Journal of Neuro-Oncology 2: 241–248 (1984).

Malignant peripheral nerve sheath tumors in childhood

Barbara S Ducatman, Bernd W Scheithauer, David G Piepgras, Herbert M Reiman
Departments of Pathology (BSD, BWS, HMR) and Neurologic Surgery (DGP), Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Keywords: nerve sheath tumor, pediatric nerve tumor, von Recklinghausen's neurofibromatosis

Summary

Malignant peripheral nerve sheath tumor (MPNST) is an uncommon sarcoma in the pediatric population; however, its presence should be considered in a child with an enlarging or painful soft-tissue mass. Diagnosis of this neoplasm depends on either the demonstration of its origin within a peripheral nerve or the association with a contiguous neurofibroma. We have identified 16 cases of MPNST involving children 16 years of age or less, which represent 12.8% of the total cases seen at the Mayo Clinic. Most of the lesions arose in children with von Recklinghausen's disease and were associated with a contiguous neurofibromatous component. The mean survival of patients who were known to have died of tumor was only 1.8 years. This sarcoma requires prompt aggressive therapy utilizing wide surgical excision. Because of the association of MPNST with von Recklinghausen's neurofibromatosis, a careful workup and family history should be obtained for the potential prognostic value and for the purpose of genetic counseling.

Introduction

Soft-tissue sarcomas, with the exception of embryonal rhabdomyosarcoma, are uncommon malignant lesions in the pediatric population (1). Benign soft-tissue proliferations are commonly seen in this age group; among these are neurofibromas, which are benign spindle cell tumors originating from Schwann cells and/or from endoneurial fibroblasts of peripheral nerves. Such tumors are usually manifestations of neurofibromatosis, an autosomal dominant phakomatosis observed in a frequency of 1 in 3,000 (2). Although neurofibromas do arise in childhood, particularly in the setting of von Recklinghausen's disease, malignant peripheral nerve sheath tumors (neurofibrosarcomas, malignant schwannomas) are most commonly found in adults with von Recklinghausen's disease. The reported incidence ranges from 2 to 29% (3–5), although the latter percentage almost certainly represents an overestimate. Reviews of the literature on malignant peripheral nerve sheath tumors indicate that as many as 17% have occurred in childhood and adolescence (6). It is the purpose of this study to better delineate the clinical, surgical, and pathologic features of such tumors as well as to evaluate prognostic indicators and therapeutic methods.

Materials and methods

The files of the Mayo Clinic Tissue Registry were reviewed for all cases of fibrosarcoma of peripheral nerves or of malignant peripheral nerve sheath tumor (MPNST). Gross specimens were examined and, when necessary, additional microsections were prepared. Original histologic slides were reviewed,

Address for reprints: Bernd W Scheithauer, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

Table 1. Patients with malignant peripheral nerve sheath tumors in childhood.

Case	Sex and age, yr	Von Reckling-hausen's disease	Presenting complaints	Location and size	Treatment	Recurrence	Metastasis	Follow-up
1	F, 13	No	Pain, mass	Brachial plexus (9/36), $7 \times 3 \times 3$ cm	Subtotal excision, radiation	Not known	Not known	Lost after 3 disease-free yr
2	M, 13	No	Mass	L posterior calf (9/75)	Subtotal excision, radiation	Not known	Not known	Lost after 4 disease-free yr
3	F, 15	No	Pain	R axilla, brachial plexus (6/80), 3×4 cm	Excision, radiation	Posterior cord of R brachial plexus (3/81)	Not known	Alive without evidence of disease at present
4	F, 15	Yes	Pain, mass	R popliteal space-popliteal nerve (3/37), $12 \times 8 \times 7$ cm	Amputation	Not known	R lung, 6th rib (7/38); mediastinum	Died (7/38)
5*	F, 12	Yes	Mass, pain, hyperes-thesia	R retroperitoneum, R femoral nerve (9/47), approx. 8-cm diam-eter	Radical excision	Retroperitoneum (11/47)	Not known	Died (12/48)
6	F, 13	Yes	Pain	L thigh-sciatic nerve (3/52), $10 \times 6 \times 6$ cm	High thigh amputa-tion	Not known	Lungs (3/54)	Died (3/54)
7*†	M, 14	Family history (mother)	Mass	L thigh-obturator nerve (6/54), 12-cm diam-eter	Hindquarter amputa-tion	Not known	Lungs (3/55)	Died (9/55)
8	F, 15	Yes	Pain	R pelvis-obturator nerve (12/64)	Excision	Not known	Not known	Died (5/66)
9	M, 13	Yes	Pain, mass	R popliteal space-popliteal nerve (10/64), $12 \times 6 \times 6$ cm	Amputation	R stump (3/65); R stump (3/66)	Postmortem – lungs	Died (10/67)
10	M, 7	Yes	Pain, mass	L thigh-L femoral nerve (7/65), $5 \times 3.5 \times 2.5$ cm	Excision	L thigh (12/65)	Not known	Lost after 8 disease-free yr
11	M, 13	Yes	Pain	L scapula (2/69); L buttock-sciatic nerve (8/71)	Incomplete excision, radiation	Not known	Not known	Died (9/71)
12	F, 12	No	Mass	R forearm-radial nerve (2/79)	Excision, radiation	Not known	Not known	Alive without tumor
13*#	M, 9	Yes	Mass	R temporal region (3/80), 5×4 cm	Excision, radiation, chemotherapy	R temporal region (6/81); R fossa, R retromaxillary region, R orbit (11/81)	Not known	Died (1/82)

Table 1. (Continued).

Case	Sex and age, yr	Von Recklinghausen's disease	Presenting complaints	Location and size	Treatment	Recurrence	Metastasis	Follow-up
14	F, 10	Yes	Pain	Region of 11th rib posterior (9/59), 6-cm diameter; retroperitoneum (10/72), 13 × 8.5 × 8 cm; pelvis (2/80)	Excision, hemipelvectomy and radiation for recurrence, chemotherapy	Not known	L humerus (10/81); R femur (2/82)	Alive with tumor
15	M, 16	No	Pain, mass	Pretibial region-saphenous nerve (3/82), 2.5 × 1.3 cm	Excision	Not known	Not known	Alive without tumor
16*	M, 13	No	Mass	L parotid-facial nerve (9/82), 5 × 2 × 1.5 cm	Excision, radiation, cesium implant; chemotherapy - vincristine, actinomycin, cyclophosphamide, doxorubicin	Not known	Not known	Alive without tumor

Cases previously reported: (7)†, (8)#, (25)*.

and in selected cases, special stains including Gomori's reticulin, phosphotungstic acid-hematoxylin (PTAH), and Bodian preparations for axons were performed. Only lesions that originated within peripheral nerves, documented by either surgical description or pathologic examination, and malignant tumors arising within neurofibromas were accepted. The clinical presentation, gross surgical observations, response to adjuvant therapy, and follow-up data were recorded.

Results

Of 125 patients with MPNST, 16 (12.8%) were children 16 years of age or less. Ten of the 16 patients (62.5%) had clinically documented von Recklinghausen's disease (Table 1). There were eight boys and eight girls with a mean age of 12.7 years (range 7 to 16) at diagnosis. The presenting symptoms were pain in five patients, an enlarging mass in five, pain and a mass in five, and pain, mass, and hyperesthesia in one. The tumor in one patient arose in a previously irradiated site 5 years after radiation therapy (case 13).

Tumor locations were variable. Seven tumors were situated in the lower extremity: two in the popliteal space (popliteal nerve), three in the thigh (popliteal nerve, femoral nerve, obturator nerve), one in the posterior aspect of the calf, and one in the pretibial region. Two lesions were situated in the brachial plexus, and one each in the regions of the posterior 11th rib, scapula, retroperitoneum (femoral nerve), pelvis (obturator nerve), temporal region, parotid region (facial nerve), and forearm (radial nerve). Eight patients were treated by tumor excision, which necessitated amputation in four. Five patients were treated by a combination of excision and radiation, and three underwent excision followed by both radiation and chemotherapy. One of the latter patients had a sarcoma that showed extensive rhabdomyoblastic differentiation (case 16) and was therefore treated with a protocol for rhabdomyosarcoma, including radiation and chemotherapy.

One patient (case 11) developed a second primary MPNST after an interval of 30 months; still another (case 14) presented with second and third primary lesions, one after 13 years and the other after 21 years. Three patients each experienced one recurrence (cases 3, 5, and 10), and two each (cases 9 and 13) had two recurrences. Five patients (cases 4, 6, 7, 9, and 14) had metastases, the most common site of involvement being the lung in four patients and the skeleton in two (one having metastasis to lung and skeleton). Most patients on whom current follow-up information is known (8/11) have died. The mean duration of survival after diagnosis was 1.8 years (range 13 months to 3 years). Four patients have survived without evidence of disease, one 24 months and the other 49 months after diagnosis, and two whose tumors were diagnosed only recently. One patient has survived with clinical evidence of tumor. Three patients were lost to follow-up after 3, 4, and 8 disease-free years.

Pathologic findings

On computed tomographic scans, the tumors were seen as soft-tissue masses (Fig. 1). The sizes of the primary tumors ranged from 3 to 12 cm. Gross-

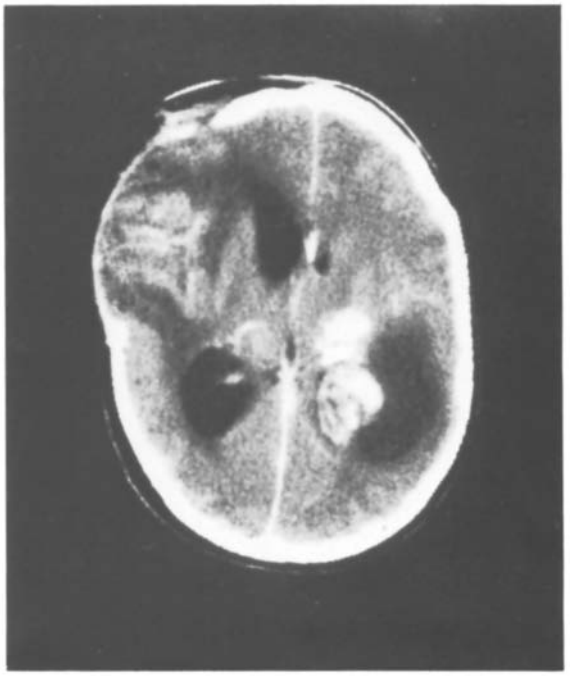

Fig. 1. (case 13). Computed tomographic scan of head shows malignant peripheral nerve sheath tumor arising within soft tissue of right temporal fossa. Also note optic chiasm glioma and thalamic glioma in this patient with von Recklinghausen's disease. The temporal fossa tumor was a postradiation sarcoma arising in the radiation field for the gliomas.

ly, an intimate relationship to nerve was evident in most of the tumors; that is, both entering and exiting nerve trunks were identified. Such a relationship also could be demonstrated on microscopic study (Fig. 2). Most tumors were firm, white to gray-yellow, and had foci of necrosis or degeneration.

Twelve of the 16 tumors were associated with a contiguous neurofibroma, 10 in patients with von Recklinghausen's disease. Such benign tumor components were composed of cells that are typical for neurofibroma, that is, spindle cells with wavy nuclei and cell bodies arranged in a loose myxoid matrix. Mitotic figures and cytologic atypia were not evident. Most lesions demonstrated a broad range of differentation within the same lesion, from low-grade tumor components with mild hypercellularity, nuclear hyperchromasia, and modest mitotic activity (Fig. 3) to high-grade components showing striking cellularity, high mitotic indices, multifocal necrosis, and occasional microvascular proliferation. In occasional tumors, Bodian stains for axons demonstrated rare nerve fibers, most being situated at the periphery of the sarcoma. Reticulin stains showed a dense intercellular pattern of reactivity. Four tumors had heterologous elements: osteosarcoma, rhabdomyosarcoma, and chondrosarcoma in case 13, rhabdomyosarcoma and angiosarcoma in case 5, and rhabdomyosarcoma in cases 7 and 16.

Discussion

Although MPNST is an uncommon sarcoma in the pediatric age group (1, 6, 9–11), it should be considered in the differential diagnosis of a rapidly evolving and painful mass in the distribution of a peripheral nerve, particularly in the setting of von Recklinghausen's disease. The diagnosis of MPNST may present a differential diagnostic problem for both the clinician and the pathologist. Key morphologic features of diagnostic utility include 1) origin within a peripheral nerve documented at surgery or by histologic examination and 2) association with a contiguous neurofibroma. A neurogenic origin may be suggested by the finding of residual axons within the tumor, utilizing the Bodian technique. However, in the absence of a gross description, such

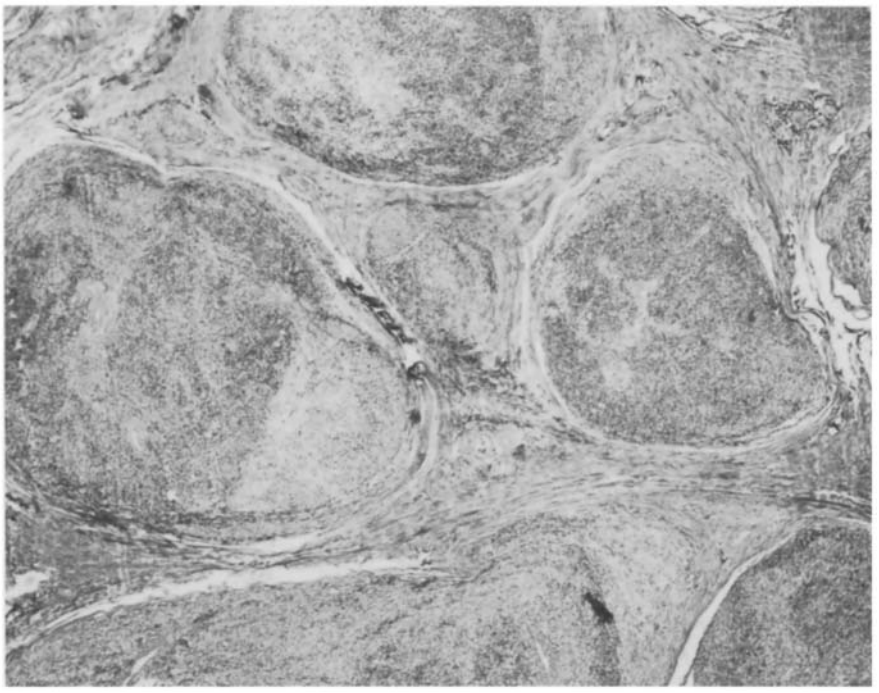

Fig. 2. (case 6). Sarcoma arising within and extending along peripheral nerve bundles. In this section, it is confined within the nerve. (Hematoxylin and eosin; ×40.)

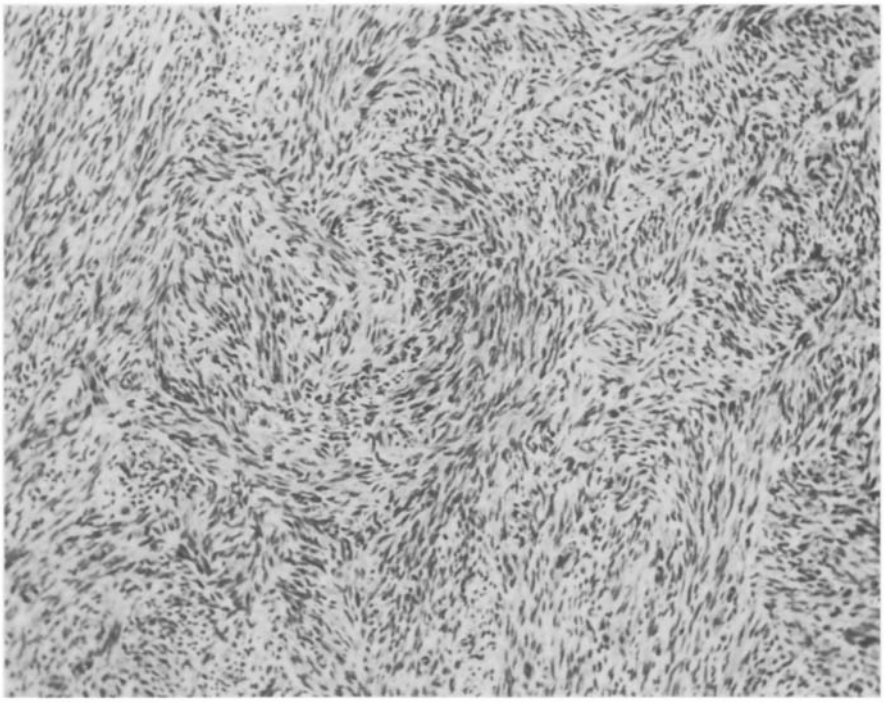

Fig. 3. (case 8). Low-grade tumor with interlacing fascicles of wavy spindle cells with mildly atypical nuclei. (Hematoxylin and eosin; ×100.)

indirect evidence may be misleading, in that sarcomas of soft tissue may rarely involve nerves secondarily.

It is not clear at present what proportion of MPNSTs are derived from Schwann cells and what proportion are derived from endoneurial fibroblasts (10, 11), although attempts have been made to better characterize these proliferations using electron microscopy as well as immunohistochemistry. Since the cell of origin is not known, we prefer to designate such a tumor as MPNST rather than malignant schwannoma or neurofibrosarcoma. Ultrastructural studies may provide evidence of schwannian differentiation; diagnostic features include elongated and frequently interdigitating cytoplasmic processes, pericellular basal lamina, cytoplasmic granular material, the relative absence of intracytoplasmic filaments, and the presence of extracellular long-spacing collagen (12). Staining with immunoperoxidase for S-100 protein, a biochemical marker present in the cytoplasm of Schwann cells, has been negative in MPNSTs reported to date, although neurofibromas as well as neurilemomas stain positively (13). Thus, although many nerve sheath sarcomas may originate from Schwann cells, the frequently undifferentiated nature of these tumors may preclude such a conclusion in the individual case.

Heterologous differentiation is an unusual and interesting feature noted in 10 to 15% of MPNSTs. Such tumor may show heterologous mesenchymal differentiation to rhabdomyosarcoma, osteosarcoma, chondrosarcoma, or rarely angiosarcoma (1, 6, 7, 14, 25). So-called malignant glandular schwannomas are medical curiosities (1, 15, 16, 25). The presence of epithelial elements should not deter one from making the diagnosis of MPNST when other morphologic criteria are present. Heterologous foci have been reported to affect the prognosis negatively, although in a study from our institution of MPNSTs with divergent differentiation, the prognosis did not differ from that of ordinary MPNSTs (25).

MPNSTs are often intimately associated with contiguous neurofibromatous components, a finding suggesting that such sarcomas may arise by a

process of malignant 'transformation' or 'degeneration' within benign Schwann cell neoplasms (10, 13, 14, 17, 18). Such progression was also suggested in our series by the high frequency of such tumors associated with von Recklinghausen's disease, a disorder predisposing to multiple neurofibromas. The finding of contiguous neurofibroma in association with MPNST is of relevance to pathologists in that careful sampling of such tumors is necessary, so that a malignant focus is not overlooked to arrive at a proper grade. In view of the broad spectrum of tumor differentiation which may be observed, we advocate extensive sampling whenever the diagnosis of MPNST is considered or a large neurofibroma is removed.

Interestingly, our second youngest patient (case 13) developed a MPNST in a previously irradiated site. An association between irradiation and the subsequent occurrence of a MPNST has been well established (8, 9, 19). The biologic effect of radiation on Schwann and fibroblastic cells has been well characterized in experimental systems (20, 21). Ionizing radiation produces chromosomal injury and induces cytologic atypia in Schwann cells and thus may be reasonably assumed to hasten the development of MPNSTs, particularly in susceptible patients. In a recent review from our institution (8), 11% of MPNSTs were found to arise in a previously radiated site.

Another interesting finding is the development of multiple primary sarcomas. These lesions were not deemed to be metastatic because of demonstrated neural involvement in one patient and of the long interval between development of the tumors in another. Both patients had von Recklinghausen's disease – an association that has been previously reported (9). Obviously, factors that predispose to MPNST may be operative at multiple sites. Patients with von Recklinghausen's disease appear to be at risk for developing other neoplasms, including Wilms' tumor, rhabdomyosarcoma, leukemia, neuroblastoma, medullary thyroid carcinoma, pheochromocytoma, and melanoma (2, 22), as well as central nervous system tumors, such as glioma, meningioma, and neurilemoma. Thus, children who survive an initial MPNST are at risk for both another primary MPNST and other malignant lesions. Careful follow-up, therefore, is mandatory.

An optimal approach to therapy has not been outlined, partly because of the great variety of anatomic sites in which MPNSTs occur. Early radical surgical resection, when feasible, is the treatment of choice (7, 10, 11, 17, 18, 23). Clearly, MPNST is an aggressive malignancy with poor long-term survival: in 11 patients with adequate follow-up, only 3 survived (1 with disease), and survival for the other 8 averaged only 22 months. Survival is reportedly worse for patients with von Recklinghausen's disease (6, 7, 9, 10); however, the small number of patients in our group does not permit such a conclusion. Aggressive surgical treatment with adjuvant therapy may prove to be most efficacious. Preliminary reports on the use of chemotherapy are encouraging (9, 24); however, the small number of patients treated with this form of adjunct therapy in our series precludes definite recommendations for its use in children.

In summary, the presence of a MPNST should be considered whenever a child with or without von Recklinghausen's disease has a rapidly enlarging or painful mass. In the absence of obvious stigmata of the disorder, a careful workup and family history should be obtained, both for their potential prognostic values and for the purpose of genetic counseling.

References

1. Enzinger FM, Weiss SW: Soft tissue tumors. CV Mosby Company, St. Louis, 1983, pp 625–654.
2. Riccardi VM: Von Recklinghausen neurofibromatosis. N Engl J Med 305:1617–1627, 1981.
3. Crowe FW, Schull WJ, Neel JV: A clinical, pathological, and genetic study of multiple neurofibromatosis. Charles C Thomas, Publisher, Springfield, Illinois, 1956.
4. Preston FW, Walsh WS, Clarke TH: Cutaneous neurofibromatosis (von Recklinghausen's disease): clinical manifestations and incidence of sarcoma in sixty-one male patients. Arch Surg 64:813–827, 1952.
5. Brasfield RD, Das Gupta TK: Von Recklinghausen's disease: a clinicopathological study. Ann Surg 175:86–104, 1972.
6. Guccion JG, Enzinger FM: Malignant schwannoma associated with von Recklinghausen's neurofibromatosis. Virchows Arch [Pathol Anat] 383:43–57, 1979.
7. D'Agostino AN, Soule EH, Miller RH: Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1015–1027, 1963.
8. Ducatman BS, Scheithauer BW: Postirradiation neurofibrosarcoma. Cancer 51:1028–1033, 1983.
9. Sordillo PP, Helson L, Hajdu SI, Magill GB, Kosloff C, Golbey RB, Beattie EJ: Malignant schwannoma: clinical

characteristics, survival, and response to therapy. Cancer 47: 2503–2509, 1981.
10. Ghosh BC, Ghosh L, Huvos AG, Fortner JG: Malignant schwannoma: a clinicopathologic study. Cancer 31: 184–190, 1973.
11. Das Gupta TK, Brasfield RD: Solitary malignant schwannoma. Ann Surg 171:419–428, 1970.
12. Taxy JB, Battifora H, Trujillo Y, Dorfman HD: Electron microscopy in the diagnosis of malignant schwannoma. Cancer 48:1381–1391, 1981.
13. Stefansson K, Wollmann R, Jerkovic M: S-100 protein in soft-tissue tumors derived from Schwann cells and melanocytes. Am J Pathol 106:261–268, 1982.
14. Woodruff JM, Chernik NL, Smith MC, Millett WB, Foote FW Jr: Peripheral nerve tumors with rhabdomyosarcomatous differentiation (malignant 'Triton' tumors). Cancer 32:426–439, 1973.
15. Woodruff JM: Peripheral nerve tumors showing glandular differentiation (glandular schwannomas). Cancer 37:2399–2413, 1976.
16. Krumerman MS, Stingle W: Synchronous malignant glandular schwannomas in congenital neurofibromatosis. Cancer 41:2444–2451, 1978.
17. Vieta JO, Pack GT: Malignant neurilemonas of peripheral nerves. Am J Surg 82:416–431, 1951.
18. White HR Jr: Survival in malignant schwannoma: an 18-year study. Cancer 27:720–729, 1971.
19. Foley KM, Woodruff JM, Ellis FT, Posner JB: Radiation-induced malignant and atypical peripheral nerve sheath tumors. Ann Neurol 7:311–318, 1980.
20. Bergström R: Changes in peripheral nerve tissue after irradiation with high energy protons. Acta Radiol (Stockh) 58:301–312, 1962.
21. Cavanagh JB: Effects of X-irradiation on the proliferation of cells in peripheral nerve during Wallerian degeneration in the rat. Br J Radiol 41:275–281, 1968.
22. Hope DG, Mulvihill JJ: Malignancy in neurofibromatosis. Adv Neurol 29:33–55, 1981.
23. D'Agostino AN, Soule EH, Miller RH: Primary malignant neoplasms of nerves (malignant neurilemomas) in patients without manifestations of multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1003–1014, 1963.
24. Goldman RL, Jones SE, Heusinkveld RS: Combination chemotherapy of metastatic malignant schwannoma with vincristine, Adriamycin, cyclophosphamide, and imidazole carboxamide: a case report. Cancer 39:1955–1958, 1977.
25. Ducatman BS, Scheithauer BW: Malignant peripheral nerve sheath tumors with divergent differentiation. Cancer (in press).