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# Intrathoracic neurogenic tumors—50 years' experience in a Japanese institution☆

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**Abstract**

**Objective**: Intrathoracic neurogenic tumors are relatively uncommon, and there have been few reports regarding their entire clinical characteristics in the Asian population. **Objectives**: We retrospectively reviewed our Japanese institutional experience of intrathoracic neurogenic tumors, with emphasis on the clinical spectrum. **Methods**: We analyzed the records of 146 patients with intrathoracic neurogenic tumors who were treated over the past 50 years. There were 60 pediatric and 86 adult patients (74 males and 72 females). **Results**: There were 51 ganglioneuromas, 37 schwannomas, 30 neurofibromas, 18 neuroblstomas, 5 gangliobastomas, and 5 others, of which 136 cases were located in the posterior mediastinum, 9 in the chest wall, and 1 in the lung parenchyma. Neurogenic tumors were most commonly seen as a pediatric mediastinal tumor (46.2%), as compared to 11.2% in the adult population ($P<0.001$). Eighty-four percent of adult patients and 60% of pediatric patients were asymptomatic. In thirteen patients (8.9%), the tumor showed an intraspinal extension, the so-called dumbbell-type. Overall, 20.5% of the neoplasms were malignant, occurring predominantly in the first 5 years of life. Complete resection was performed in 95.7% cases for benign tumors and 63.3% for malignant tumors, including a laminectomy for six cases of the dumbbell-type. There were no operative deaths and minimal morbidity. **Conclusions**: Age seemed to be the most important clinical parameter for distinguishing between histological type and rate of malignancy for neurogenic tumors. Recognition of this clinical spectrum will lead to the immediate and appropriate surgical intervention.


*Keywords:* Neurogenic tumor; Dumbbell tumor; Clinical characteristics

## 1. Introduction

Neurogenic tumors are relatively uncommon, though they comprise 15–25% of all primary mediastinal tumors [1–3]. Intrathoracic neurogenic tumors are found almost exclusively in the posterior mediastinum around the paravertebral area or arising from the intercostal and sympathetic nerves, and only rarely are represented as an intrapulmonary mass. Neurogenic tumors originate in the embryonic neural crest cells, which constitute the ganglia, paraganglionic, and parasympathetic systems. In pediatric populations, these tumors are the most common comprising 34–58% [1,3–5]. In our series of Japanese patients, neurogenic tumors comprised 46% of all pediatric mediastinal tumors, and Shields reported an incidence of 40.1% in cases collected from nine institutions from North American and Europe [5]. To date, few reports on this disease in Asian populations have been published in the English literature. The individual physician thus has scant opportunity to understand their clinical characteristics including histological variety, malignancy rate, and therapeutic strategy. The classification of neurogenic tumors is on the basis of cell origin, however, terminology for these tumors has varied

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and can be confusing due to difficulties in pathological classification. The purpose of this study was to conduct an institutional review of intrathoracic neurogenic tumors, with emphasis on the clinical spectrum of the disease related to age, along with presentation of some cases with unusual clinical manifestations.

## 2. Materials and methods

### 2.1. Subjects

We performed a retrospective review of the medical records of 146 patients with intrathoracic neurogenic tumors, including 136 mediastinal tumors, who were treated at Osaka University Hospital over the 50 years from 1951 to 2000. During the same period, a total of 806 mediastinal tumors were treated at our institution. The 146 present cases included 136 tumors that originated in the posterior mediastinum, nine in the intercostal nerve, and one in the intrapulmonary region. The age range at presentation was from 6 months to 73-years-old, with a mean of 35.5 years. There were 74 males and 72 females, for a male/female ratio of 1.03. Complete records were available for all patients with neurogenic tumors and were reviewed for patient demographic data, clinical presentation, diagnostic procedure, tumor characteristics, patient treatment, and outcome.

### 2.2. Statistical analysis

Comparison for categorical values of two groups was made by $\chi^2$-test (StatView 5.0 Abacus Concepts, Berkeley, CA). Statistics was admitted for any $P$ value less than 0.05.

## 3. Results

There were 146 patients with intrathoracic neurogenic tumors who were treated at Osaka University Hospital between 1951 and 2000. The age range at presentation was from 6 months to 73-years-old (average 35.5 years). There were 60 pediatric patients (<15 years of age, 26 males and 34 females) and 86 adult patients (48 males and 40 females). Regarding tumor location, 136 were found in the posterior mediastinum, nine in the intercostal space, and one in the intrapulmonary area. Neurogenic tumors were the most common among pediatric mediastinal tumors at 46.2%, as compared to 11.2% in the adult population ($P<0.001$).

Table 1 and Fig. 1 show the classification of pathologic types of tumors and their distribution by age. There were 51 ganglioneuromas (34.9%), 37 schwannomas (25.3%), 30 neurofibromas (20.5%), 18 neuroblstomas (12.3%), 5 gangliobastomas (3.4%), 2 primitive neuroectodermal tumor (PNET), and 3 were other types. Nerve cell tumors such as ganglioneuromas or neuroblastoma comprised the majority seen in pediatric patients, and benign

Table 1
Comparison of adults and children for histologic type of neurogenic tumor

| Histologic class | Adults, 86 cases | Children, 60 cases | $P$ value |
|---|---|---|---|
| Gender | M/F: 48/38 | M/F: 27/33 | 0.20 |
| Malignancy (%) | Benign/malignant, 81/5 (5.8%) | Benign/malignant, 35/25 (41.7%) | <0.001 |
| Ganglioneuroma | 18 (M/F: 8/10) | 33 (M/F: 17/16) | <0.001 |
| Schwannoma | 37 (M/F: 21/16) | 0 | <0.001 |
| Neurofibroma | 28 (M/F: 16/12) | 2 (M/F: 0/2) | <0.001 |
| Neuroblastoma | 0 | 18 (M/F: 8/10) | <0.001 |
| Ganglioblastoma | 0 | 5 (M/F: 1/4) | 0.023 |
| PNET | 0 | 2 (M/F: 1/1) | 0.081 |
| Neurofibrosarcoma | 2 (M/F: 2/0) | 0 | 0.23 |
| Pheochromocytoma | 1 (M/F: 1/0) | 0 | 0.40 |
| Others | 2 (M/F: 0/2) | 0 | 0.23 |

M/F, male/female; PNET, primitive neuroectodermal tumor.

ganglioneuroma also tended to occur in the younger age group, whereas nerve sheath tumors such as schwannoma or neurofibroma appeared less frequently in children than adults (Fig. 1). Fig. 2 shows the malignancy rate by age group. Overall, 30/146 (20.5%) of neurogenic tumors were malignant and those occurred predominantly in the first 5 years of life. The malignancy rate of patients under 5 years, 5–14-years-old, and over 15-years-old were 80.0, 14.3, and 5.7%, respectively.

Clinical characteristics of the intrathoracic neurogenic tumors are shown in Table 2. In this series, 67.1% of the patients (83.7% of the adults and 60.0% of the children) were asymptomatic and their tumors were chance findings on routine chest X-rays. Three patients with an intrathoracic neurogenic tumor (two neuorfibroma and one schwannoma) had von Recklinghausen disease. Neurological disturbances produced by the tumors were relatively uncommon, as only six of the adult patients complained of back pain or numbness in the upper extremities that was affected by the tumor. Among the children, symptomatic patients were more common than adults and showed neurologic and respiratory problems, as well as constitutional symptoms of pyrexia weight loss or asthenia and expanding neck masses, which

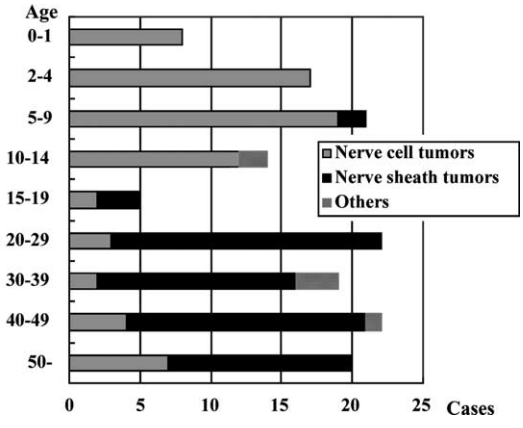


Fig. 1. Tumor type according to patient age.

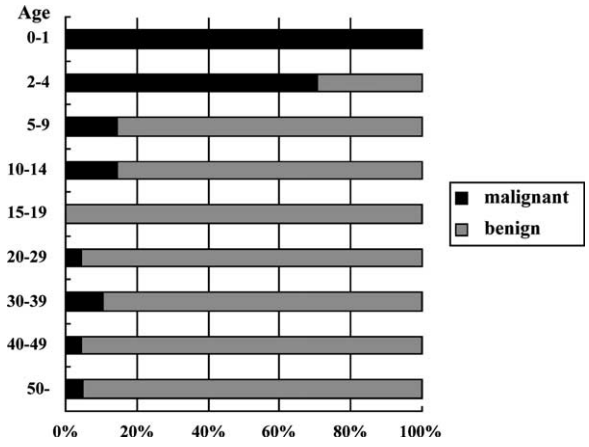


Fig. 2. Malignancy rate according to patient age.

were due to malignant tumors such as neuroblastoma. Miscellaneous symptoms such as gait disturbance were also seen in pediatric patients with malignant neurogenic tumors, probably due to asthenia or neurological disturbance. Rare symptoms included severe diarrhea caused by the vasoactive intestinal peptide producing neuroblastoma and paroxysmal hypertension in a patient with noradrenalin producing pheochromocytoma. In 13 (8.9%) patients (five with schwannoma, four with neuroblastoma, two with ganglioneuromas, one with neurofibroma, and one with PNET), the tumors showed an extension into the spinal canal, so-called dumbbell tumors (seven right and six left), four of which were accompanied by symptom of spinal compression.

Diagnostic evaluations in all cases began with conventional chest X-rays. Standard chest radiographs identified the intrathoracic neurogenic tumors in all patients. Computed tomography (CT) was performed in patients after 1980, which revealed a round well circumscribed smooth mass. Magnetic resonance imaging (MRI) was performed recently, and revealed the tumors to have a bright signal intensity on T2-weighted images, indicating a cystic content, which was a characteristic sign to differentiate solid mediastinal masses from cystic masses. Furthermore, extension into the spinal canal was clearly shown. Since all the dumbbell tumors necessitating laminectomy were located above Th7, we did not perform a spinal angiography to identify the artery of Adamkiewicz.

Table 2
Symptoms and signs in patients with neurogenic tumors

| Symptom | Children ($n=60$) | Adults ($n=86$) | Total | $P$ value |
|---|---|---|---|---|
| Asymptomatic | 36 (60.0%) | 72 (83.7%) | 98 (67.1%) | 0.48 |
| Cough | 5 (8.3%) | 1 (1.1%) | 6 (4.1%) | 0.32 |
| Neck swelling | 4 (6.6%) | 1 (1.1%) | 5 (3.4%) | 0.07 |
| Chest pain | 3 (5.0%) | 6 (7.0%) | 9 (6.2%) | 0.69 |
| Fever | 3 (5.0%) | 1 (1.1%) | 4 (2.7%) | 0.16 |
| Gait disturbance | 3 (5.0%) | 0 | 3 (2.1%) | 0.04 |
| Horner's syndrome | 2 (3.3%) | 2 (2.2%) | 4 (2.7%) | 0.71 |
| Sweating | 1 (1.7%) | 1 (1.1%) | 2 (1.4%) | 0.81 |
| Neuralgia | 0 | 1 (1.1%) | 2 (1.4%) | 0.41 |
| Dumbbell | 6 (10.0%) | 7 (8.1%) | 13 (8.9%) | 0.70 |
| Others[a] | 3 (5.0%) | 3 (3.5%) | 6 (4.1%) | 0.65 |

[a] Diarrhea, pneumothorax, hypertension.

For these patients, surgical excision was definitely diagnostic and therapeutic. Removal was performed via a posterior or axillary thoracotomy, which was chosen with regard to tumor size, location, and extension until video-assisted thoracic surgery (VATS) was introduced. A complete resection was performed for 111/116 (94.9%) benign tumors including 13 VATS resections, and 19/30 malignant tumors (63.3%), including a laminectomy for six cases of the dumbbell-type. In these six cases (three right and three left), intraforaminal portion was resected by the orthopedic surgeon. In a patient with preoperatively undiagnosed pulmonary mass (Fig. 3), the intraparenchymal tumor was found to be a typical schwannoma of Antoni A type with a palisade arrangement. There were no operative deaths and minimal morbidity, including transient or mild Horner syndrome after resection of superior–posterior mediastinal tumors. There were no tumor-related death in 96 patients with benign tumors who were followed-up for more than 5 years.

One patient with a benign lesion required a surgery for recurrence of a residual tumor in the spinal cord due to

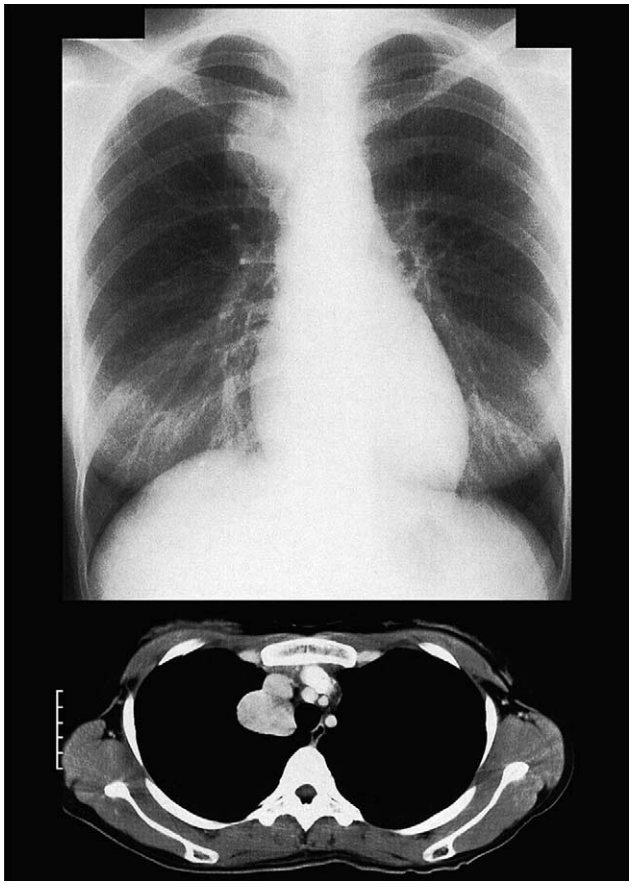

Fig. 3. Chest X-ray (left) and CT (right) images revealing a well-circumscribed mass, which was found to be an intrapulmonary schwannoma at surgery.

an incomplete initial resection, which was extirpated with the use of laminectomy. Another patient with a thymic tumor had a concurrent neurogenic tumor in the posterior mediastinum, thus the thymic tumor was resected under a median sternotomy as an initial diagnosis of thymoma and the neurogenic tumor was removed concurrently via a posterolateral approach. A 12-year-old female, who previously underwent chemotherapy for ganglioblastoma at the age of 2 years, was hospitalized for surgery for a large ganglioneuroma that was diagnosed by needle biopsy. Since the tumor was large and adherent to right lung and extended beyond the contralateral side of the descending aorta, a staged resection was performed via a right and left thoracotomy, because of the technical difficulties. We also experienced a patient who has mediastinal ganglioneuroma and retroperitoneal pheochromocytoma with different histological entity, and which were both resected using an endoscopic procedure.

Regarding the malignant neurogenic tumors in children, preoperative stage according to the Evans et al. [6] was as follows: stage I, 9; stage II, 5; stage III, 4; stage IV; 5. Seven early staged patients, who received complete resection, survived more than 5 years. Patients who underwent incomplete resection or biopsy showed poor prognosis. Adjuvant chemotherapy was given to patients with advanced stage neuroblastoma and PNET. Recently induction chemotherapy was given to 3 patients with neuroblastoma, followed by surgery. In a case of PNET (Fig. 4), high-dose chemotherapy was done with support of auto bone marrow transplantation, after complete resection of the tumor. However, the tumor recurred in the right thorax 4.5 years after surgery and the patient died 6 months later despite the salvage chemotherapy. Radiation therapy was employed for adult patients with malignant schwannoma after resection.

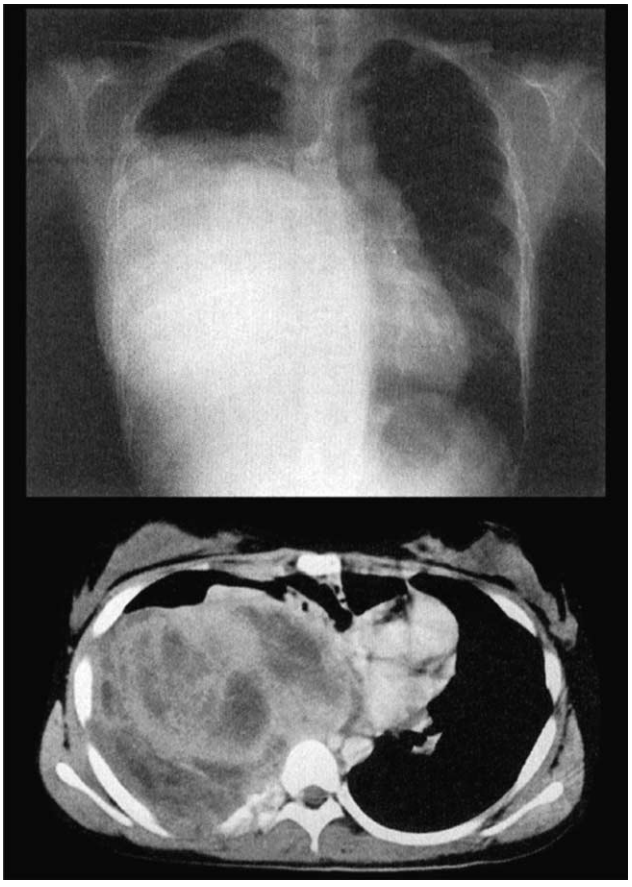

Fig. 4. Chest X-ray (upper) and CT (lower) images revealing a large mediastinal tumor (PNET) adherent to the chest wall.

## 4. Discussion

Neurogenic tumors typically originated from the posterior mediastinum followed by intercostal nerves (chest wall), though one in our series was derived from the pulmonary parenchyma. Intrapulmonary neurogenic tumor is rare, and no more than 50 cases have been reported as intrapulmonary schwannoma in English and Japanese literature. Overall, 30/146 (20.5%) of these neoplasms were malignant occurred predominantly in the first 5 years of life. Further, 5.8% of the neurogenic tumors found in adults were malignant, in contrast to a malignancy rate of 41.7% in pediatric patients ($P < 0.001$).

Neurogenic tumors are classified as nerve cell (ganglion) tumors, such as ganglioneuroma and neuroblastoma, nerve sheath tumors, including schwannoma and neurofibroma, and paraganglionic tumors. In our series of Japanese patients, paraganglionic tumors were rare, as we had only one case of malignant pheochromocytoma. Similar to previous reports from western countries [2,7,8], nerve cell tumors were more common in children than in adults (Fig. 1). Further, the malignancy rate was higher in infants and young children, at 100% under 2 years of age, 71% for patients 2–4 years of age, and 16% for those 5–14 years of age, which was quite similar to a European series [2]. In contrast, nerve sheath tumors were more common in adults (78%) than children (3.3%). Schwannoma was the most common neurogenic tumor seen in adults, however, it was not observed in any patients under 15 years of age in our series. Recklinghasuen nerofibromatosis is an uncommon genetic disease that results in the presence of multiple neurogenic tumors. We encountered only two patient with this condition, and one of them had a malignant schwannoma. Ribet and Cardot [2] noted that only 14.1% of their patients with thoracic neurogenic tumors were associated with Recklinghasuen nerofibromatosis, whereas approximately half of adult patients with malignant neurogenic tumors were reported to have this disease [9]. As mentioned previously, we experienced two cases of PNET. Askin and colleagues [10] first described malignant small cells in the thoracopulmonary region during childhood that may be presented as a chest wall or paravertebral mass. Using electromicroscopical analysis, they identified neurosecretary granules and a cell process suggesting neuronal differentiation. This is now categorized as PNETs. Clinically, PNET are seen in older children or adolescents

with female predominance. Our patient showed a typical outcome in comparison to previous reports [10].

Symptoms associated with neurogenic tumors are varied and listed in Table 2. Horner's syndrome was found with some tumors, particularly those in the upper mediastinum. There were few respiratory symptoms, such as dyspnea or cough, found related to tumor enlargement, however, gait disturbance (Ataxia), a peculiar symptom, was prominent in patients with neuroblastoma. Since a neuroblastoma produce cathecholamines, detection of urinary secretion of these by-products, including vanillylmadelic acid (VMA) and homovanillylmadelic acid (HVA), is utilized for mass screening for asymptomatic patients [11], and the oncogene c-myc is also being evaluated. We experienced only a single patient with neuroblastoma that also exhibited severe diarrhea caused by vasoactive intestinal peptide.

Preoperative evaluations were done by radiographic imaging alone in general, except for cases of suspected adult malignant lesions, which were examined by needle aspiration biopsy. Conventional chest X-ray was an initial step for diagnosis even this series encompassed over a half decade. CT scan and MRI techniques have greatly enhanced the accuracy of diagnosis for mediastinal and chest wall lesions as well as distinguishing them from cystic lesions. A radiologically identified dumbbell tumor was seen in 8.9% of the patients in the current series. MRI allows precise identification with the involvement of spinal cord by a tumor; thus, it should be performed preoperatively for patients with suspected neurogenic tumors to exclude intraspinal extension. In addition, evaluation of the Adamkiewicz should be performed to avoid spinal cord injury in dumbbell tumors located in the lower posterior mediastinum [12]. A routine check-up of the abdominal cavity has not established in the diagnostic and therapeutic modalities for benign mediastinal tumors. However, the coexistence of retroperitoneal neurogenic tumors, though rare, should be recognized during the management of patients with a mediastinal neurogenic tumor.

Watchful observation of mediastinal and intrathoracic neurogenic tumors is rarely justified, since surgical removal alone leads to definite diagnosis as well as provides therapy. Intrathoracic neurogenic tumors are essentially amenable to primary surgical therapy. We observed one patient over 5-year period, since she had been treated for post-renal transplant chronic rejection. However, it was hard to remove the tumor via a transthoracic or VATS approach at surgery, because of a foramenal extension.

Benign intrathoracic neurogenic tumors are good candidates for VATS resection, which can be achieved safely and effectively with rapid recovery and less pain resulting in shortening hospital stay [13]. In particular, we applied a thoracoscopic approach assisted with a fine manipulation through the supraclavicular fossa [14] for removal of the superior mediastinal mass.

On the other hand, surgery for dumbbell-type tumors is more complex, as it requires cooperation with an orthopedic surgeon. Akwari and associates [15] first reported that 9.8% of their patients with neurogenic tumors had an extension through an intervertebral foramen. We encountered 13 (8.9%) patients with dumbbell-type out of 146 patients with neurogenic tumors, and one third of them had complaints due to spinal compression. Six patients received a one-stage combined posterolateral thoracotomy and concomitant laminectomy [15,16] in the current series. We recently used a posterior approach in two cases with the patient in the prone position, in which a laminectomy and extradural dissection were done by an orthopedic surgeon assisted with VATS dissection via the thorax, as reported by McKenna et al. [17].

Neuroblastoma remains a challenge to the pediatric surgeons in terms of the multimodality therapy. Recently induction therapy followed by surgical resection was done in our series. The evidence that prognosis of mediastinal neuroblastoma was better than other neuroblastoma may support the potential role of the complete resection when possible [18].

In summary, we reviewed our institutional experience with intrathoracic neurogenic tumors, with emphasis on the clinical spectrum of the disease, as well as diagnosis and treatment. The majority of these tumors, whether benign or malignant, were asymptomatic, yet easily diagnosed using current radiologic imaging techniques. Age may be the most important clinical parameter for distinguishing between histological type and rate of malignancy. In the adult, benign neurogenic tumors can be treated by VATS resection, however, operative approach for the dumbbell tumors should be considered with orthopedic surgeons. Malignant neurogenic tumors in children need multimodality therapy, however, complete resection remains a crucial role. Recognition of the clinical spectrum of neurogenic tumors can lead to immediate and proper surgical intervention.

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