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Malignant Peripheral Nerve Sheath Tumors: The St. Jude Children's Research Hospital Experience

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Background: Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon in young patients. To contribute to the understanding of these tumors, we reviewed the records of all patients treated for PNSTs at one institution over a 30-year period.

Methods: We reviewed the records of eight patients treated for benign PNSTs and 28 patients treated for 29 MPNSTs. We focused on the latter group, statistically testing several clinical factors for their significance in affecting survival.

Results: Five-year survival in patients with MPNSTs was 39%. The most significant prognostic factor was gross tumor resectability ($p = 0.0004$). Five-year survival for patients with resectable tumors was 65%, whereas no patient with unresectable disease survived >25 months. Tumor grade, site, and patient race were also significant factors by univariate analysis but were not significant when adjusted for resectability.

Conclusion: Gross tumor resection is crucial in treating malignant PNSTs. Supplemental radiation therapy is recommended for positive microscopic margins. More effective treatment is still being sought for unresectable disease.

Key Words: Malignant peripheral nerve sheath tumors—Pediatric.

Malignant peripheral nerve sheath tumors (MPNSTs) are uncommon in children and young adults. We review our experience with 28 patients treated for MPNSTs over a 30-year period at St. Jude Children's Research Hospital. These tumors account for ~5% of soft-tissue sarcomas in children. In a recent review from this institution, only synovial sarcoma was more common among nonrhabdomyosarcomas (1). These tumors have previously been known by several names, including malignant schwannoma, malignant neurilemmoma, neurogenic sarcoma, and neurofibrosarcoma, but MPNST is now the term preferred by most authors (2–4). MPNSTs have a relatively poor prognosis compared with other childhood malignancies. The majority of reported 5-year survival rates range from 34 to 44% (3–7). These tumors are relatively resistant to chemotherapy and radiation therapy, and therefore, surgery continues to be the mainstay of treatment. We describe our experience with MPNSTs, evaluate several prognostic factors, discuss current treatment strategies, and review the findings of other investigators.

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MATERIALS AND METHODS

Of 2,813 children and adolescents with solid tumors seen between 1964 and 1993 at St. Jude Children's Research Hospital, 36 were identified who met the strict clinical and pathological criteria for the diagnosis of PNST. Of these, eight were benign, whereas 28 patients had malignant tumors. In this

TABLE 1. *Malignant peripheral nerve sheath tumors: patient characteristics, treatment, and outcome*

Pt. no.	Race	Sex	Age (yr)	NF-1	Site	Size (cm)	IRS group	Grade	Surgery	Chemo/RT	Survival
1	W	F	10	—	Neck	n/a	III	1–2	Bx	−/+	DOD, 15 mo
2	B	F	13	+	Pelvis	15	III	3	Bx	−/+	DOD, 10 mo
3	W	M	16	+	Neck	17	IIa	3	WLE	+/+	DOD, 5 mo
4	W	F	14	+	Pelvis	n/a	IV	1–2	Bx	+/−	DOD, 10 mo
5	B	F	17	+	Thorax	14	III	3	Bx	−/−	DOD, 3 mo
6	W	F	11	—	Neck	3.5	IIc	1–2	WLE	+/−	NED, 15 yr
7	W	F	14	—	Leg	4.2	IIa	3	WLE	−/−	DOD, 43 mo
8	W	F	29	−	Axilla	5	—	1–2	—	—	(Autopsy)
9	B	M	10	—	Head	7	III	3	Bx	−/−	DOD, 11 mo
10	W	M	17	+	Leg	7	Ib	1–2	WLE	−/−	NED, 12 yr
11	W	M	16	+	Thorax	18	IV	3	Bx	−/−	DOD, 12 mo
12	W	M	5	—	Abdomen	n/a	IIa	3	WLE	−/−	DOD, 17 mo
13	W	F	19	—	Neck	11	Ib	3	WLE	−/−	DOD, 21 mo
14	W	M	13	—	Head	5	III	3	Bx	+/−	DOD, 16 mo
15	W	F	6	—	Axilla	2	IIa	3	WLE	+/+	NED, 10 yr
16	W	M	15	—	Thorax	14	III	3	Bx	−/+	DOD, 25 mo
17	B	F	16	+	Neck	12	IV	3	Bx	+/+	DOD, 20 mo
18	W	F	14	—	Abdomen	6	IIa	3	WLE	−/−	NED, 7 yr
19	W	M	13	—	Arm	2	Ib	1–2	WLE	−/−	NED, 6 yr
20	W	F	16	+	Leg	13	IIa	1–2	WLE	+/+	NED, 6 yr
21	B	F	25	—	Axilla	8	IIa	1–2	Amp	−/+	NED, 5 yr
22	W	M	17	+	Arm	8	IIa	1–2	WLE	−/+	NED, 4 yr
23	W	M	20	−	Leg	23	IIa	3	Amp	+/−	NED, 2 yr
24	B	F	13	−	Leg	10.5	III	3	Bx	+/+	DOD, 11 mo
25	B	M	13	—	Leg	9	Ib	3	Amp	+/−	DOD, 27 mo
26	W	M	18	+	Arm	9	IIb	1–2	Amp	−/−	
					Pelvis	20	III	3	Bx	+/+	AWD, 12 mo
27	W	F	3	+	Abdomen	16	IV	3	Bx	+/+	AWD, 14 mo
28	W	M	11	—	Shoulder	2.1	IIa	1–2	WLE	−/+	NED, 5 mo

NF-1, neurofibromatosis type 1; IRS, Intergroup Rhabdomyosarcoma Study; RT, radiation therapy; n/a, not available; Bx, biopsy; WLE, wide local excision; Amp, amputation; DOD, died of disease; NED, no evidence of disease; AWD, alive with disease

study, we focused on the latter group. We reviewed the medical records of the 28 patients diagnosed with MPNSTs. Data collected included age, race, gender, presence of neurofibromatosis type 1 (NF-1), site, size, grade, surgical treatment, and the use of adjuvant chemotherapy or radiation therapy or both. Clinical group was determined based on clinical, surgical, and pathological data using the Intergroup Rhabdomyosarcoma Study (IRS) classification (8). All histopathological slides were evaluated by one author (D.M.P.) and graded using the Pediatric Oncology Group (POG) sarcoma grading system (9). Tumors were classified as low grade (grades 1 and 2) or high grade (grade 3). The survival interval was defined as the time from diagnosis to death or last follow-up. The duration of survival was estimated using the method of Kaplan and Meier. The prognostic importance of presenting features was assessed using the exact log rank test and Cox regression. The prognostic importance independent of IRS group was assessed by the exact log rank test adjusted for IRS group effect. Correlations between IRS group and other binary variables were examined by the Fisher exact text. Age and size data adjusted for IRS group were evaluated by the Wilcoxon rank test.

RESULTS

Patient characteristics

Twenty-eight patients were diagnosed with 29 MPNSTs (Table 1). Fifteen were female patients (54%), and seven were black (25%). Ages ranged from 3.1 to 29.8 years (median, 14.1 years). Eleven patients (39%) had NF-1. Median ages of patients with and without NF-1 were 16.2 and 13.3 years, respectively.

The most common site was the extremity, with 13 of the 29 lesions (45%). Of these, seven were located in the upper extremity or axilla, and six were in the lower extremity or groin. Ten tumors (34%) were located in the trunk, and six (21%) were in the head and neck.

One patient (no. 26) with NF-1 was diagnosed with two separate MPNSTs. The first was a low-grade tumor of the left forearm, the second, diagnosed 6 months later, was an unresectable grade 3 triton tumor of the pelvis. The pelvic lesion was treated with subtotal resection followed by radiation therapy and chemotherapy. He is alive with disease 18 months after diagnosis of the initial lesion.

Three patients, none of whom had NF-1, devel-

oped MPNSTs in a previously irradiated area. One previously reported patient (no. 9) developed an MPNST 7 years after irradiation of a ganglioneuroma of the supranasal region (10). He died 11 months after incomplete resection. Another patient (no. 21) was diagnosed with a low-grade MPNST of the right axilla 13 years after mantle radiation therapy for Hodgkin's lymphoma. She is alive with no evidence of disease 5 years after a forequarter amputation. A third patient (no. 23) was found to have a high-grade tumor in the right groin 16 years after radiation therapy for rhabdomyosarcoma of the bladder. He is alive with no evidence of disease 2 years after hemipelvectomy and postoperative chemotherapy.

The MPNST was a third malignancy in patient number 8. She was treated for Hodgkin's lymphoma at age 15 and osteosarcoma of the left clavicle at age 24, and subsequently died at age 29 from recurrence of her osteosarcoma. Autopsy revealed a small, low-grade MPNST in the left axilla. This lesion was located in a nonirradiated area.

Clinical course

All of the 28 tumors with antemortem diagnoses were first seen with a mass or pain or both. Two patients also had weakness, and another noted muscle atrophy. Four patients had metastases at the time of diagnosis: metastatic sites were the lung in two patients, liver and lung in one, and the omentum in one.

The initial surgical procedure was wide local excision in 12 cases (43%), amputation in four (14%), and biopsy in 12 (43%); (attempted resections with gross residual tumor were classified as biopsies). By definition, the 16 patients who had wide local excision or amputation were in IRS clinical groups I and II, and the 12 biopsy patients were in groups III and IV. There were four patients in group I (14%), 12 in group II (43%), eight in group III (29%), and four in group IV (14%). Eleven of 12 extremity lesions (92%) were resected, compared with five of 16 in the trunk and head and neck (31%). Ten tumors (36%) were classified as having low-grade histology and 18 (64%) as having high-grade histology. Two of the high-grade lesions were triton tumors.

Supplemental chemotherapy or radiation therapy or both was given in 18 cases (64%). One of four IRS group I lesions and eight of 12 group II lesions were treated with adjuvant therapy. Nine of 12 patients with unresectable tumors (IRS groups III and IV) received palliative therapy. Multiagent chemotherapy alone was used in six cases, radiation therapy alone in six cases, and both modalities in six cases.

Three patients (nos. 15, 21, and 28) with microscopic residual disease (IRS group II) received brachytherapy followed by external beam radiation therapy. One of these patients (no. 15), who had a recurrent high-grade tumor, also received combination chemotherapy. All three are alive and disease-free at an average of 6 years after initial diagnosis and 2 years after completion of therapy.

Eleven patients experienced recurrences 3 to 104 months (median, 11 months) after initial diagnosis. Recurrences were local in seven patients. Metastatic recurrences were in the lung in two patients, the brain in one, and the lumbar spine in one. High-grade tumors appeared to recur sooner than low grade, at a median 9 months versus 50 months, respectively. One patient (no. 20) underwent two thoracotomies for resection of lung metastases. She is alive and disease-free, now more than 6 years after initial diagnosis.

Survival

Of the 27 patients with antemortem diagnoses, 12 are currently alive. Fifteen patients died 3 to 43 months (median, 15 months) after diagnosis. The survival plot for all patients is shown in Fig. 1. The estimated 5-year survival rate was 39%.

The most significant factor influencing survival was gross tumor resectability. Figure 2 shows survival plots for patients with resectable versus unresectable tumors. Estimated 2-year survival was 79% with resectable lesions versus 22% with unresectable lesions ($p = 0.0004$). Survival ranged from 3 to 25 months (median, 12 months) for patients with unresectable disease. The estimated 5-year survival rate for patients with resectable tumors was 65%. Of those with resectable lesions, there was no significant difference in survival between IRS group I and group II.

Four patients underwent early amputation for bulky extremity lesions that invaded a neurovascular bundle or bone or both. Two of the four (nos. 21 and 23) are alive with no evidence of disease, whereas one patient (no. 25) died of recurrent disease 27 months after amputation. The fourth (no. 26) has no evidence of recurrence of his arm lesion and is alive with an unresectable second primary in the pelvis, as noted previously.

Low-tumor grade, location in an extremity, and white race were all significant favorable prognostic

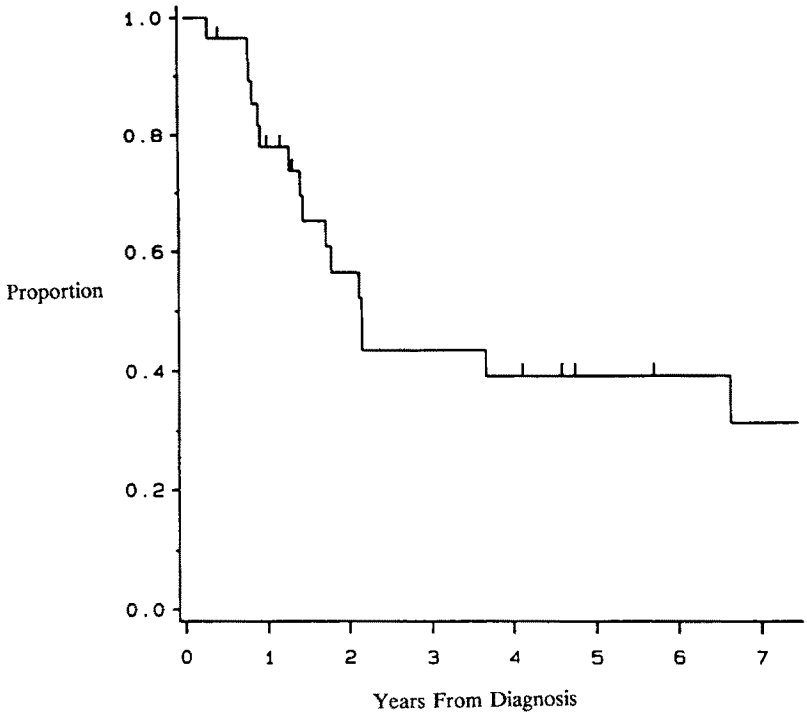

FIG. 1. Kaplan–Meier survival plot for all patients with an antemortem diagnosis of malignant peripheral nerve sheath tumor.

factors by univariate analysis ($p = 0.02$ for each factor). However, when the log rank tests for grade, location, and race were adjusted for IRS group, none of these factors was statistically significant ($p = 0.20$, 0.88, and 0.13, respectively). No significant differences in survival were found based on age, gender, tumor size, or NF-1.

DISCUSSION

In general, the majority of PNSTs are benign. In a study of children with these tumors, 67 of 83 (81%) were benign (11), and in a large series of children and adults, 607 of 631 (96%) had benign histology (2). However, in our review, only eight of 37 (22%) PNSTs were benign, which almost certainly is related to our referral pattern. In this study, therefore, we focused only on the malignant tumors.

The characteristics of our patients were similar to those seen in previous series of MPNSTs. The female to male ratio in our series was 1.2:1. Although one series had an equal number of female and male patients (3) and another had fewer female than male subjects (5), most have reported a ratio similar to ours (4,6,7,12,13).

Eleven of our 28 patients (39%) had NF-1, a smaller proportion than that reported in most other series. One series (12) had only 26% with NF-1, but all others ranged between 40 and 70% (3–6,11,13,14). The prevalence of MPNST in patients with NF-1 in one study was only 4.6%, but this figure represents a 4,600-fold greater risk than that seen in the general population (6). Several series of combined pediatric and adult patients have shown a lower mean age for patients with NF-1 (28–36 years) than for those without NF-1 (40–48 years; 3,4,6,13). In our study of children and adolescents, the patients with NF-1 had a slightly higher median age.

In our series, the extremities were found to be the most common site of MPNSTs. Other series have varied, with either the trunk, the extremities, or the head and neck reported as the more common site (5,6,11,15).

Previous irradiation is a well-known risk factor for the development of a MPNST. Three patients (11%) in our series had received radiotherapy, as had 4 to 11% of patients in previous studies (2–4,6,11,13). The latency period is defined as the time between the radiation therapy and the diagnosis of a MPNST. A review of several studies revealed latency periods ranging from 2 to 30 years, with an overall mean of 15.5 years (2,3,6,13,16). Latency periods were 7, 13, and 16 years in our three patients. Previous malignancy in addition to previous radiation exposure has been associated with poor

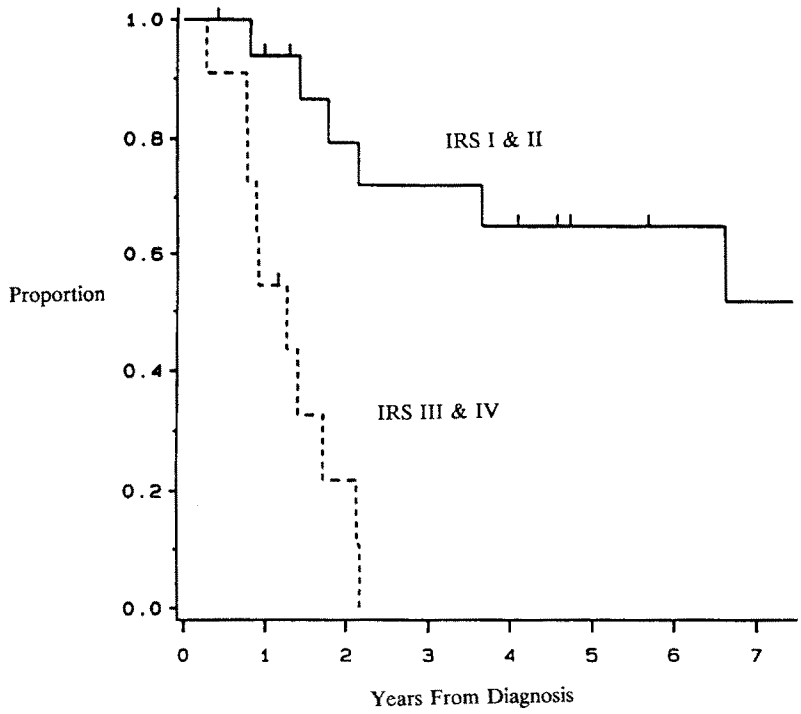

FIG. 2. Kaplan–Meier survival plots for Intergroup Rhabdomyosarcoma Study (IRS) groups I and II (resectable) and IRS groups III and IV (unresectable) malignant peripheral nerve sheath tumors.

outcomes. In one study, 14 patients who had radiation-induced second malignancy died at an average of 14 months from the second diagnosis (13). Two of the three patients in our study, however, are alive and disease-free 2 and 5 years after initial treatment.

MPNSTs are aggressive tumors with relatively poor outcomes in young patients. Reported 5-year survival rates in most series of adults and children range from 34 to 44% (3–7). The estimated 5-year survival in our series was 39%. This compares with an earlier study of malignant PNSTs in children and adolescents that found a 3-year survival of 37.5% (14). One series of adults and children found that age <30 years was associated with a significantly decreased survival (4). In that series, median survival was 13 months for patients <30 years versus 216 months for patients > 30 years.

In our study, gross tumor resectability was found to be the most significant factor affecting survival. The median survival of our patients with unresectable disease was 12 months, with none surviving >25 months. This compares with a 65% estimated 5-year survival for patients with resectable disease. There was no significant survival difference between IRS groups I and II, indicating that the quality of microscopic margins was not a significant factor. It should be noted, however, that with positive or "close" margins, we recommend supplemental radiation therapy if reexcision is not feasible.

Several factors other than radiation exposure and age <30 years have been associated with decreased survival in previous series. These include high tumor grade, central location, large size, the presence of NF-1, the need for resection by amputation, and tumor recurrence (3,4,6,7,12–14). In our study, grade, location, and race were found to be significant prognostic factors by univariate analysis. However, these factors were not independent of IRS group, as demonstrated by the fact that 92% of extremity lesions were resectable, compared with 31% of central lesions. Similar associations were found for grade and race.

In addition to tumor grade, other histological findings have reportedly been associated with poor outcomes. The MPNST with rhabdomyosarcomatous differentiation (i.e., the triton tumor) is a high-grade tumor with a reported 5-year survival as low as 12% (17–19). Our two patients with triton tumors are alive with disease and are undergoing treatment 12 and 14 months after diagnosis. A recent review of MPNSTs with glandular differentiation also indicated that this histology was associated with a poor outcome (20). Of 19 patients with malignant glandular PNSTs in that series, only two (11%) were alive and free of tumor.

MPNSTs usually metastasize hematogenously, most commonly to the lungs. Long-term survival has been reported after resection of pulmonary metastases (3). One patient in our series underwent two pulmonary resections for lung metastases and is currently free of disease. Because lymph node metastases are uncommon, being reported in 0 to 7% of cases (3,4,12,14), lymph node dissection is not routinely indicated.

No studies have shown that adjuvant chemotherapy significantly affects survival. Radiation therapy is recommended for all patients by one author (4), for IRS group II patients only by another (14), and for microscopic or gross residual disease by three others (2,3,6). Adjuvant radiation would appear to offer the most benefit to group II patients, for control of microscopic residual disease. We have recently used brachytherapy followed by external beam radiation in three group II patients with microscopic residual disease near vital structures, and early results are encouraging. In a study of lower extremity MPNSTs, brachytherapy was used in five patients, but no definite conclusions could be made regarding local control or survival in this subset of patients (3). Further study is needed to determine whether radiation therapy significantly improves local control and overall survival. Occasional responses to chemotherapy have been documented (4,5), but no consistently effective regimen has been identified. The management of unresectable tumors is controversial, and further investigation is needed to identify an effective treatment regimen. A POG study in which we are participating is now considering the use of preoperative chemotherapy in the treatment of grade 3, unresectable primary, or metastatic tumors.

At present, surgery is the mainstay of therapy for MPNSTs. Early radical surgery is recommended by all authors. Incisional biopsy for an accurate tissue diagnosis and tumor localization via computed tomography or magnetic resonance imaging or both are necessary before radical resection. Our data indicate that resection of all gross tumor is of key importance. Although our data on four patients do not clearly show a benefit of early amputation, we believe it is indicated if a functional extremity cannot be salvaged with gross tumor resection plus possible radiation therapy. If microscopic margins are positive, we then recommend radiation therapy. Brachytherapy is indicated when wide resection margins are limited by critical structures such as the brachial plexus or other major nerves and blood vessels.

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