also included in the category of PNNST.³⁴ Malignant PNNSTs can arise from tumors such as breast or lung cancers that directly extend or metastasize to a nerve, or they can be osteogenic or soft-tissue sarcomas that can displace or adhere to the nerve or encase it and, in a few cases, actually invade it. Lymphomas and melanomas can metastasize and secondarily involve the nerve,³⁴ and primary lymphoma involving the peripheral nervous system has also been reported.¹⁶

Until now, various series have been published reporting the results of surgical treatment of these tumors. Obviously, they differ in number of patients, histopathology, location, follow-up, and methodological analysis of results.^{1-3, 5-15, 17, 19-21, 23-27, 29-32, 35-42, 44, 46-48, 52-59}

The aim of this study was to report the results of surgical treatment in our series of cases of BPNSTs, MPNSTs, and PNNSTs with long-term follow-up and to analyze the role of some clinical and surgical factors with respect to prognosis and the risk of tumor recurrence. We also review the pertinent literature and discuss our results in its context.

Methods

We retrospectively reviewed clinical and outcome data for cases in which a peripheral nerve tumor at any anatomical location was resected at the Institute of Neurosurgery, Catholic University, Rome, between January 1983 and December 2013. All operations were performed by

the senior author (E.F.). Of a total of 200 patients, 150 (77 male, 73 female) had follow-up data available for analysis. These 150 patients underwent resection of a total of 173 tumors. The mean age of the patients at the time of the 173 operations was 46.94 ± 15.47 years. The mean duration of follow-up after resection was 112.14 ± 81.10 months (range 12–360 months). Clinical data are summarized in Table 1.

Changes in pain level were assessed using a visual analog scale (VAS). We evaluated motor and sensory outcome using the Louisiana State University (LSU) grading system, as described by Donner and colleagues.¹⁸ The neurological evaluation was performed by different physicians preoperatively and at follow-up.

We also studied the impact of sex, age, diagnosis of NF, tumor histopathology, tumor size, tumor location, and extent of resection (subtotal vs gross-total resection) on the recurrence of these tumors. Gadolinium-enhanced MRI studies were performed 3 months, 6 months, and 1 year after the operation and annually thereafter. Local recurrence was defined as evidence of a contrast-enhancing lesion on T1-weighted MR images obtained after gadolinium administration.

Statistical comparison of continuous variables and ordinal variables was performed by means of the Student's t-test and Wilcoxon signed-rank test, as appropriate. Comparison of categorical variables was performed by means of the χ^2 statistic, using the Fisher exact test.

A multivariate logistic regression model was used to estimate the odds ratio for recurrence of tumor, while adjusting for baseline variables, including diagnosis of NF, tumor histopathology, tumor size, tumor location, and extent of resection. Differences were considered statistically

TABLE 1. Demographic and clinical characteristics of 150 patients (173 peripheral nerve tumors) operated on at the Catholic University of Rome, January 1983–December 2013

Characteristic	Value
Sex (M/F)	77/73
Mean age (yrs)	46.94 ± 15.47
No. of patients w/ NF	13
Tumor histopathology	
BPNST	135
MPNST	6
PNNST	32
Tumor size	
≤ 3 cm	60
3–5 cm	72
> 5 cm	41
Tumor location	
Cervical plexus	21
Brachial plexus	32
Thoracic/lumbar root	35
Lumbar plexus	1
Upper limb	31
Lower limb	50
Other	3
Mean follow-up (mos)	112.14 ± 81.10

significant at $p < 0.05$. Statistical analyses were conducted using StatView version 5 software (SAS Institute, Inc.).

A literature search was conducted in the PubMed database using, as search terms, “nerve sheath tumor”, “schwannoma”, “neurofibroma”, “MPNST”, “PNNST”, AND “surgery.” A similar search in the Cochrane Library yielded no results. We then excluded review articles, case reports (including series of fewer than 5 cases), articles dealing with purely intradural schwannomas (including vestibular and spinal ones) or orbital schwannomas, and redundant series. The 47 articles included in the review are summarized in Table 2^{2,3,5,7,11,13–15,17,19,21,23,25–27,30,32,35,36,39,42,44,47,48,54,55,57,58} and Table 3.^{1,6,8–10,12,20,24,29,31,37,38,40,41,46,52,53,56,59}

Results

Pain, Motor, and Sensory Outcomes

Comparing preoperative and follow-up scores for all 173 operations, we found a statistically significant improvement in the overall mean values for the VAS score for pain (3.96 ± 2.41 vs 0.95 ± 1.6 , $p = 0.0001$, 95% CI 2.69–3.31), the motor strength score (4.38 ± 0.89 vs 4.54 ± 0.82 , $p = 0.0146$, 95% CI 0.043–0.28), and the sensory function score (4.07 ± 1.22 vs 4.41 ± 1.0 , $p < 0.0001$, 95% CI 0.20–0.47) after tumor removal (Fig. 1).

When the cases were stratified by tumor location, type, and size, a statistically significant improvement of motor strength was observed, particularly after surgery for tumors in the brachial plexus ($p = 0.0457$, 95% CI 0.003–0.56) and upper limb ($p = 0.0016$, 95% CI 0.14–0.49), BPNSTs ($p = 0.0011$, 95% CI 0.097–0.36), and tumors with a maximum dimension less than 5 cm ($p = 0.0187$, 95% CI 0.029–0.33 and $p = 0.0021$, 95% CI 0.12–0.54 for ≤ 3 cm and 3–5 cm, respectively) (Fig. 2).

Regarding sensory function, a statistically significant improvement was observed after surgery for tumors involving the brachial plexus ($p = 0.0043$, 95% CI 0.19–1.05), upper limb ($p = 0.0016$, 95% CI 0.14–0.51), lower limb ($p = 0.0118$, 95% CI 0.083–0.51), BPNSTs ($p < 0.0001$, 95% CI 0.22–0.54), and tumors less than 5 cm ($p = 0.0003$, 95% CI 0.16–0.53 and $p = 0.0001$, 95% CI 0.30–0.77 for ≤ 3 cm and 3–5 cm, respectively) (Fig. 3).

FIG. 1. Bar graph comparing mean scores for pain (VAS), motor strength, and sensory function obtained preoperatively and at follow-up after 173 surgical procedures for resection of peripheral nervous system tumors in 150 patients. (The mean values were calculated based on the number of surgical procedures.) All scores were significantly improved at latest follow-up (FU). Error bars indicate standard error of the mean.

FIG. 2. Bar graph comparing mean motor function scores obtained preoperatively and at follow-up after resection of 173 peripheral nervous system tumors. Motor function scores were significantly improved after resection of brachial plexus and upper-limb tumors, BPNSTs, and tumors less than 5 cm in maximum dimension. Error bars indicate standard error of the mean.

Considering simultaneously all variables in the statistical comparisons, we found a statistically significant improvement of motor strength after resection of brachial plexus BPNSTs that were 3–5 cm in maximum dimension ($p = 0.045$) and upper-limb BPNSTs that were 3 cm or smaller ($p = 0.014$) and a statistically significant improvement of sensory function after resection of brachial plexus BPNSTs that were 3–5 cm ($p = 0.013$), upper-limb BPNSTs that were 3 cm or smaller ($p = 0.0082$), and lower-limb BPNSTs that were 3–5 cm ($p = 0.0103$).

Gross-total resection was achieved in 150 of 173 operations and was associated with statistically significant improvement in motor strength ($p = 0.0251$) and sensory function ($p < 0.0001$).

Tumor Recurrence

We observed recurrence in 14 of 173 tumors. When

FIG. 3. Bar graph comparing sensory function scores obtained preoperatively and at follow-up after resection of 173 peripheral nervous system tumors. The sensory function score was significantly improved after resection of brachial plexus, upper-limb, and lower-limb tumors as well as after resection of BPNSTs and tumors less than 5 cm in maximum dimension. Error bars indicate standard error of the mean.

TABLE 2. Literature review of surgical series of peripheral nerve tumors with more than 30 cases

Authors & Year	No. of Pts	Histopathology (%)	Location (%)	Follow-Up (mos)*	Prognostic Factor†	Stat
Anghileri et al., 2006	205	MPNST (100)	Head/neck (4), trunk (51), extremities (45)	112 (54–160)	Recurrent disease↓, tumor size >5 cm↓, central location↓, GTR†, RT†, grade (for OS)	M
Artico et al., 1997	119	Schwannoma (61), neurofibroma (34), plexiform neurofibroma (4)	Brachial/lumbar plexuses (13), extremities (87)	72 (12–192)	Schwannoma histology†, NF↓ (for EOR, postop neuro deficits, PFS, recurrence)	NA
Bates et al., 2014	125	Pediatric MPNST (100)	NA	30	Metastasis↓, surgery† (for OS)	M
Biswas et al., 2007	30	Schwannoma (100)	Head/neck (100)	NA	NA	NA
Cherqui et al., 2007	88	Schwannoma (64), neurofibroma (32), MPNST (5)	Paraspinal (100)	18 (6–120)	Neurofibroma histology↓ (for EOR & postop neuro deficits), malignant histology↓ (for OS)	NA
Dafford et al., 2007	44	Schwannoma (18), neurofibroma (68), MPNST (5), PNNST (9)	Pelvic plexus (100)	14 (8–48)	Malignant & neurofibroma histology↓ (for EOR), malignant histology↓ (for OS), NF↓ (for EOR & postop neuro deficits)	NA
Das et al., 2007	226	Schwannoma (24), neurofibroma (38), MPNST (9), BPNNST (15), MPNNST (14)	Brachial plexus (100)	NA	NF↓ (for EOR), malignant histology↓ (for EOR & OS)	NA
Date et al., 2012	35 (36 tumors)	Schwannoma (100)	Extremities (100)	11.2 (1–48)	Type of surgery (intracapsular vs extracapsular resection lower incidence of neuro deficits)	U
Desai, 2012	115	Schwannoma (61), neurofibroma (39)	Brachial plexus (100)	31 (11–58)	Neurofibroma histology↓ (for neuro deficits)	NA
Dozois et al., 2009	89	Schwannoma (31), neurofibroma (19), ganglioneuroma (1), MPNST (39), PNNST (9)	Pelvis (100)	74.4 (0–528)	Malignant histology↓, GTR† (for PFS & OS), intracapsular surgery↓ (in malignant tumors)	U
Fan et al., 2014	146	MPNST (100)	Head/neck (23), trunk (44), extremities (34)	132.6 (1–238)	No independent prognostic factors; univariate analysis: NF↓, tumor size >5–10 cm↓, AJCC staging, GTR†, expression of TP53↓ & MDM2↓ (for PFS); chemo/RT†, tumor size, NF↓ (for OS)	M
Gachiani et al., 2007	34	MPNST (100)	Brachial plexus (56), lumbar plexus (6), extremities (38)	45	NA	NA
Goel et al., 2008	60 (62 tumors)	BPNNST (100)	C-2 nerve root (100)	64 (6–180)	NA	NA
Goertz et al., 2014	65	MPNST (100)	Extremities (75), trunk (15), head (9)	32 (1–126)	Metastasis↓ (for OS)	U
Gu et al., 2014	41	Schwannoma (100)	Cervical dumbbell (100)	42.5 (24–108)	Extraforaminal tumor size >5.4 mm↓ (for GTR)	NA
Ikuta et al., 2014	45	Neurofibroma (33), MPNST (67)	Extremities (58), trunk (42)	60	Tumor size >10 cm↓ (for OS); tumor size, hyaluronan expression↓ (for PFS)	M
Kehoe et al., 1995	104	Schwannoma (67), neurofibroma (24), neuroma (2), PNNST (2), NA (5)	Brachial plexus (16), extremities (81), NA (3)	NA	NA	NA
Kim et al., 2004	546	Schwannoma (23), neurofibroma (43), MPNST (7), BPNNST (20), MPNNST (6)	Brachial plexus (40), extremities (59), other (1)	NA†	Neurofibroma histology in NF↓ (for EOR), malignant histology↓ (for EOR & OS)	NA
Kim et al., 2012	30	Schwannoma (100)	Extremities (100)	58.8 (32–79)	Larger tumor size↓ (for postop deficits)	U
Li et al., 2007	82	Schwannoma (99), MPNNST (1)	Retroperitoneal (100)	63 (6–384)	GTR† (for recurrence), malignant histology↓ (for OS)	NA

(continued)

TABLE 2. Literature review of surgical series of peripheral nerve tumors with more than 30 cases (continued)

Authors & Year	No. of Pts	Histopathology (%)	Location (%)	Follow-Up (mos)*	Prognostic Factor†	Stat
Needle et al., 1997	121 (168 tumors)	Plexiform neurofibroma (100)	Head/neck (43), trunk (29), extremities (28)	81.6 (24–294)	Age ≤10 yrs↓, head/neck location↓, GTR↑ (for PFS)	M
Rekhi et al., 2010	63	MPNST (100)	Extremities (56), trunk (33), head/neck (10), NA (2)	12	Age <30 yrs↓, tumor size >5 cm↓, tumor grade, tumor stage (for PFS)	U
Sinkkonen et al., 2014	44	Schwannoma (100)	Head/neck (95), brachial plexus (5)	1	Neck tumors↓ (for postop complications), CN VII & XII tumors↓ (for postop deficits)	NA
Sordillo et al., 1981	165	MPNST (100)	NA§	NA	NF↓, central location↓, prior irradiation↓ (for OS)	U
Ujigo et al., 2014	76	Schwannoma (100)	Brachial plexus (9), extremities (58), other (33)	33 (6–90)	Tinel sign↓ (for postop neuro deficits)	NA
Vetrano et al., 2014	42 (53 tumors)	Schwannoma (66), neurofibroma (25), MPNST (9)	Brachial/lumbar plexuses (11), extremities (57), spinal roots (23), other (9)	6	Neurofibroma histology↑ (for postop neuro deficits), lumbosacral plexus tumors↓ (for pain), short symptom duration↑ (for pain & postop neuro deficits)	U
Wong et al., 1998	134	MPNST (100)	Head/neck (20), trunk (30), pelvis (23), extremities (27)	53 (7–280)	Prior irradiation↓, GTR↑ (for OS) GTR↑, RT↑, brachytherapy↑ (for local recurrence) larger tumor size↓ & grade (for metastases)	M
Yafit et al., 2015	53	Schwannoma (100)	Head/neck (40), brachial plexus (60)	30 (6–156)	NA	NA
Present series	150 (173 tumors)	BPNST (78), MPNST (3), PNNST (18)	Cervical plexus (12), brachial/lumbar plexuses (19), extremities (47), spinal roots (20), other (2)	112.1 (12–360)	NF↓, malignant↓ & PNNST↓ histology (for recurrence); univariate analysis for neuro deficits: brachial plexus↑ & extremity↑ location, BPNST histology↑, tumor size <5 cm↑, GTR↑	M

AJCC = American Joint Committee on Cancer; BPNNST = benign peripheral non-neural sheath tumor; CN = cranial nerve; EOR = extent of resection; GTR = gross-total resection; M = multivariate analysis; MPNNST = malignant peripheral non-neural sheath tumor; NA = not available; neuro = neurological; pts = patients; RT = radiotherapy; stat = statistical analysis; U = univariate analysis.

* Median or mean value (range).

† An upward-pointing arrow (↑) indicates positive prognostic value; a downward-pointing arrow (↓) indicates negative prognostic value.

‡ Mean follow-up 46 mos for MPNST and 20 mos for PNNST.

§ Central tumors more frequent in NF patients.

TABLE 3. Literature review of surgical series of peripheral nerve tumors with less than 30 cases

Authors & Year	No. of Pts	Histopathology (%)	Location (%)	Follow-Up (mos)*	Prognostic Factors	Stat
Abernathy et al., 1986	13	Schwannoma (100)	Sacral/intrapelvic (100)	108 (5–399)	GTR†	NA
Bernthal et al., 2014	23	Atypical neurofibroma (48), low-grade MPNST (52)	Head/neck (48), brachial plexus (9), trunk (9), extremities (35)	47 (15–198)	GTR†, NF↓ (for local recurrence)	NA
Çağlı et al., 2012	13	Giant schwannoma (100)	Sacrum	97.2 (12–180)	NA	NA
Canavese & Krajchich, 2011	14 (20 tumors)	Plexiform neurofibroma in NF (100)	Extremities (75), trunk (25)	65.5 (24–145)	Tumor size >15 cm↓, GTR† (for recurrence) tumor size, age <10 yrs↓ (for wound healing problems)	U
Casanova et al., 2000	24	MPNST (100)	Head/neck (25), trunk (42), extremities (33)	230 (114–150)	GTR†, tumor size >5 cm↓, RT† (for OS)	NA
Chong et al., 2000	5	Schwannoma (100)	Intrapatrotid (100)	28 (5–108)	Nerve-sparing surgery† (for postop neuro deficits)	NA
Dunn et al., 2013	23	MPNST in NF (100)	Trunk/pelvis (52), other (48)	51.7	GTR† (for OS); univariate analysis for PFS: GTR† & peripheral location†	M
Go et al., 2012	21 (22 tumors)	Schwannoma (68), neurofibroma (18), MPNST (5), PNNST (9)	Brachial plexus (100)	13.7 (2–41)	GTR†, malignant histology↓	NA
Hussein & Goda, 2009	16	Schwannoma (31), neurofibroma (6), MPNST (19), PNNST (44)	Paravertebral dumbbell (100)	(3–36)	Malignant histology↓ (for complications & OS)	NA
Kar et al., 2006	24	MPNST (100)	Head/neck (4), trunk (25), extremities (63), pelvis (8)	38	Cellular differentiation and tumor grade (for OS & PFS)	M
Kuo et al., 2013	17	Schwannoma (94), MPNST (6)	Peripancratic plexuses (100)	37 (6–196)	GTR† (for recurrence), pancreatectomy↓ (for postop complications)	NA
Lee et al., 2014	19	Schwannoma (100)	Brachial plexus (100)	37.2 (12–90)	NA	NA
Loree et al., 2000	17	MPNST (100)	Head/neck (100)	139.2 (41–432)	Female sex†, grade, NF↓ (for OS); tumor size > 5 cm↓, GTR†, RT† (for local recurrence)	U
Millan & Casal, 2014	5	Schwannoma (80), neurofibroma (20)	Brachial plexus (100)	41	NA	NA
Sawada et al., 2006	17 (18 tumors)	Schwannoma (100)	Extremities (100)	11.3 (3–42)	Nerve-sparing surgery† & Tinel sign↓ (for postop neuro deficits)	U
Tomii et al., 2013	19	Schwannoma (84), neurofibroma (11), mixed tumor (5)	Cervical dumbbell (100)	41.6 (7–79)	NA	NA
Torossian et al., 1999	15	Schwannoma (100)	Head/neck (100)	50.6 (5–201)	Microsurgery† (for recurrence)	NA
Wanebo et al., 1993	28	MPNSTs (100)	NA	44	Age <30 yrs↓, central location↓, tumor size > 10 cm↓, GTR† (for OS & PFS), NF† (for PFS)	U
Yang et al., 2014	18	Schwannoma (50), neurofibroma (33), other (17)	Lumbar dumbbell (100)	36 (16–64)	Malignant histology↓	NA

* Median or mean value (range).

looking at possible prognostic factors we found that a history of NF ($p = 0.0034$), a diagnosis of MPNST or PNNST ($p < 0.0001$), and subtotal resection ($p = 0.0042$) were associated with higher risk of tumor recurrence.

In logistic regression analysis, a history of NF (OR 9.28%, 95% CI 1.62–52.94, $p = 0.0121$) and a diagnosis of MPNST (OR 0.03%, 95% CI 0.002–0.429, $p = 0.0098$) or PNNST (OR 0.081%, 95% CI 0.013–0.509, $p = 0.0077$) emerged as independent prognostic factors for tumor recurrence.

Results From the Literature Review

Our review of the literature included 28 studies with at least 30 patients or tumors (Table 2) and 19 with less than 30 patients or tumors (Table 3). Combining these cases with the present series resulted in a total of 2002 cases of BPNST, 1251 cases of MPNST, and 257 cases of PNNST for analysis, with a mean follow-up of 53.3 months (range 1–112.1 months), 74.8 months (range 6–230 months), and 84.6 months (range 3–119.6 months), respectively. Studies were analyzed for the following parameters, when available: median overall survival (OS) and progression-free survival (PFS), 5- and 10-year OS and PFS, and recurrence rate. With respect to BPNSTs, the median OS and PFS were not reached at the most recent follow-up evaluation in the studies in which these data were available; both 5- and 10-year OS were 100%, and both 5- and 10-year PFS were 96.4%. The recurrence rate was 3.8%. With respect to MPNSTs, the median OS and PFS were 68.6 months (range 23–132.6 months) and 27.4 months (range 11–57.6 months), respectively; the 5- and 10-year OS were, respectively, 52.7% and 42.9%; and the 5- and 10-year PFS were, respectively, 36.4% and 23.3%. The recurrence rate was 43.8%. Insufficient data were available to derive aggregate outcome measures for PNNSTs.

Discussion

In this study we report the results of our surgical series of BPNSTs, MPNSTs, and PNNSTs. Our approach is to perform a surgical treatment at the first diagnosis in all symptomatic cases and in asymptomatic patients with MRI evidence of increasing tumor size. Moreover, we try to identify possible prognostic factors influencing the clinical outcome (VAS, motor strength score, and sensory score) and the risk of recurrence. In our opinion, the main strengths of this study are the long follow-up, the large number of patients/tumors, and the use of multivariate analysis (regression analysis). In fact, when looking at the literature (see Tables 2 and 3) we found only 3 studies with a duration of follow-up longer than in our series,^{10,21,40} 3 papers with a greater number of patients and wider tumors than our study,^{2,14,35} and only a few articles analyzing surgical results and possible prognostic factors using a multivariate analysis.^{2,5,20,21,30,31,42,57} The main limit of this study is the retrospective nature of the data, which could affect the results despite the strict statistical analysis.

Considering the impact on clinical outcome, we found an improvement of motor strength and sensory function particularly after resection of tumors located in the brachial plexus and upper limb and BPNSTs. It has been pre-

viously demonstrated that some locations can affect the postoperative functional outcome. Sinkkonen et al., in their study of head and neck and brachial plexus schwannomas,⁴⁷ reported that functional outcome was better for patients with brachial plexus tumors and that tumors of the seventh and twelfth cranial nerves were associated with higher rates of postoperative complications and new-onset deficits. Vetrano et al.⁵⁵ showed that tumors located at the lumbosacral plexus were associated with more postoperative pain than tumors in the extremities, brachial plexus, or spinal roots. Moreover, the same authors⁵⁵ showed that a diagnosis of neurofibroma predicts a better functional outcome, although in large series of brachial plexus,^{3,17} lumbar plexus, and extremity,³ and paraspinal tumors,¹¹ the diagnosis of neurofibroma was associated with a higher risk of developing neurological deficits compared with a diagnosis of schwannoma. However in considering surgical series in which cases of BPNST, MPNST, and PNNST were analyzed together, the histopathological finding of BPNST emerged as a good prognostic indicator for extent of resection, reduced risk of complications, and reduced risk of postoperative deficits.^{13,14,29,35}

We found a statistically significant better functional outcome after resection of tumors that were less than 5 cm in maximum dimension. The role of tumor size has been the object of extensive investigation in the literature and this factor has been found to be a good prognostic indicator for PFS and OS in various series.^{2,5,10,21,30,44,56} Moreover, smaller tumor size has been found to be associated with a lower incidence of postoperative deficit,³⁶ local recurrence,^{9,40} and possible metastasis in cases of MPNST.⁵⁷

The extent of resection is another factor frequently analyzed in previous series. In our study we achieved a gross-total resection in 86.7% of all the tumors in this series, and gross-total resection was associated with a statistically significant improvement in motor and sensory function. Moreover, we found that a subtotal resection was associated with a higher risk of tumor recurrence. These data are in agreement with previous observations that the extent of resection affects the duration of PFS and OS^{2,10,19–21,42,52,56} and the risk of recurrence.^{6,9,37,39,40,57}

Considering the risk of recurrence in the present series, the variables that emerged as independent prognostic factors were a history of NF and a diagnosis of MPNST or PNNST. When a recurrence is diagnosed at follow-up MRI, our initial approach is “wait and see,” performing an MRI study every 3–6 months to detect a lesion increase. In these cases a reoperation is considered with adjuvant radio-chemotherapy if malignant features are observed on histopathological examination.

Although Wanebo et al.⁵⁶ found that NF was associated with better PFS in patients with MPNSTs, data in the literature are otherwise consistent with the finding that a history of NF is associated with a worse prognosis in terms of PFS and OS,^{3,21,40,48,56} and recurrence risk.^{3,6} Moreover, data from the literature also support our finding of a strong association between malignant histology and worse prognosis.^{11,13,14,19,24,29,35,39,59} PNNST includes different entities, both benign and malignant, that, in our series, showed a higher risk of recurrence compared with BPNST. This finding could be explained by the fact that, of 32 PNNSTs

in our series, 13 (40.5%) showed malignant features on histopathology and 5 of these (38.5%) recurred after surgery. These findings also seem to be confirmed by series including patients with PNNSTs, especially cases in which malignant features are observed.^{13,14,19,24,29,35}

Conclusions

Tumors of the peripheral nervous system represent a broad spectrum of different pathologies in terms of malignancy and outcome. However, taking into account our results and literature analysis, some conclusions can be drawn. A total resection should always be attempted in all cases of peripheral nerve tumors irrespective of the supposed diagnosis and tumor dimensions, because it is associated with better prognosis in terms of functional outcome and OS in all series. Obviously, it is easier to achieve a total resection in cases of benign tumors with lower dimensions, and this fact explains the better prognosis of these cases (BPNSTs, smaller tumor size). Patients with a history of NF and malignant histology remain a challenge both for neurosurgeons and oncologists due to the higher recurrence rate in these subgroups and the lack of standardized adjuvant therapies.

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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: Montano, Fernandez. Acquisition of data: Montano, D'Alessandris, D'Ercole, Lauretti, Di Bonaventura, La Rocca, Bianchi. Analysis and interpretation of data: Montano, D'Ercole, Fernandez. Drafting the article: Montano, Pallini, Fernandez. Critically revising the article: Montano, D'Alessandris, Fernandez. Reviewed submitted version of manuscript: Montano, D'Alessandris, Fernandez. Approved the final version of the manuscript on behalf of all authors: Montano. Statistical analysis: Montano. Study supervision: Montano, Lauretti, Pallini, Fernandez.

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