Solitary Malignant Schwannoma

TAPAS K. DAS GUPTA,* M.D., PH.D., RICHARD D. BRASFIELD, M.D.

From the Gastric and Mixed Tumor Services of the Department of Surgery, Memorial Hospital for Cancer and Allied Diseases and James Ewing Hospital, New York City

SOLITARY malignant schwannomas are rare tumors. Since these tumors are derived from nerve sheaths and not from axons there is controversy regarding histogenesis and terminology. Proponents of the connective tissue hypothesis include Penfield,[9] and Tarlov [11]; those of the Schwannian theory, Inglis,[5] Masson,[6] Vieta and Pack,[12] and Murray and Stout.[7, 8] We believe there is histological and histochemical evidence to consider that cells involved in the development of these tumors are schwannian and should be designated as schwannomas or neurilemomas, either benign or malignant. The association of schwannomas or neurilemomas to von Recklinghausen's disease is known and in this report all instances of von Recklinghausen's disease have been excluded; only true solitary malignant schwannomas were studied. It is the purpose of this paper to present the natural history and principles of management of this rare type of tumor.

Clinical Material

Records of 232 patients with solitary malignant schwannomas not associated with von Recklinghausen's disease seen at the Memorial and James Ewing Hospitals constitute the material reviewed. The terms schwannoma and neurilemoma are used interchangeably. Of the 232 patients, 17 were lost to follow-up and 31 were treated recently. These 48 patients were excluded in reporting end results. All patients however, are used to illustrate characteristic features of the tumors.

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* Present address: Department of Surgery, Division of Surgical Oncology, University of Illinois College of Medicine, Chicago, Illinois.

Sex, Age and Race

One hundred and thirty (56%) were men and 102 (44%) were women (Table 1). Age at onset of the tumors ranged from 1 to 79 years, with 97 (42%) patients between 30 to 50 years of age. Thirty-four (15%) occurred in patients between 20 to 29 years of age (Table 1).

There were only 11 Negro patients (5%). Since there is a preponderance of Caucasian patients in these hospitals no conclusions about racial incidence were attempted.

Anatomic Distribution (Table 2)

Eighteen (8%) tumors were located in the head and neck region, 69 (30%) in the upper extremity, 38 (16%) in the trunk and 89 (38%) in the lower extremity. Eighteen (8%) of 232 tumors were found in various unusual sites (Fig. 1).

Clinical History

Patients with solitary malignant schwannomas were primarily seen because of the presence of a mass. One hundred and sixty-nine (73%) had painless tumors; 15 (7%) complained of pain along the course of peripheral nerves and the tumors were diagnosed by examining physicians. Twenty-two patients (9%) had painful tumors. The time the mass was known to exist before medical opinion was sought could not be ascertained in 32 patients. Of the remaining 200, 129 consulted physicians within 6 months of recognition of a tumor,

TABLE 1. *Age and Sex*

Age (yr.)	Male	Female	Total
0–9	5	7	12
10–15	8	9	17
20–29	14	20	34
30–39	30	23	53
40–49	29	15	44
50–59	27	16	43
60–69	15	7	22
70–79	2	5	7
	130	102	232

TABLE 2. *Anatomic Location of Primary Tumors*

Sites	No. of Tumors
Head and neck	18
Upper extremity	69
Trunk	38
Lower extremity	89
Miscellaneous*	18
	232

* Includes 4 in the retroperitoneal region, 3 in mediastinum, 4 in pelvis, 2 in the perineum, 1 in the iliac fossa, and 4 in the pharynx and larynx.

37 within the first year, 26 within the second year and the remainder within 3 to 5 years. The size of the primary tumor varied: 76 tumors were less than 5 cm. in maximum diameter, 59 between 5 to 10 cm., 18 between 10 to 15 cm., 10 between 15 to 20 cm., and 12 tumors were larger than 20 cm. In 57 records the exact dimensions were not stated.

The status of primary tumors when first seen was of prognostic significance as is evident from results of treatment (Table 3). Eighty-nine patients were first seen with intact primary tumors, without evidence of local or distant metastases (Stage I). One hundred and ten were referred because of local recurrences at the site of previous excisions (Stage II-a). In six, the locally recurrent lesions were extensive but no evidence of distant metastases could be demonstrated (Stage II-b) and in 27 patients there were distant metastases (Stage III).

Malignant Schwannomas of the Head and Neck Region (Table 2)

Eighteen tumors were in the head and neck, eight in the lateral part of the neck, five in the anterior neck, one in the cheek and the remaining four in the posterior neck. Only one tumor in the lateral neck was associated with pain; all others were asymptomatic.

The diagnosis of malignant schwannoma in the head and neck region was based on histological examination. In previously reported benign schwannomas [2] there was a propensity of occurrence in the lateral neck, and these tumors should be considered in the differential diagnosis of tumors of this region. The following history illustrates the necessity for histological diagnosis.

Case Reports

Case 1. A 63-year-old man was under treatment for lymphoma since 1956. In 1960 he presented with a tumor in the suboccipital region (Fig. 2) which was considered a recurrence of lymphoma. He received radiation therapy of 1,200 rads to the occipital region without a histological diagnosis. Since the tumor did not shrink, an excision was carried out. The specimen consisted of

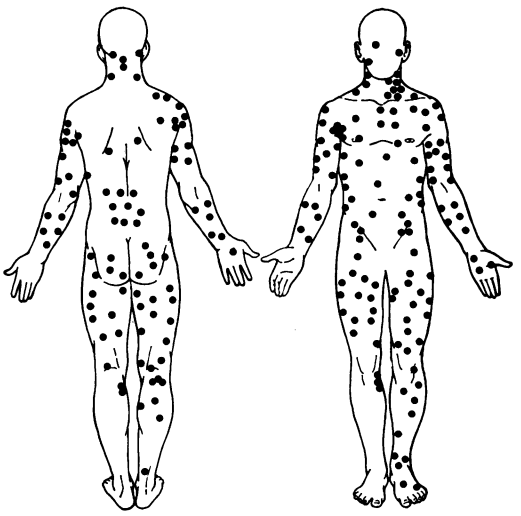

FIG. 1. Scattergram showing the sites of origin of solitary malignant schwannomas. The high incidence in the extremities and lateral neck is conspicuous.

TABLE 3. *Status of Primary Tumor and End Result*

	No. of Patients*	5 Year N.E.D.
Stage I		
Intact primary tumor without any metastases	89 (81)	51
Stage II		
(a) Locally recurrent tumors without metastases	110 (101)	40
(b) Extensive local recurrence	2 (2)	0
Stage III†		
Primary tumors with evidence of distant metastases	31	0

* Numbers in parentheses represent patients eligible for 5-year follow-up.

† None of Stage III patients were salvaged.

an ovoid mass of grayish-white tissue measuring 7 × 6 × 4 cm. (Fig. 3). Histological examination showed malignant schwannoma (Fig. 4). The tumor recurred in 1962 and was again excised. A second recurrence, with infiltration of the occipital bone, occurred in 1964. This was excised, and the specimen included parts of occipital bone. The third recurrence was 5 months later and at this time a 5 ×4 cm. segment of occipital bone was excised. The dura was intact and the defect was closed by a scalp flap. The patient developed a fourth recurrence, and died in August 1965 of bilateral pulmonary metastases. Autopsy was not performed.

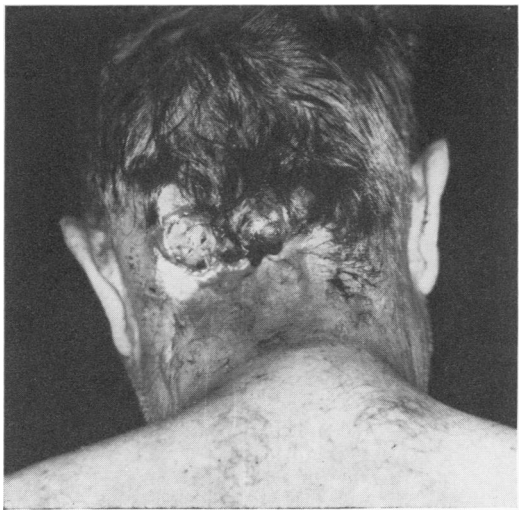

FIG. 2. A large lesion in the suboccipital region. The tumors were associated with suboccipital nerves.

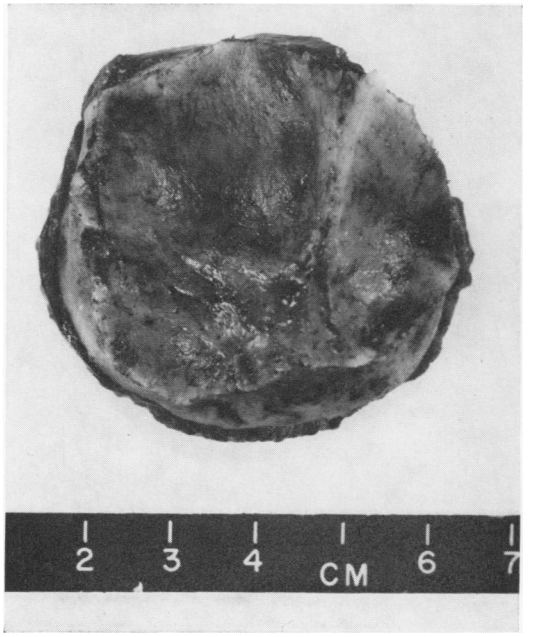

FIG. 3. The operated specimen, with limited excision. The tumor recurred shortly after excision.

Malignant Schwannomas of the Upper Extremity (Table 2)

Sixty-nine patients with solitary malignant schwannomas of the upper extremities were encountered. Of the 69, 23 were in the shoulders and axillae, 22 in the arms (Figs. 5 and 6), 18 in forearms and six in the wrists and hands. Of these 69, in only six could the tumors not be shown to arise from peripheral nerves. In five patients the tumors were directly related to the trunks of the brachial plexus. In 16 tumors of the shoulders, the subscapular nerves were associated with the tumors.

Malignant Schwannomas of the Trunk

Thirty-eight patients had malignant schwannomas arising in the soft tissues of the trunk. Of these, 11 were in the anterior chest, nine in the lumbosacral region and five in the anterior abdominal wall. The remaining 13 were distributed in the posterior and lateral trunks (Fig. 7). In only 10 was the tumor associated with pain.

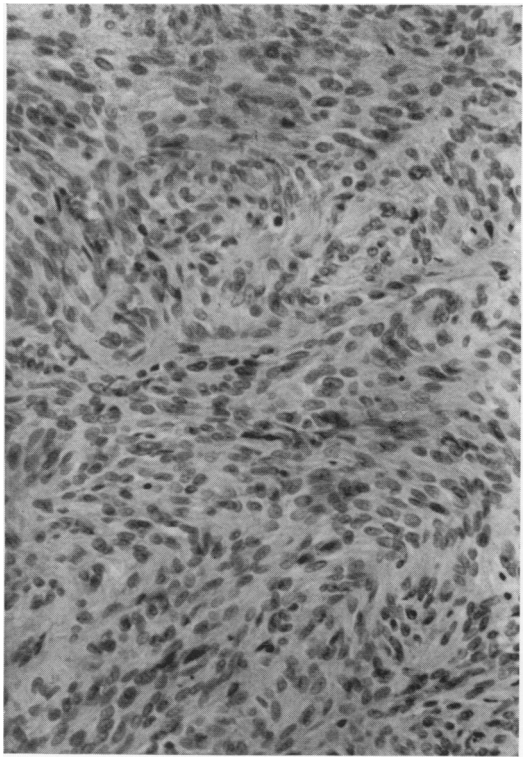

FIG. 4. Photomicrograph of the specimen from patient in Fig. 2. (H&E, ×150.)

Malignant Schwannoma of the Lower Extremity

Eighty-nine patients had tumors in the lower extremities. The most frequent site was the thigh (Figs. 8 to 10). Forty-three were on the surface of the thigh, 17 on the legs, 10 on the buttocks, eight in the area of knee joints, six on the feet and ankles, and five on groin areas. In five patients peripheral nerve of origin of the tumors could not be dissected. Seven of the 89 tumors arose from sciatic nerves and all five in the groin were associated with branches of femoral nerves. Two patients with tumors arising from the sciatic nerve were originally thought to have sciatica, and the diagnosis of tumor was delayed for more than 6 months.

Malignant Schwannomas in Miscellaneous Sites

Eighteen patients had malignant schwannomas in various other sites, four in the retroperitoneal region, three in the pharynx and larynx, four in the pelvis, two in the perineum, three in the mediastinum and two in the iliac fossa. In all the presenting feature was a tumor mass and relationships to nerves could not be demonstrated as in extremities or lateral neck areas. The diagnosis was established microscopically.

Diagnosis

In contrast to benign solitary schwannomas,[2] malignant tumors are not common in the head and neck, only 18 were recorded. The diagnosis is established histologically. In tumors of the trunk and extremities most patients have a cutaneous lesion of moderate size and the diagnosis of malignant schwannoma should be considered. Furthermore, in most patients careful search will find the nerve of origin unless the tumor is so large as to destroy surrounding tissues. Occasionally the tumors are pigmented; in three instances the lesions were considered to be melanomas. One histological diagnosis of malignant melanoma was made elsewhere, and a recurrent lesion was found to arise from a peripheral nerve. Histological specimens showed both original and recurrent tumors to be malignant schwannoma. Symptoms referable to a major peripheral nerve in young patients should be suspected of arising from a peripheral nerve tumor as the following history illustrates.

Case 2. A 25-year-old woman developed pain and tingling in the right foot and was treated for sciatica for about one year without relief. A tumor was found in the subgluteal region and at biopsy was a malignant schwannoma. Wide soft tissue resection disclosed that the lesion arose from the sciatic nerve and a segment of the nerve was resected.

In general, when making a diagnosis of malignant schwannoma the following con-

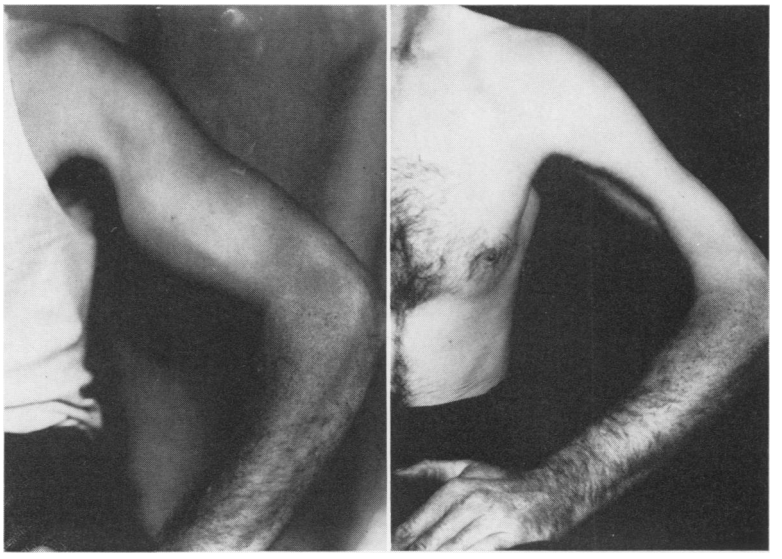

FIG. 5. (left) A solitary malignant schwannoma in the arm; the tumor originated from the median nerve. FIG. 6. (right) Postoperative view. The tumor mass, along with the nerve segment excised.

ditions should be considered: (1) fibrosarcoma, (2) desmoid, (3) dermatofibrosarcoma, (4) lipoma, (5) liposarcoma, and (6) rhabdomyosarcoma. Occasionally a melanoma or sclerosing angioma may cloud the issue.

Malignant Schwannoma and Associated Malignant Tumors

Fourteen (7%) of 232 patients had second primary malignant tumors. There was no preponderance of histological types, three had adenocarcinomas of the colon, three had carcinomas of the breast, one had lymphosarcoma, two had melanomas, one had bronchiolar carcinoma, one had desmoid and three had basal cell carcinoma.

Treatment

One hundred and thirty-two patients were treated primarily by resection (Table 4). Of these, 55 had wide local excisions of the tumors and 48 had wide soft tissue resections. Twenty-eight patients required amputations, of which 16 were local, viz., of the foot, of the mid-thigh or of the forearm, and 12 patients had major exarticulations. One patient had pelvic exenteration (Table 5). Following primary operative procedures, 61 of 132 patients developed local recurrences (Table 6), the largest incidence in patients who had local excisions. Forty of the 55 required one or more secondary operative procedures to control local recurrences. Of 48 patients treated by wide soft tissue resections, 10 developed local recurrences and secondary or tertiary operative procedures were performed. In patients who had minor amputations, nine of 16 developed local recurrences and in 12 who had major exarticulations, two developed local recurrences. All patients with recurrences were treated by excision. In some patients adjunctive radiation or chemotherapy were also used.

Sixty-nine patients were given an initial course of radiation therapy. Of these, 15 had approximately 2,000 rads and operations were subsequently carried out. The remaining 54 patients were treated primarily by radiation therapy, thirty-one had excisions later. Radiation dosage varied from 3,000 to 9,000 rads, depending on the location and size of the tumors. Three patients were treated by interstitial radiation therapy.

Thirty-one patients were treated palli-

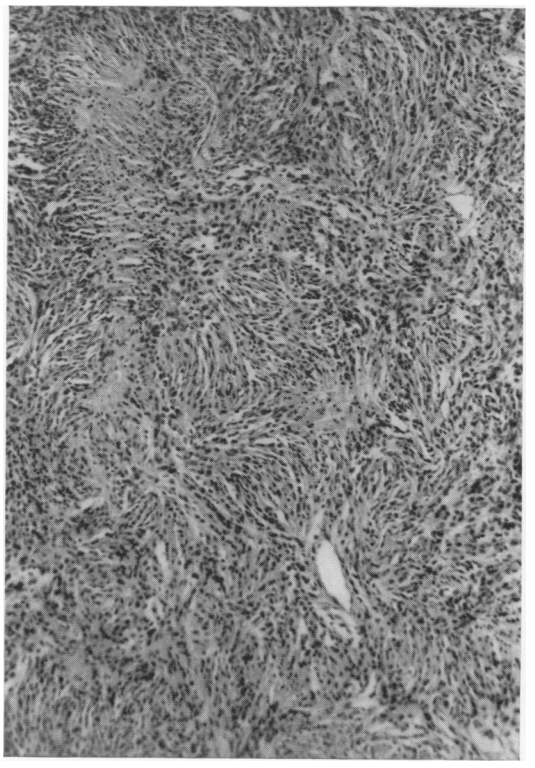

FIG. 7. Photomicrograph from the specimen in patient shown in Fig. 5. (H&E, ×63.)

atively, including excision, radiation therapy, and local and systemic chemotherapy. No advantage of one form of therapy was apparent in these patients. Of the chemotherapeutic agents, no agent was found to be significantly more effective than the others.

Results

Ninety-one of 184 (49.4%) patients eligible for long-term follow-up survived for 5 years or more free of disease (Table 3). Of these, 51 of 81 (63%) with Stage I tumors lived for 5 years and of 101 in Stage II-a, only 49 (40%) survived for 5 years without recurrence. No patient in Stage II-b or Stage III survived for 5 years.

One hundred and thirty-two patients were treated primarily by operation and of the 124 determinate patients, 62 (50%) lived for 5 years and 40 lived for 10 years (Table 4). Fifteen patients received preoperative radiation and of 12 eligible patients, seven lived for 5 years. Fifty-four patients received an initial curative course of radiation therapy. Of 48 eligible, 22 lived for 5 years. Most of these 54 patients, however, required subsequent operations.

Of 132 patients treated by operation, 55 had local excisions and 48 had soft tissue resections. Of 96 eligible patients, 27 (28%) lived for 5 years (Table 5). Of 12 patients in whom major amputations were carried out, three lived for 5 years (Table 5). Major amputation was resorted to only after local operative procedures failed. Sixty-one of 132 patients developed local recurrences after initial operation (Table 6); of the eligible 59, 25 lived for 5 years and 16 for 10 years subsequent to secondary operations for recurrences. Of 12 major exarticulations, 11 were performed for locally recurrent disease; there were recurrences in the operative area in two,

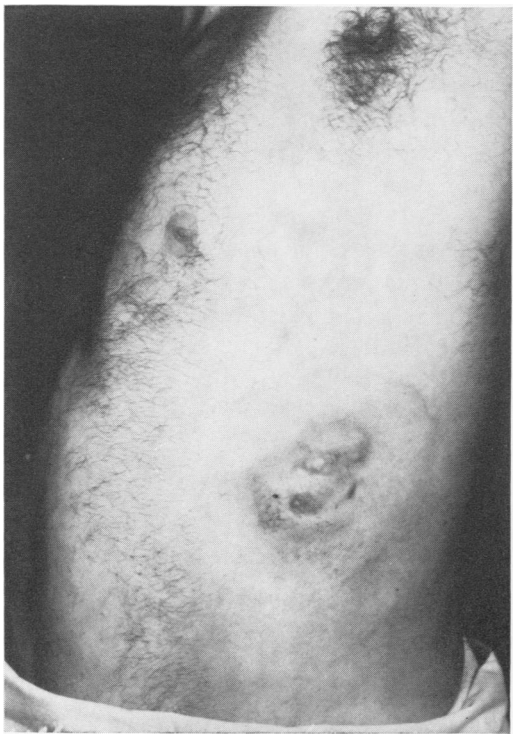

FIG. 8. A solitary malignant schwannoma arising in the intercostal nerve.

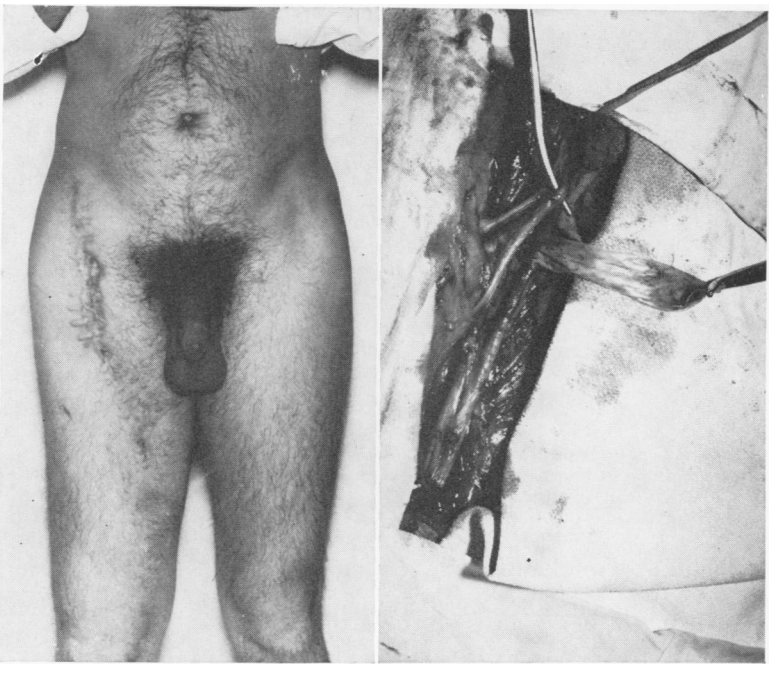

FIG. 9. (left) Tumor site in the anterior thigh of a 50-year-old man, who had local excision. Recurred promptly. Note recurrent mass under the scar. FIG. 10. (right) The operated area in patient in Fig. 9. The blood vessels are retracted medially with a penrose drain. Note the branches of the femoral nerve entwining into the tumors.

suggesting that amputation was done at a late stage. Thirty-five of 132 patients treated by operation alone died from tumors within 5 years and two died between 5 to 10 years.

Sixty-nine patients received radiation therapy, fifteen preoperatively of whom seven survived 5 years and three survived 10 years (Table 4). Fifty-four patients were initially treated by radiation therapy and of these, 22 lived for 5 years and 17 for 10 years. Of the 54, however, 31 required wide excisions since radiation did not affect the course of the disease. Of the 31 so treated, 21 lived for 5 years and 16 for 7 years. Thus, in only one patient was the primary tumor controlled by radiation therapy alone. Seventeen who received radiation therapy died of malignant schwannoma within 5 years and 21 within ten years. Of 15 receiving preoperative irradiation, five died within 5 years and one between 5 to 10 years.

Of 31 patients treated palliatively, all but two died within 5 years. Of the two with known disease, one lived for 5 years and the other for 7 years. Twelve patients died of other causes and apparently there was no recurrent tumor.

Autopsy Findings

Postmortem examinations were carried out on 20 patients who died of solitary malignant schwannomas and 18 of these had pulmonary metastases. As with most soft tissue sarcomas there is a high incidence of pulmonary metastases with malignant schwannomas. True nodal involve-

TABLE 4. *Malignant Schwannoma—End Result and Type of Treatment (201 Patients)**

Type of Treatment	No. of Patients†	5 Years N.E.D.	10 Years N.E.D.
Surgery alone	132 (124)	62	40
Radiation and surgery combined	15 (12)	7	3
Radiation therapy alone	54 (48)	22	17

* In 31 patients treatment was palliative.

† Numbers in parenthesis represent patients eligible for 5-year follow-up.

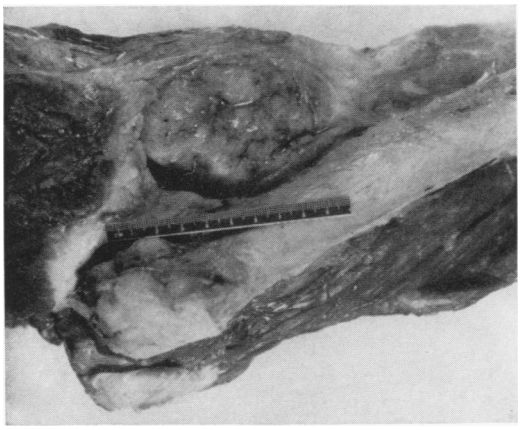

FIG. 11. The amputation specimen bisected. Note the large tumors involving and infiltrating the muscular compartments.

ment due to lymphatic metastases was not observed.

Of 12 patients in whom the original tumors were in the extremities, six were not treated by major amputation. Autopsies in these six showed that recurrences were present proximally high in the perineural sheaths of peripheral nerves of origin of the primary tumors.

Metastatic disease in the other viscera were occasionally found but no trend could be deduced from this review.

Discussion

Malignant solitary schwannomas arising in the peripheral nerves develop in practically every anatomic region. To avoid confusion about histogenesis of primary malignant tumors of peripheral nerves, D'Agostino *et al.*[3, 4] included only tumors which could be shown to arise from major peripheral nerves. The selection by these authors was rigorous, but excluded a number of patients who might have had malignant schwannomas. Not all schwannomas arise from large named peripheral nerves, and a number occur in smaller branches and the relationship is often overlooked.

The diagnosis of neurofibrosarcoma has been made in the past for a number of soft tissue sarcomas, but as Stout [10] pointed out true malignant peripheral nerve neoplasms are rare. In 1935, he classified these tumors as fibrosarcomas but in 1949, on the basis of tissue cultures by Murray and Stout he revised the diagnosis.[7, 8] Although connective tissue, particularly collagen, is conspicuous in schwannomas, there is histological and histochemical evidence that the cells involved are schwannian. The microscopic diagnosis of malignant schwannoma is difficult because the tumors often consist of fusiform elements packed in interlacing bundles and resemble fibrosarcoma. Furthermore, soft tissue sarcomas, notably fibrosarcomas, infiltrate surrounding peripheral nerves creating an impression of peripheral nerve origin.

Tumors arising from large peripheral nerves are usually fusiform and appear to be surrounded by a capsule. Although the nerve appears to enter and traverse the

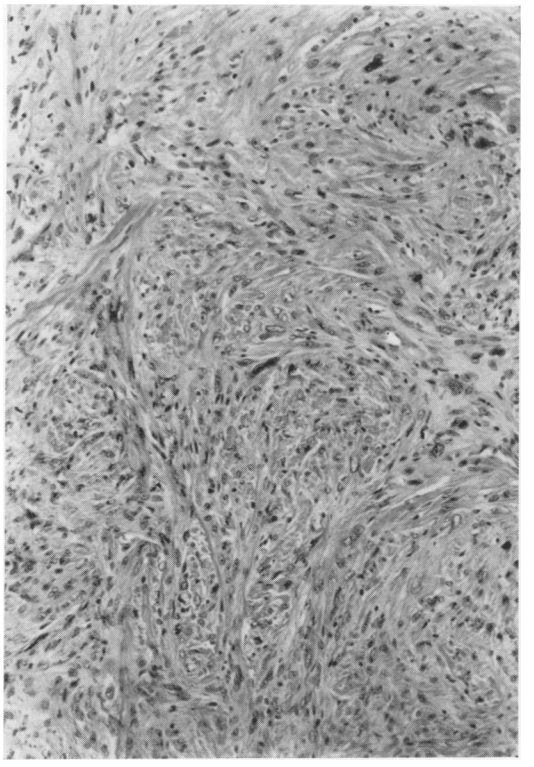

FIG. 12. Photomicrograph from the specimen in Fig. 11. The highly malignant nature of the tumor is apparent. H&E, ×100.

TABLE 5. *Malignant Schwannoma—End Results According to Type of Surgical Treatment (132 Patients)*

Type of Operation	No. of Patients	5 Years N.E.D.	10 Years N.E.D.
1. Local excision	55 (51)	15	11
2. Soft tissue resection	48 (45)	12	6
3. Minor amputation	16 (15)	7	5
4. Hemipelvectomy	2 (2)	1	1
5. Hip joint disarticulation	5 (5)	1	1
6. Interscapulothoracic amputation	5 (5)	1	0
7. Pelvic exenteration	1 (1)	0	0
Total	132/124	37	24

neoplasm, it is impossible to trace it in the tumor. The emergence is obvious in a large peripheral nerve, but in the mediastinum or in smaller nerves this feature is not always demonstrable.

The cut surface can have a faint-to-marked whorled pattern like that of uterine leiomyoma. Areas of cystic degeneration or hemorrhage appear in large tumors.

Solitary malignant schwannomas of the extremities constitute 68% of tumors in this series. In only 11 of 158 was it impossible to demonstrate a relationship to a peripheral nerve. The lateral portion of the neck was the predominant site in the head and neck and cutaneous nerves were involved. In the trunk the relationship was to intercostal nerves. Most tumors could be shown to be associated with peripheral nerves.

There are no clinical findings characteristic of malignant schwannoma. The chief reason the patient seeks advice is a soft tissue mass which is gradually enlarging. In spite of peripheral nerve origin few patients have symptoms of defective peripheral nerve function. Neurological examination may disclose some deficit, which otherwise goes unnoticed.

Management of these tumors is radical excision based on location, shape, size and local spread. The tumor plus its bed and any attached muscle, bone, fascia or blood vessel should be resected *en bloc*. If the nerve of origin is identified the nerve should be resected through a normal segment. The proximal margin of resection should be examined by frozen section.

Of 55 patients who received inadequate local operations as primary therapy, 40 developed local recurrences and required secondary and tertiary operations. Only 15 of 51 patients followed who were treated by local excision survived free of tumor for 5 years. On the other hand, of 48 patients treated by wide soft tissue excision 10 had local recurrences. All 10 patients lived 5 years or longer after secondary operations.

When radical local excision is performed,

TABLE 6. *Malignant Schwannoma—Incidence of Recurrence Depending on the Type of Operation and Survival After Treatment of Recurrence*

Type of Operation	No. Patients	No. Recurrence	5 Years N.E.D.	10 Years N.E.D.
1. Local excision	55	40 (38)	13	5
2. Wide soft tissue resection	48	10 (10)	10	8
3. Minor amputation	16	9 (9)	0	1
4. Hemipelvectomy	2	0	0	0
5. Hip joint disarticulation	5	1 (1)	1	1
6. Interscapulo-thoracic amputation	5	1 (1)	1	1
7. Pelvic exenteration	1	0	0	0
Total	132	61/59	25	16

restoration of nerve continuity is not feasible. Since 68% of malignant schwannomas arise in peripheral nerves of the extremities, a study of peripheral nerve allografting is indicated. It has been shown experimentally [1] that predegenerated grafts are not rejected.

With tumors near the shoulder or hip joints or in patients in whom, there is nodular enlargement in a peripheral nerve the primary treatment is major amputation. Minor amputations, like local excisions, are associated with local recurrences (Table 6). Thus if amputation is decided upon it should be a major amputation. In this review, end results following major exarticulation do not represent an accurate picture, because most major amputations were done after local recurrences or in large fungating tumors. There is no evidence that preoperative radiation therapy alters the course of these tumors.

The effectiveness of a radical surgical approach is evident; of 124 patients eligible for 5 year follow-up study 62 (50%) survived free of tumor for at least 5 years.

Summary

Records of two hundred and thirty-two patients with solitary malignant schwannomas were analyzed. One hundred and thirty were men and 102 were women. Age at onset ranged from 1 to 79 years. Eighteen of these tumors were located in the head and neck region, 69 in upper extremities, 38 in trunk area and 89 in lower extremities. It is emphasized that the diagnosis must be established histologically. One hundred and thirty-two patients were treated primarily by resection. Following primary procedures 61 of 132 developed local recurrences. The incidence of local recurrence was least in patients receiving adequate wide excision, including major amputations. Fifty-four patients were treated primarily by radiation, 31 of these required subsequent excisions. Thirty-one patients were treated palliatively. Ninety-one of 184 (49.4%) patients eligible for long-term follow-up survived for 5 years or more. Of 124 determinate patients treated primarily by operation, 50% lived for 5 years or more. Most patients treated originally by radiation required subsequent operation and of the eligible 48, 22 lived for 5 years or more. This tumor like other soft tissue tumors, metastasized commonly to the lungs. Radical excision seems to be the best method of control.

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