Primary Intrathoracic Neurogenic Tumors: Clinical, Pathological, and Long-Term Outcomes

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Abstract

Background Intrathoracic neurogenic tumors (INTs) are uncommon neoplasms arising from nerve tissues. We report our single-center experience in treating these rare INTs.

Methods Using a prospective institutional database, clinical, surgical, and pathological records of patients receiving resection of INT between May 1998 and June 2018 were analyzed. Survival was calculated by Kaplan–Meier method.

Results There were 82 patients (24 females) with an average age of 53 years (29–75 years). Mean diameter was 32 mm (range, 12–68 mm). Histology included 49 schwannomas (11 malignant), 15 neurinomas (2 malignant), 14 neurilemmomas, and 4 paragangliomas. Tumor was located in the posterior mediastinum in 52 patients, in the thoracic inlet in 12, in the anterior mediastinum in 7, in the lung parenchyma in 5, and in the chest wall in 3. In three (3.6%) patients, the tumor showed an intraspinal extension. Symptoms were reported in 51 patients (62.2%) and included cough in 23, dyspnea in 15, neurologic symptoms in 11, and wheezing in 2. Operation was performed by thoracotomy in 42 (51.2%) cases and less invasive technique in 40 (48.8%) cases. Resection was completed in 80 patients (97.6%). Postoperative radiotherapy was administered in two cases. Intraoperative and postoperative mortalities were nil. Morbidity occurred in four patients (4.8%) including two prolonged air leaks, one hemothorax, and one chylothorax. Five-year survival was 97% (mean follow-up, 4.9 years). Malignant tumors had a worse prognosis ($p = 0.02$). No recurrence occurred during the follow-up neither for malignant nor for benign tumors.

Conclusion The treatment of choice for INTs is complete resection which will be tailored to tumor size, location, and extension. Long-term prognosis is favorable for benign neurogenic tumors.

Keywords
- mediastinal tumor
- nerves
- peripheral
- outcomes

Introduction

Primary intrathoracic neurogenic tumors (INTs) are unusual neoplasms arising from any of the neural elements in the thorax. They originate from the neural crest cells during the development of peripheral nervous system.[1–3] The most common location of these tumors, in 90 to 95%, is the paravertebral area in the superior mediastinum or chest wall, and exceptionally may be located inside the lung.[4] INTs account up to 34% of all mediastinal tumors and ~95% of tumors of the posterior mediastinum. Sometimes, these tumors may be located in the middle mediastinum originating from the vagus or phrenic nerves. Approximately 10% of INTs can extend into the spine giving rise dumbbell-shaped tumors.[5]

Classification of INTs is based on the origin of tumor cells: nerve sheath, nerve cells (ganglia), paraganglia, or peripheral nerve (►**Table 1**)[1,6,7] and represents 34 to 58% of all pediatric and ~20% of all adult mediastinal

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Table 1 Classification of primary intrathoracic neurogenic tumors according to their origin

Cell type	Benign	Malignant
Nerve sheath origin	Schwannoma (neurilemmoma) Neurofibroma	Malignant schwannoma Neurogenic sarcoma
Autonomic nervous system Paraganglionic nervous system	Ganglioneuroma Sympathetic: pheochromocytoma Parasympathetic: paraganglioma	Ganglioneuroblastoma Malignant pheochromocytoma Malignant paraganglioma

neoplasms.[1–6] The rate of malignancy in children is 40 to 60%, while in adult, it is 5 to 10%.[7]

Although most patients are asymptomatic at presentation, and observation alone may be considered as an option without surgery because they may remain stable for years, the majority of INTs should be removed because of the possible malignancy of tumors, dimensions, and extension into the spinal canal.

For many years, these tumors have been approached by a standard posterolateral thoracotomy.[2,5,8] Recently, less invasive approaches including video-assisted thoracoscopic surgery (VATS)[9–12] and robotic approach[13,14] have been used.

The aim of this study was to review our institutional experience in the treatment of INTs evaluating clinical, pathological, and long-term outcomes of these rare lesions.

Methods

This retrospective study was approved by our Institutional Review Board. We collected and analyzed the following data: demographics, presenting symptoms, surgical management, pathological features, and outcomes for patients with INT (benign or malignant) resected from May 1998 to June 2018 (►**Table 2**).

All patients received the following preoperative evaluations: detailed history and medical examination, chest X-ray, standard blood test, cardiorespiratory evaluation by spirometry and electrocardiography, and computed tomography (CT) scan. Positron emission tomography (PET) scan was performed in all the patients since 2002 as preoperative workup for undiagnosed intrathoracic lesion. Magnetic resonance imaging (MRI) was performed only in selected cases to evaluate the invasion and extent into the spinal canal and the relationship with nearby mediastinal structures in case of mediastinal lesions or the surrounding structures in case of the tumor located in the thoracic apex.

The study of collateral blood supply of vertebral vessel is important in case of tumors with intraspinal extension. In this setting, the usefulness of preoperative angiography to detect the position of the Adamkiewicz artery is controversial. In these cases, we prefer to use MRI which gives us sufficient information about collateral blood supply of vertebral vessel.

INTs' CT-guided biopsy has been performed when differential diagnosis of intrathoracic lesion was not possible. In every case, a core needle biopsy was performed.

Table 2 Clinical, surgical, and pathological characteristics of the population

Characteristic	Total
Patient population	82
Male/female	58 (70.7%)/24 (29.3%)
Mean age (range, SD)	53 y (29–75, 13.3)
Side (right/left)	33 (40.2%)/49 (59.8%)
Mean diameter (range, SD)	32 mm (12–68, 18.2)
Symptoms at diagnosis	51 (62.2%)
Cough	23 (28.1%)
Dyspnea	15 (18.3%)
Neurologic symptoms	11 (13.4%)
Wheezing	2 (2.4%)
Tumor location	
Posterior mediastinum	52 (63.4%)
Thoracic inlet	12 (14.6%)
Anterior mediastinum	7 (8.5%)
Lung parenchyma	5 (6.1%)
Chest wall	3 (3.7%)
Intraspinal extension	3 (3.7%)
Operation	
Thoracotomy	35 (42.7%)
Transmanubrial approach	7 (8.5%)
VATS	29 (35.4%)
Robotic	11 (13.4%)
Histology	
Benign	69 (84.1%)
Schwannoma	38 (46.3%)
Neurilemmoma	14 (17.1%)
Neurinoma	13 (15.8%)
Paraganglioma	4 (4.9%)
Malignant	13 (15.9%)
Malignant schwannoma	11 (13.5%)
Neurogenic sarcoma	2 (2.4%)
Residual disease	
R0	80 (97.6%)
R1	2 (2.4%)
Postoperative radiation	
No	80 (97.6%)
Yes	2 (2.4%)

Abbreviations: SD, standard deviation; VATS, video-assisted thoracoscopic surgery.

The follow-up included a clinical interview and CT scan performed at 1, 6, 12 months, and every 1 year after surgery. To confirm patients' status and survival, patients were followed up by phone call until July 2018.

Operative Techniques

Operative technique for resection of INTs included thoracotomy, transmanubrial approach, VATS, robotic approach, and posterior hemilaminectomy. Regardless of the surgical approach, the patients were intubated with a double-lumen tube and placed in a lateral position for thoracotomy or less invasive techniques and in a supine position for the transmanubrial approach. In case of thoracotomy, the surgical incision was performed through an intercostal space adjacent to the tumor limits to avoid entering the mass; in case of mini-invasive techniques, the approach differs according to VATS or robotic. For VATS approach, a 0-degree camera was inserted through a port at the midaxillary line through the sixth or seventh intercostal space and two working ports were usually positioned according to the tumor location. For robotic approach, the ports were positioned according to the tumor location (anterior mediastinum or posterior mediastinum) as previously described.[15] In every case, the tumor was mobilized with blunt dissection after the incision of the pleura covering the mass. Endoclips were used to tie intercostal and vertebral vessels supplying the tumor. After resection, the tumor was removed from the chest cavity by a specimen bag. INTs located in the lung parenchyma were treated by wedge resection or by lobectomy. In case of INT with intraspinal extension, the thoracic surgical approach was combined with an orthopaedic/neurosurgical approach via a laminectomy or hemilaminectomy.

Statistics

Discrete variables are reported as number and percentage, while for continuous variables, median and range or mean and standard deviation are reported as appropriate. Categorical variables are presented with absolute and relative frequencies. Survival was estimated by the Kaplan–Meier method. Pearson's chi-square or Fisher's exact test was used for evaluation of nominal variable. The p-values of < 0.05 were considered significant.

Results

Preoperative Assessment

A retrospective review of 14,365 thoracic surgical procedures performed at our division of thoracic surgery from 1998 to 2018 identified 82 patients operated on for INT representing 0.57% of all our surgical thoracic activity. Median age of patients was 53 years (range, 29–75 years). There were 58 men (70.7%) and 24 (29.3%) women (►**Table 2**). INTs were located on the right side in 33 (40.2%) patients and on the left side in 49 (59.8%) patients. In our series, the majority of INTs were benign ($n = 69$, 84.1%) mainly represented by schwannoma in 38 (46.3%), neurilemmoma in 14 (17.1%), and neurinoma in 13 (15.8%) cases. Paraganglionic tumors were rare as we had only four (4.9%) cases. We encountered only one patient with this condition who was associated with malignant schwannoma of the posterior mediastinum.

Symptoms associated with INTs are varied and listed in ►**Table 2**. In our series, a high rate of patients, 62.2% ($n = 51$), had clinical symptoms at presentation, which were mainly respiratory in 40 (48.8%) patients and included cough in 23 (28.1%), dyspnea in 15 (18.3%), and wheezing in 2 (2.4%). Neurologic symptoms at presentation occurred in 11 (13.4%) patients and included Horner's syndrome in 7 patients and neuralgia in 4 patients.

Preoperative evaluation included chest X-ray and chest CT scan in all 82 patients (►**Figs. 1A** and **2A**), PET in 79 (96.3%) (►**Figs. 1B** and **2B**), and MRI in 32 (39.0%). Tumor was located in the posterior mediastinum in 52 (63.4%) patients (►**Fig. 1C**), in the thoracic inlet in 12 (14.6%) (►**Fig. 2C**), in the anterior mediastinum in 7 (8.5%), in the lung parenchyma in 5 (6.1%), and in the chest wall in 3 (3.7%), and it presented an intraspinal extension in 3 (3.7%) (►**Table 2**). Preoperative diagnosis of INT was obtained in 24 (29.3%) patients by core needle biopsy performed under CT. No patient received preoperative therapy. Neurologic examination was required and performed in all cases of patients with neurological symptoms.

PET scan was used in 79 (96.3%) patients showing an increased uptake value for malignant tumors versus benign ones (mean maximum standard uptake value: 12.4 ± 4.2 vs. 5.7 ± 2.6, respectively; $p = 0.006$).

Surgical Approach, Final Pathologic Identification, and Short-Term Outcomes

The most frequently performed surgical approach was thoracotomy in 35 (42.7%) patients (5 posterolateral and 30 lateral muscle sparing procedures), and a transmanubrial approach in 7 (8.5%). VATS was performed in 29 (35.4%) patients and a robotic approach in 11 (13.4%) (►**Table 2**). All these less invasive approaches were completed and there was no conversion to thoracotomy. For lesions located in the chest wall ($n = 3$, 3.7%), three mass excisions together with chest wall resection were performed. All these three cases included benign schwannomas; in these three cases, the chest wall defect was repaired by prosthetic materials.

For INTs located inside the lung parenchyma, a wide wedge resection with almost 2 cm of free margins was performed in four (4.9%) cases and a lobectomy in one case. In the three patients presenting with an intraspinal extension of the INT, a hemilaminectomy was performed by the orthopaedic by a posterior approach after the removal of the tumor by the thoracic surgeon performed by VATS ($n = 2$) or thoracotomy ($n = 1$).

Neither intraoperative nor postoperative mortality occurred. Postoperative complications were reported in four (4.9%) patients and included prolonged air leaks ($n = 2$), hemothorax ($n = 1$) requiring reintervention for hemostasis, and chylothorax ($n = 1$) treated conservatively. No postoperative neurological complications occurred in our series. Of the seven patients with preoperative incomplete Horner's syndrome, two patients had a complete resolution of neurological symptoms, while in five patients, these neurological symptoms remained postoperatively. The average hospital stay was 4.6 days (range, 3–11 days); median postoperative stay was 4 days for minimal invasive group ($n = 40$) versus 6 days for open group ($n = 42$) ($p = 0.004$).

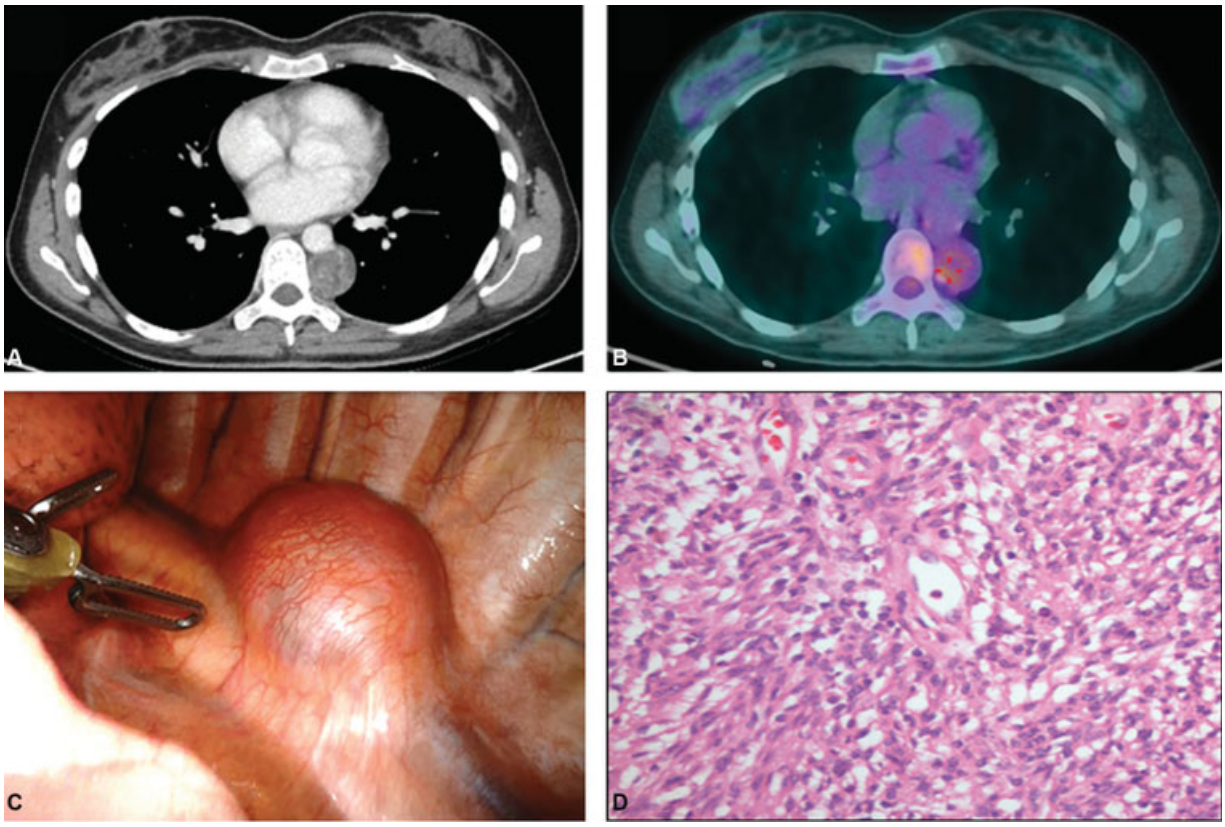

Fig. 1 (A) CT scan of a 56-year-old woman showing a left paravertebral schwannoma with the suspicious of aortic infiltration. (B) PET scan showing an inhomogeneous area of FDG uptake. (C) Intraoperative view of the robotic resection of the tumor. (D) Histopathological examination (HE ×20) showed a benign tumor composed of crowded, swirling nuclei of Schwann cells organized in fascicular areas. CT, computed tomography; FDG, fluorodeoxyglucose; HE, hematoxylin and eosin; PET, positron emission tomography.

Final pathology of the resected specimens revealed the following results: benign lesions occurred in 69 (84.1%) patients and malignant in 13 (15.9%) patients. Among the benign INTs, there were schwannoma in 38 (46.3%) cases (►**Fig. 1D**), neurilemmoma in 14 (17.1%), neurinoma in 13 (15.8%), and paraganglioma in 4 (4.9%). Among the malignant INTs, there were malignant schwannoma in 11 (13.5%) (►**Fig. 2D**) patients and neurogenic sarcoma in 2 (2.4%) (►**Table 2**). Resection was considered complete (R0) in 80 (97.8%) patients; 2 (2.2%) patients among malignant group of patients had microscopic infiltration of the margins (R1).

Follow-up and Survival

Follow-up was completed in all 82 patients. The mean follow-up was 4.9 years (range, 1.2–13.3 years) with an overall 5-year survival rate of 95% (►**Fig. 3**). Patients with malignant tumor had a worse prognosis ($p = 0.02$) (►**Fig. 4**). No recurrence occurred during the follow-up neither for malignant nor for benign INTs.

Postoperative radiation therapy was given to two (2.4%) patients, both with R1 disease. The treatment was effective and the patients did not have any local or distant recurrence.

Comment

Primary INTs are uncommon neoplasms and usually asymptomatic accounting for 95% of all the posterior mediastinal tumors.[1–4,6–8] The classification of neurogenic tumors includes (1) nerve cell (ganglion) tumors (ganglioneuroma and neuroblastoma), (2) nerve sheath tumors (schwannoma and neurofibroma), and (3) paraganglionic tumors.[1–4,6–8] Recklinghausen neurofibromatosis is an unusual genetic disease characterized by the presence of multiple neurogenic tumors. In our experience, we observed only one case with this disease that was associated with malignant schwannoma of the posterior mediastinum. In Ribet and Cardot's experience,[6] the Recklinghausen neurofibromatosis was associated with INTs in 14.1% of patients and approximately in half of the adult patients with malignant neurogenic tumors.

Preoperative radiological evaluation of INTs should include, in every case, a CT scan. All patients with INTs located in the posterior mediastinum, even if asymptomatic, should receive a CT scan for (1) evaluating the intraspinal extension of the tumor and (2) analyzing tumor location, margins, and features. However, the use of CT scan alone is not enough to correctly evaluate the neuroforaminal involvement.[16] MRI is considered the method of choice for the study of the intraforaminal involvement of the tumor. However, neither of these two methods is capable to differentiate the nature (benign vs. malignant) of the tumor.[17] In our experience, MRI was performed in 32 (39.0%) patients and we did not miss any intraspinal involvement in 4 patients.

The role of PET scan in the preoperative evaluation of INTs is not clear. Recent studies[18] emphasize the PET scan's role in the

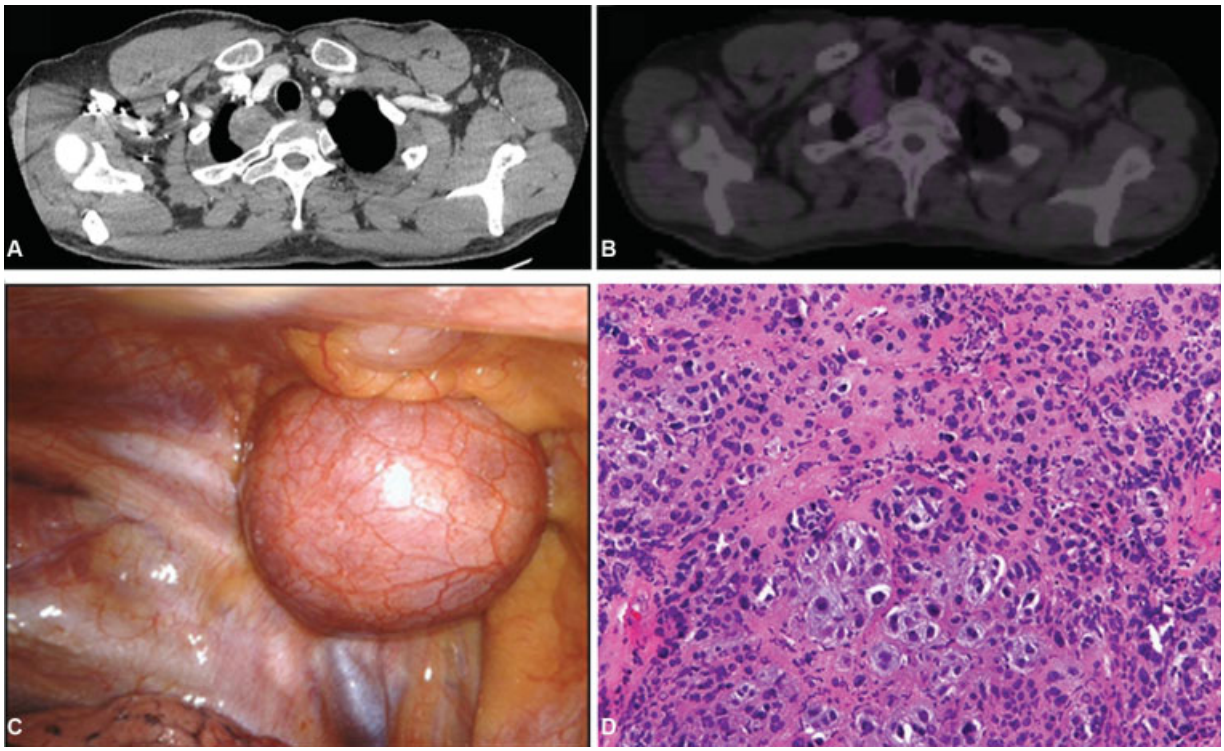

Fig. 2 (A) CT scan of a 49-year-old man showing a right paravertebral apical malignant schwannoma. (B) PET scan showing an inhomogeneous area of FDG uptake. (C) Intraoperative view of the tumor resection. (D) Histopathological examination (HE ×20) showed epithelioid Schwann cells that were distinctive and featured small round reniform nuclei with pinpoint nucleoli and occasional pseudoinclusions, some displaying atypical mitotic figures or necrosis. CT, computed tomography; FDG, fluorodeoxyglucose; HE, hematoxylin and eosin; PET, positron emission tomography.

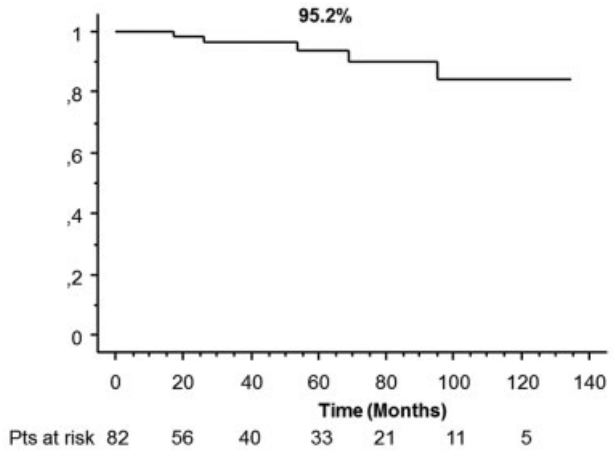

Fig. 3 Overall survival curve of the entire population.

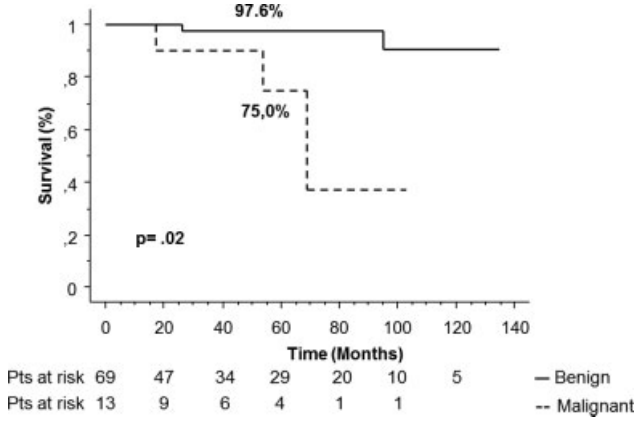

Fig. 4 Survival according to tumor nature: benign (*solid line*) versus malignant (*dotted line*) intrathoracic neurogenic tumors.

diagnosis of neurogenic tumors, above all, in case of schwannoma.[19] However, caution should be used in this preoperative tool to distinguish benign from malignant nature of INTs.

Preoperative needle biopsy of suspicious INTs is not generally required, above all for tumor located in the posterior mediastinum, because it is not useful for a definitive histological classification, and in case of benign tumor, the diagnosis has no impact on clinical management. Preoperative diagnosis appears necessary in case of tumor located in the anterior mediastinum or in the thoracic inlet to differentiate from a primary lymphatic disease or lung cancer (i.e., Pancoast's tumor), respectively. In our series, a preoperative diagnosis was performed in 24 (29.3%) patients by core needle biopsy performed under CT. All these cases were located in the anterior mediastinum ($n = 7$), chest wall ($n = 3$), thoracic inlet ($n = 12$), and lung parenchyma ($n = 2$).

In general, the radiographic appearance suspicious for INTs is sufficient to justify an early surgical exploration and resection in consideration of the continued growth of the tumor and the risk of malignancy.[10] More often, the absence of intraforaminal extension of INTs allows to remove them by VATS or thoracotomy[2–4,9–12] and, as recently reported, by a

robotic approach.[13,14] Both these two minimally invasive techniques (VATS and robotic approach) have recently gained acceptance as a valid alternative to thoracotomy for INTs located in the posterior. These less invasive techniques have many advantages: they allow (1) a good exposure of the mediastinum, (2) a reduction of surgical trauma, and (3) a brief hospital stay.[10–12] Thoracotomy is in general suggested for huge tumors, suspected to be malignant, and positioned in the costophrenic angle or in the apex of the thoracic.[10,20] Of 82 patients in our series, 40 (48.8%) underwent a minimally invasive approach for resecting INTs: 29 (35.4%) patients underwent VATS resection and 11 (13.4%) a resection by a robotic approach; an open approach was performed in 35 (42.7%) cases. In all cases, we had satisfactory results. VATS or robotic approach was used in case of small tumors (<6 cm). None of minimal invasive approaches needed conversion to open thoracotomy.

Occasionally, INTs situated in the apex of the thorax may extend into the neck creating particular difficulties for surgeons. In fact, in this particular area, tumor may be very close to vascular and nervous structures of the thoracic inlet, so that the superior border of the tumor may be not easily exposed. For this situation, different approaches have been proposed: a thoracotomic approach,[21] thoracoscopy,[22] anterior chest approach,[23,24] and a combination of these approaches.[20] However, thoracotomy and thoracoscopy may not be very useful to assess the anatomic relation of the tumor with vessels and nerves increasing the risk of vascular and nervous injuries during resection.[25] In our 12 cases of INTs located at the thoracic inlet (14.6%), we performed a transmanubrial approach in 7 (8.5%) cases due to the huge lesions and the suspicious of vascular and neurological involvement, and a lateral thoracotomy in the fourth intercostal space in the other 5 (6.1%) cases. These later cases were smaller, without suspicious of tissue infiltration, and well capsulated. We consider that for huge tumor of the apex and with the suspicious or the clear radiological evidence of neuro/vascular infiltration, the transmanubrial approach should be considered as the preferred surgical approach that allows the best control of all the anatomical structures and preserve the functions of the important nerves.

In case of tumors located in the apex, to avoid damaging the upper ganglion, we adopted the following precautions: since most neurogenic tumors have a well-defined capsule, they can be resected by simple enucleation; the pedicle of the tumor is always identified; and when the upper ganglion is directly involved, the nervous pedicle of the tumor is clipped and cut or resected by ultrasonic energy devices avoiding damage of the upper ganglion.

A particular consideration is required in case of dumbbell tumors, whose resection may be particularly difficult due to its location, intraspinal extension, and dimension. For this reason, it is important to establish before surgery the presence and degree of intraspinal extension and to evaluate each singular case in a multidisciplinary team that should include thoracic surgeons, orthopaedics, and/or neurosurgeons. For dumbbell tumors, various approaches have been suggested: a single-stage posterior approach by laminectomy, hemilaminectomy with partial costotransversectomy,[26] costotransversectomy with extension to a posterolateral thoracotomy,[27] and through a combined posterior and transthoracic approach performed either in one or two stages.[28] Advocates claim that this last approach seems useful and safe[29] with a minor risk for the segmental stability.[30] For this combined approach, both thoracoscopy and thoracotomy may be used for removing the thoracic component. In case of lesions completely located inside the chest and with a small extension into the spinal canal, their resection may be performed by thoracotomy or thoracoscopy alone.

In our series, all the three cases of dumbbell tumors were removed by a two-stage intervention performed through a combined orthopaedic and thoracic surgical approach: in all the three cases, the tumor was first approached by the thoracic surgeon by VATS ($n = 2$) or thoracotomy ($n = 1$) with the patient in a lateral position and then by the orthopaedic who performed a hemilaminectomy in a prone position. We amputate the tumor at the neuroforamen only in one case due to its enlarged size. In our experience, postoperative and long-term outcomes after resection of dumbbell tumors were very good, without any postoperative complications.

Intrapulmonary localization of INT is very rare; of these, schwannoma represents the most common type in this anatomic region[7] accounting for 0.2% of all pulmonary neoplasms and in a literature review, 62 cases of schwannomas with intrapulmonary or bronchial location have been reported.[30] In our study, five (6.1%) cases of lung parenchymal neurogenic tumors have been diagnosed, four schwannomas and one intrapulmonary paraganglioma.

From a surgical point of view, it is difficult to demonstrate statistically significant conclusions in this cohort due to the small number of patients and the different pathological features of these tumors. According to our experience, we think that surgical resection plays a positive role as part of the treatment paradigm for these intrathoracic neoplasms. The observation of the long-term results in terms of survival of the entire population allows us to confirm that there is a survival benefit for surgical treatment of these rare cancers. In fact, comparing the two population of patients with or without malignant features, it is evident the best prognosis for patients with benign tumors even if the 5-year survival rate for the malignant group remains considerably high (75%).

In conclusion, at the light of our experience, we may confirm that the surgical treatment of INTs guarantees good long-term results proving it to be the treatment of choice of these tumors. In fact, we confirm that long-term prognosis is favorable for benign INTs even if malignant INTs reach a satisfactory 5-year survival rate (75%, in our series). Surgical approach should be personalized according to location, tumor size, and extension of the tumor. In case of benign INTs without neuroforaminal involvement, they can be completely removed by thoracoscopy. Thoracotomic approach is indicated for large tumors. In case of INTs located at the thoracic inlet or extended in the cervical region, a transmanubrial or a combined transthoracic approach is recommended. In case of dumbbell tumors, it is suggested to use a posterior approach with hemilaminectomy

plus thoracotomy/VATS. Careful evaluation and preoperative diagnosis are essential and intraoperative attention to avoid neurologic complications can lead to a successful operation with excellent results. Finally, adjuvant radiotherapy should be considered as an appropriate and effective treatment in case of incomplete resection of malignant INTs.

Conflict of Interest
None declared.

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