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Toshiyuki Kunisada* Akira Kawai† Toshifumi Ozaki‡
Shinsuke Sugihara** Kohji Taguchi†† Hajime Inoue‡‡

*Okayama University,
†Okayama University,
‡Okayama University,
**Okayama University,
††Okayama University Hospital,
‡‡Okayama University,

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Toshiyuki Kunisada, Akira Kawai, Toshifumi Ozaki, Shinsuke Sugihara, Kohji Taguchi, and Hajime Inoue

Abstract

In this study, we reviewed the clinical features of 11 patients with malignant schwannoma who were treated in our institute. Five patients had coexistent von Recklinghausen's disease and one of them showed multifocal occurrence. Patients with the centrally located tumors had a poorer prognosis than those with the others. The overall 3-year survival rate was 36%; 40% in patients with von Recklinghausen's disease and 33% in the others. At the time of the last follow-up, 9 patients had died of the tumor, one continued to be tumor free, and one was alive with tumor. Postoperative local recurrence developed in 5 patients (45%); 4 out of 6 patients (67%) who underwent a marginal excision and one out of 3 (33%) who underwent primary amputation. There was no local recurrence in patients after a wide excision with at least 3cm of normal tissue removed surrounding the tumor in all directions. Nine patients (82%) developed pulmonary metastasis. The effect of adjuvant chemotherapy was not clear in this study. The high risk of pulmonary metastasis in this disease indicates the necessity of more effective adjuvant chemotherapy.

KEYWORDS: malignant schwannoma, clinical analysis, von Recklinghausen's disease

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A Clinical Analysis of Malignant Schwannoma

Toshiyuki KUNISADA*, Akira KAWAI. Toshifumi OZAKI, Shinsuke SUGIHARA, Kohji TAGUCHI[a] and Hajime INOUE

Department of Orthopaedic Surgery, Okayama University Medical School, and [a]Department of Pathology, Okayama University Hospital Okayama 700, Japan

In this study, we reviewed the clinical features of 11 patients with malignant schwannoma who were treated in our institute. Five patients had coexistent von Recklinghausen's disease and one of them showed multifocal occurrence. Patients with the centrally located tumors had a poorer prognosis than those with the others. The overall 3-year survival rate was 36%; 40% in patients with von Recklinghausen's disease and 33% in the others. At the time of the last follow-up, 9 patients had died of the tumor, one continued to be tumor free, and one was alive with tumor. Postoperative local recurrence developed in 5 patients (45%); 4 out of 6 patients (67%) who underwent a marginal excision and one out of 3 (33%) who underwent primary amputation. There was no local recurrence in patients after a wide excision with at least 3 cm of normal tissue removed surrounding the tumor in all directions. Nine patients (82%) developed pulmonary metastasis. The effect of adjuvant chemotherapy was not clear in this study. The high risk of pulmonary metastasis in this disease indicates the necessity of more effective adjuvant chemotherapy.

Key words: malignant schwannoma, clinical analysis, von Recklinghausen's disease

Malignant schwannoma is a relatively rare soft tissue tumor which accounts for approximately 2-10% of all soft tissue sarcomas (1, 2). A unique feature of this tumor is its relationship with peripheral nerves. The sites most frequently involved are major nerve trunks such as the sciatic nerve, the brachial plexus and the sacral plexus (3). The tumor tends to grow along the epineurium and/or the perineurium (1, 3) and produce satellite lesions around the primary tumor.

Malignant schwannoma is known to occur in patients with von Recklinghausen's disease (4-6). The incidence of the tumor arising in patients with this disease is 4.6% in contrast to the incidence of 0.001% in the general clinic population (7). In patients with von Recklinghausen's disease, multicentric tumors also sometimes occur (7, 8).

These unique features of malignant schwannoma make it difficult to treat the tumor. In this paper, we review the results of the treatment for patients with malignant schwannoma and discuss the prognostic factors.

Subjects and Methods

During the period between 1971 and 1995, 11 patients with histologically confirmed malignant schwannoma were treated in our institute. There were 7 males and 4 females, with ages ranging from 14 to 75 years (mean, 44 years). Six tumors were located in the thigh, 3 in the trunk, and 2 in the upper arm. As for the initial surgery, 8 patients underwent local excision, of which 2 were wide excision with 3 cm of normal surrounding tissue removed and 6 were marginal excisions. Three patients underwent primary amputation. Two patients had postoperative chemotherapy composed of adriamycin, vincristine, actinomycin D and cyclophosphamide. The postoperative follow-up period ranged from 2 to 52 months with an average of 19 months.

Clinical records of these patients were examined to establish the presence or absence of von Recklinghausen's disease. Patients were considered to have von Recklinghausen's disease according to the criteria of National Institutes of Health (NIH) (9). Five patients (45%) had coexistent von Recklinghausen's disease. The average age of patients with von Recklinghausen's disease was 42 years, and without the disease, 47 years.

Survival curves were generated by the Kaplan-Meier method.

* To whom correspondence should be addressed.

Results

Table 1 summarizes the features of the 11 patients with malignant schwannamas who were involved in this study. The chief complaint among the 9 patients was increasing tumor volume with associated pain in 7 patients and without pain in 2 patients. Two patients who had tumors in a paravertebral site complained of pain occurring in the regions which were innervated by the involved nerves (Th1, Th5). The primary tumor locations are shown in Fig. 1 (Fig. 1A shows patients with von Recklinghausen's disease. Fig. 1B shows patients without von Recklinghausen's disease). One patient with von Recklinghausen's disease had multifocal tumors in the thigh, retroperitoneum, and trunk (Fig. 1A). There was no difference in the distribution pattern of tumors between patients with and without von Recklinghausen's disease. However, patients with tumors located in the trunk had a statistically shorter average survival period (4 months) than patients with tumors located peripherally (26 months).

Postoperative local recurrence developed in 5 patients

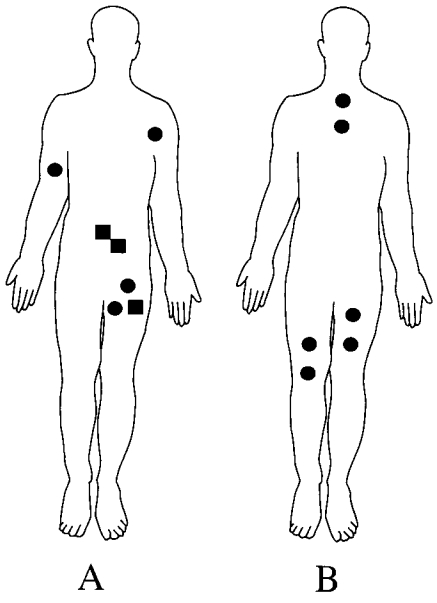

Fig. 1 Location of malignant schwannoma. **A**: With von Recklinghausen's disease. Squares indicate multifocal occurrence in one patient. **B**: Without von Recklinghausen's disease.

Table I Patient characteristics

Case	Age	Sex	Location	von Recklinghauzen's disease	Follow-up (months)	Operation	Chemotherapy	Local recurrence	Pulmonary metastasis	Outcome
1	33	F	Buttock	+	4	Amputation	−	+	+	DOD
2	68	M	Upper arm	+	10	Amputation	−	−	+	DOD
3	52	M	Thigh	+	27	Wide excision	−	−	−	CDF
4	30	M	Thigh, Retroperitoneum L3, 4	+	17	Marginal excision	−	+	+	DOD
5	25	M	Upper arm	+	52	Marginal excision	−	−	+	DOD
6	45	M	Paraspinal muscle (Th5)	−	2	Marginal excision	−	+	+	DOD
7	14	F	Thigh	−	5	Marginal excision	+	−	+	DOD
8	55	M	Th1	−	5	Marginal excision	−	+	−	DOD
9	53	F	Thigh	−	23	Wide excission	−	−	+	AWD
10	75	F	Thigh	−	15	Amputation	−	−	+	DOD
11	40	M	Thigh	−	49	Marginal excision	+	+	+	DOD

M: male, F: female, CDF: continuously disease free, AWD: alive with disease, DOD: dead of disease.
L3, 4: The 3rd and 4th lumbar vertebrae; Th5, Th1: The 5th and 1st thoracic vertebrae.

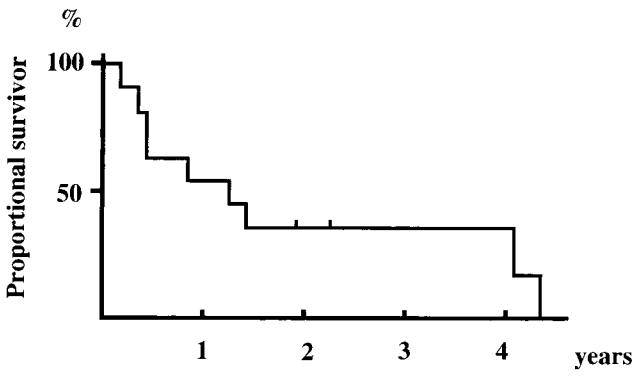

Fig. 2 Survival curve for patients with malignant schwannoma.

(45 %); 4 out of 6 patients (67 %) who underwent a marginal excision and one out of 3 patients (33 %) who underwent primary amputation. There was no local recurrence in patients who underwent a wide excision. Two patients with von Recklinghausen's disease (40 %) and 3 patients without it (50 %) had local recurrence.

Nine patients (82 %) developed pulmonary metastasis; 5 within 1 year, 2 between 1 and 2 years, 2 after 3 years. Pulmonary metastasis developed in 4 out of 5 patients (80 %) with von Recklinghausen's disease and in 5 out of 6 patients (83 %) without this disease. Two patients who had postoperative chemotherapy developed pulmonary metastasis.

At the time of the last follow-up, 9 patients had died

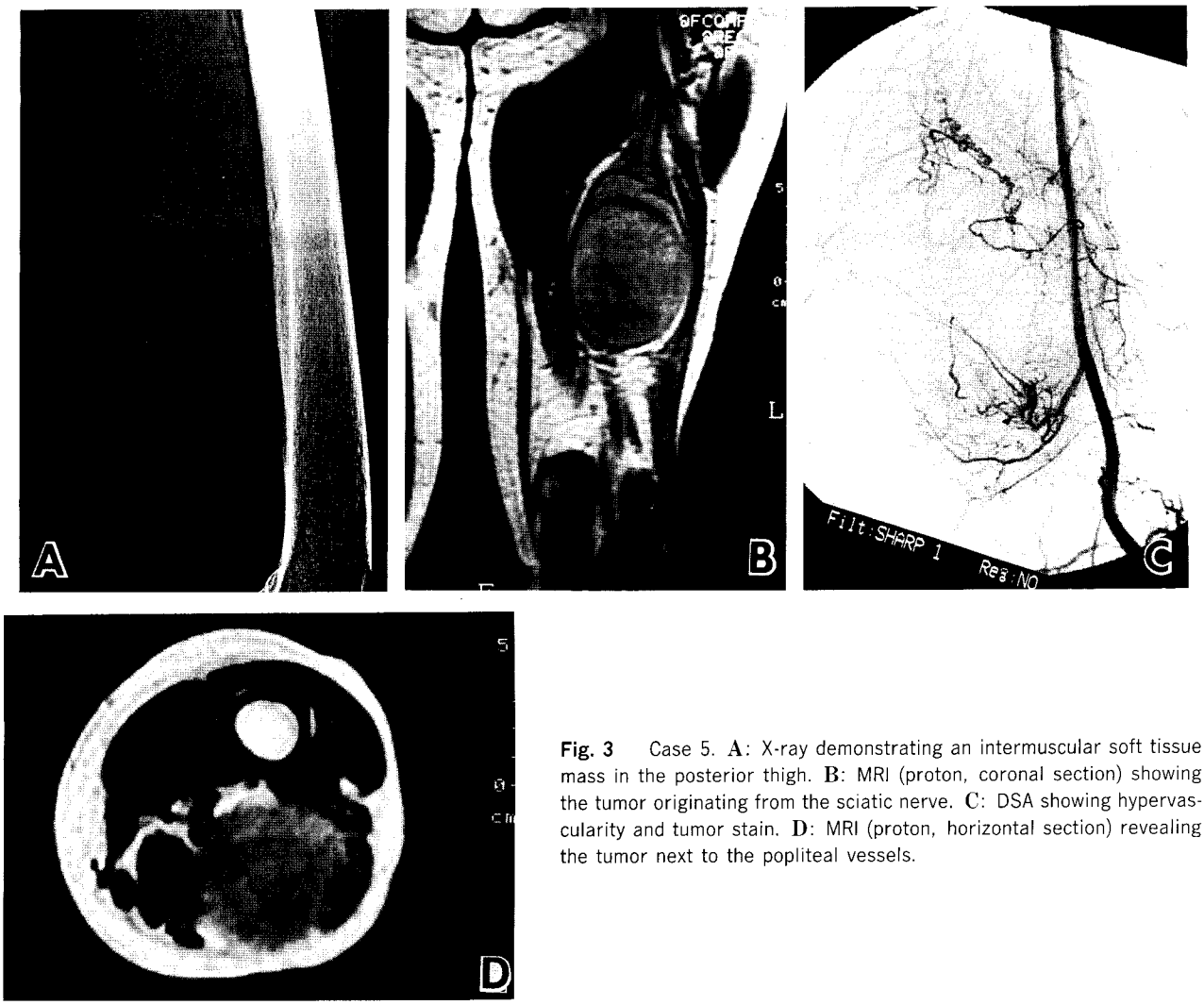

Fig. 3 Case 5. **A**: X-ray demonstrating an intermuscular soft tissue mass in the posterior thigh. **B**: MRI (proton, coronal section) showing the tumor originating from the sciatic nerve. **C**: DSA showing hypervascularity and tumor stain. **D**: MRI (proton, horizontal section) revealing the tumor next to the popliteal vessels.

of the tumor, one continued to be tumor free, and one was alive with an existing tumor. The overall 3-year survival rate was 36%; 40% in patients with von Recklinghausen's disease and 33% in the others (Fig. 2).

Case Presentation

Case 5. A 53-year-old woman had a 4-month history of a rapidly enlarging, painful mass in the left thigh. She did not have von Recklinghausen's disease. Physical examination revealed a large fist-sized, elastic firm and tender mass in the middle posterior region of the left thigh. There was muscle weakness and sensory change (hypesthesia) in the left lower leg. Inguinal lymph-nodes were not palpable. The range of motion of the hip and knee was not disturbed.

X-rays revealed a soft tissue mass in the intermuscular space in the posterior thigh. No calcification or bone invasion was observed (Fig. 3A). Computed tomography (CT) and magnetic resonance imaging (MRI) showed a 10 × 6.5-cm tumor within the sciatic nerve surrounded with adductors and hamstring muscles (Fig. 3B, D). Digital subtraction angiography (DSA) revealed hypervascularity, tumor stain and an A-V shunt in the tumor (Fig. 3C). Primary metastasis was not shown on the chest X-p.

Open biopsy revealed spindle tumor cells which were arranged in a tight wavy pattern or interlacing bundles (Fig. 4). There were numerous mitotic figures along with nuclear pleomorphism. Immunohistochemical staining revealed S-100 protein within the tumor cells. Wide excision of the tumor with the popliteal vessels and surrounding muscles (adductors, semitendinosus, semimembranosus, biceps) was performed. As the tumor originated from the sciatic nerve, the nerve was removed with the tumor. The 11.5-cm segment of the removed popliteal vessels was replaced with an 8-mm Gore-tex artery graft and an autogenous saphenous vein graft. Postoperative evaluation of the surgical margin was adequate width with at least 3 cm of normal tissue covering. No adjuvant chemotherapy or irradiation was performed. The patient developed pulmonary metastasis 11 months after the operation. Pulmonary metastasectomy

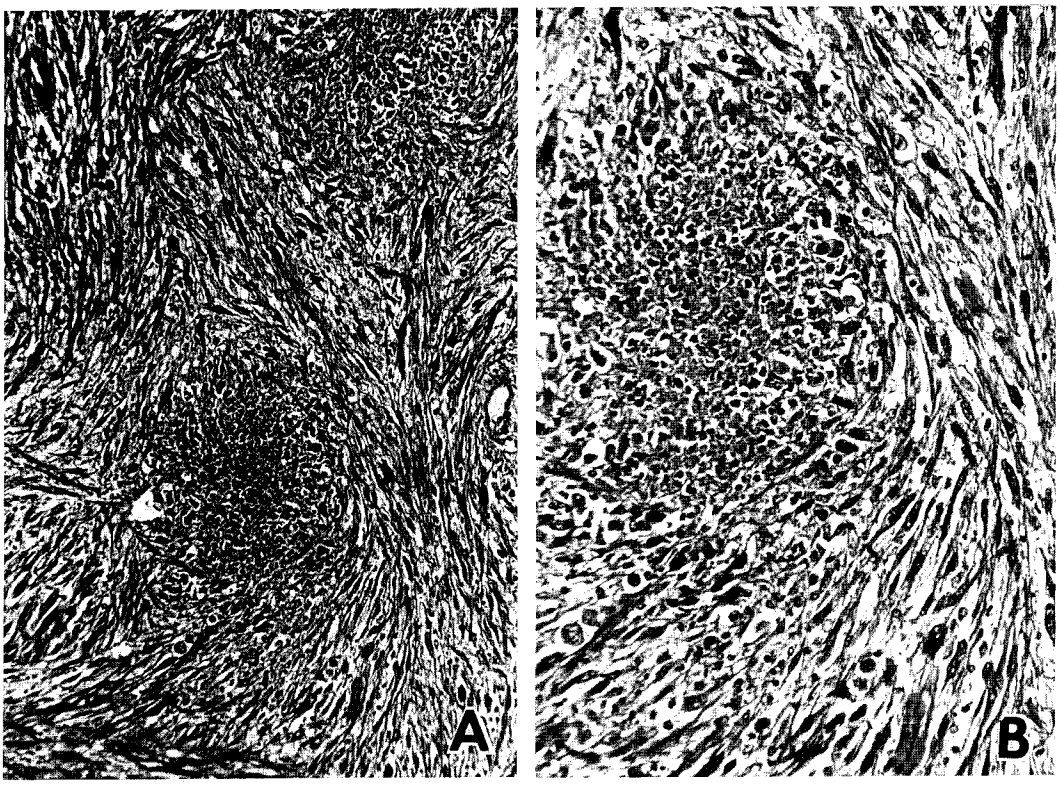

Fig. 4 Specimens of the open biopsy (HE) of Case 5. **A**: × 100. **B**: × 200; The spindle tumor cells with nuclear pleomorphism are arranged in a tight wavy pattern.

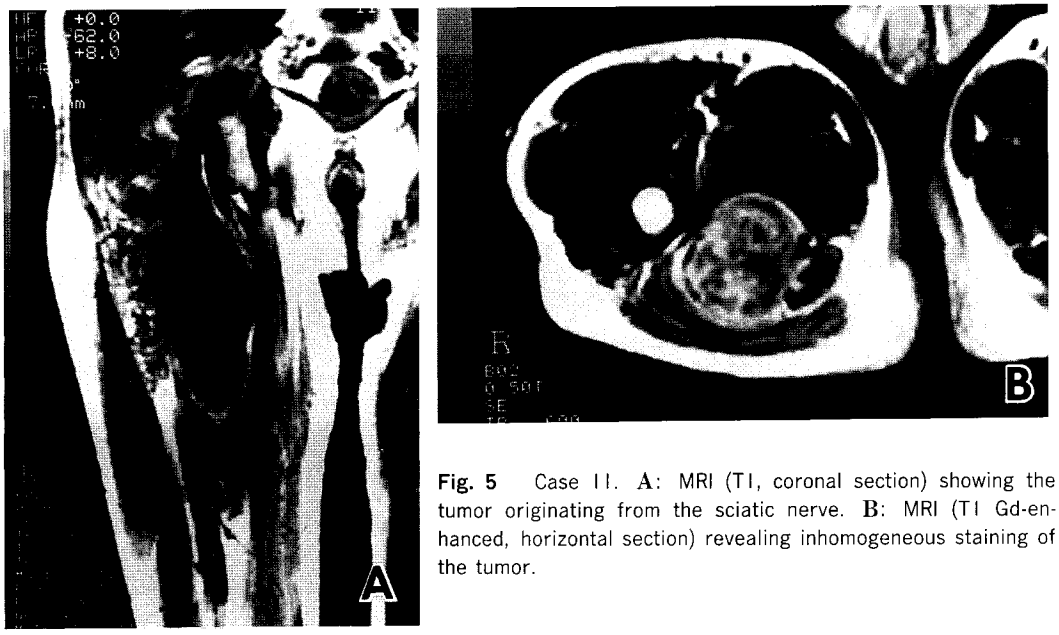

Fig. 5 Case 11. **A**: MRI (T1, coronal section) showing the tumor originating from the sciatic nerve. **B**: MRI (T1 Gd-enhanced, horizontal section) revealing inhomogeneous staining of the tumor.

was performed, however, it resulted in incomplete excision of the tumors.

Twenty-two months after the initial operation she was alive with multiple metastases in both lungs. However, she had no evidence of local recurrence.

Case 11. A 52-year-old man was observed with the chief complaint of severe pain in his right lower leg. His medical history was significant for the diagnosis of von Recklinghausen's disease at the age of 32 years. Physical examination revealed multiple café-au-lait spots and cutaneous neurofibromas. Examination of the extremities revealed an approximately 8 × 10-cm, elastic firm and tender mass in the posteromedial region of the right proximal thigh. Neurological examination showed hypesthesia and referred pain in the right lower leg where the sciatic nerve innervated.

CT and MRI revealed a large mass which originated from the sciatic nerve, surrounded by the medial and lateral hamstrings (Fig. 5). DSA demonstrated hypervascularity and a tumor stain. The chest X-ray was clear.

The biopsy specimen showed spindle cells with moderate nuclear pleomorphism which were arranged in wavy bundles. En bloc excision of the tumor with the sciatic nerve, surrounding muscles (medial and lateral hamstrings and adductor magnus and brevis) and the periosteum of the right femur was performed. Postoperative evaluation of the surgical margin was an adequately wide margin of 3 cm of normal surrounding tissue.

Twenty-seven months after the operation, the patient had no evidence of local recurrence or distant metastasis. He could walk well with a short leg orthosis for drop foot due to sciatic nerve palsy.

Discussion

Five malignant schwannoma patients (45 %) had coexistent von Recklinghausen's disease. The association of von Recklinghausen's disease and malignant schwannoma has been described in previous reports (1, 3, 7, 8). Sordillo *et al.* (8) demonstrated that 40 % of their patients with malignant schwannoma had von Recklinghausen's disease and Ducatman *et al.* (7) reported that the risk of developing malignant schwannoma appeared to be 4600 times greater in patients with von Recklinghausen's disease than in the general population. Malignant schwannomas associated with von Recklinghausen's disease tend to occur in younger patients, are located more centrally, develop multifocally and are histologically less differentiated than those without the disease (1, 3, 7, 8). Ghosh *et al.* (10) reported that the 5-year survival rate for patients with malignant schwannomas was 30 % for those with von Recklinghausen's disease compared with 66 % in the general patient population. Other authors showed that the association with von Recklinghausen's disease was one

factor leading to a poor prognosis (1, 7, 8). The fact that the tumors occurring in the trunk or proximal extremities are less amenable to early detection and treatment, and the tendency of multifocal occurrence may contribute to the poorer prognosis for patients with von Recklinghausen's disease. In this study the patients with von Recklinghausen's disease showed no tendency for tumors to occur in a central location and one of the patients had multifocal occurrence. Patients with von Recklinghausen' s disease did not appear to have a poorer prognosis than those without this disease, as suggested formerly. However, patients with centrally located tumors had a poorer prognosis than others.

Local recurrence developed in 33 % of the patients who underwent primary amputation and in 67 % of those who underwent a marginal excision, whereas, no local recurrence was observed in patients who underwent a wide excision with 3 cm of normal tissue surrounding the tumor in all directions. This data suggests that tumors should be excised with at least a 3-cm wide surgical margin to avoid local recurrence.

The overall 3-year survival rate of patients was only 36 % in this study. The rate of pulmonary metastasis in this series of this patients (82 %) was higher than that of other cases of soft tissue sarcoma which were treated in our institute, such as malignant fibrous histiocytoma (24 %) and liposarcoma (8 %) (11). Previous papers showed that the rate of distant metastasis of malignant schwannoma ranged from 28 % to 63 % and that the most common metastatic site was the lung (1, 7, 8). Ducatman *et al.* (7) reported that patients with large malignant schwannomas ($\geqq$ 5 cm) statistically had a poorer prognosis than others. The high rate of pulmonary metastasis and the fact that 8 of our 11 patients had tumors larger than 5 cm may have contributed to the poor prognosis in this study.

Some reports (7, 8, 12, 13) have shown that adjuvant chemotherapy for malignant schwannoma did not affect the survival of the patients significantly. However, Goldman *et al.* (14) reported that chemotherapy consisting of vincristine, adriamycin, cyclophosphamide and imidazole carboxamide resulted in complete remission of pulmonary metastasis of malignant schwannoma. In this study, two patients who received adjuvant chemotherapy developed pulmonary metastases. The role of adjuvant chemotherapy in the treatment of malignant schwannoma remains unclear in this study because of the limited number of patients and the short follow-up periods. The high risk of pulmonary metastasis in this disease indicates the necessity of more effective adjuvant chemotherapy. More intensive chemotherapy using colony-stimulating factors and/or autogenous bone marrow transplantation may contribute to an improvement of results in the treatment of these patients.

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