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CASE STUDY

DIAGNOSTIC CRITERIA AND THERAPEUTIC ADVANCES IN INTRATHORACIC SCHWANNOMA

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ABSTRACT

Background: Schwannoma is a benign neoplasm derived from Schwann cells. It is usually located in the intracranial nerves, however intrathoracic presentation is possible, leading to compression of adjacent structures and symptoms. The absence of findings on physical examination and the presence of mild symptoms (or absent) and common to other diseases makes the challenging diagnosis, accomplished through imaging. Treatment consists of surgical resection by thoracotomy or thoracoscopy. This study aimed to review these subjects, with an emphasis on the diagnostic and therapeutic approaches currently available. Method: Articles were selected by searching the Scopus, Scielo, PubMed and Web of Science databases using the Key words: schwannoma, neurinoma, neurilemmoma, nerve tissue neoplasm, thoracotomy, thoracoscopy and mediastinal neoplasms. Results: Intrathoracic schwannoma often presents as asymptomatic and is identified during routine imaging tests. The recommended treatment is surgical resection by thoracoscopy or thoracotomy.

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INTRODUCTION

Tumors of neurogenic origin make up 20% of such tumors in adults and 25% in children; the vast majority are benign and are classified as tumours originating from nerve cells (ganglioneuroma and neuroblastoma) and nerve sheath tumours (Schwannomas and neurofibromas) (Ruiz-Velasco et al., 2011). Schwannoma (neurilemmoma) was recognized and identified for the first time in 1910 by Verocay and is defined as a neoplasm exclusively composed of Schwann cells of the nerve sheath, which generally affect sensitive fascicles of the cranial and intercostal nerves (Rodríguez et al., 2004). Schwannomas are derived from Schwann cells belonging to the peripheral nervous system whose role is to produce myelin for axons (Ortigara et al., 2006). They occur in close proximity to

the nerve of origin, are greyish encapsulated masses, and can present cystic areas (Ortigara et al., 2006). They are usually benign, grow slowly, and can emerge at any age, although they are more common in people over 40 years old, and show no preference for sex or ethnicity (Ortigara et al., 2006). Schwannomas occur most commonly as cranial nerve VIII tumors (acoustic neuroma) (Ortigara et al., 2006). Although they are asymptomatic and are discovered accidentally by imaging tests, when extradural, their most common presentation is through tumour masses that can compress surrounding structures, becoming symptomatic in the process, as is the case for schwannomas from intrathoracic organs (Ortigara et al., 2006; Sawas et al., 2009; McCarthy and Cox, 2014; Westphal et al., 2002). Most tumours of intrathoracic organs originate in the posterior mediastinum (posterior paraspinal groove), and only 5.4% arise from the chest wall (McClenathan and Bloom, 2004). These tumors are difficult to diagnose and suspicion of diagnosis is the result of analysing the format of surgical specimens and cell arrangement and the immunohistochemical detection of the S-100 protein

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(Rodríguez *et al.*, 2004). A mutation of the tumor suppressor gene NF2 shows a close relationship with the presence of schwannoma (Ortigara *et al.*, 2006). The recommended treatment is surgical resection by thoracotomy or thoracoscopy. In the medical literature, few cases of mediastinal schwannomas exclusively treated by thoracoscopy have been reported (Ortigara *et al.*, 2006; Sawas *et al.*, 2009; McCarthy and Cox, 2014; Westphal *et al.*, 2002).

MATERIALS AND METHODS

This review article was based on electronic searches in the PubMed, Scielo, Scopus and Web of Science databases. We collected data from case reports, cohort studies and literary reviews using the keywords “schwannoma”, “neuroma”, “neurilemmoma”, “nerve tissue neoplasm”, “thoracotomy”, “thoracoscopy” and “mediastinal neoplasms”. The method raised the following guiding question: “What are the main results and scientific evidence identified in national and international publications, concerning the therapeutic approach to intrathoracic schwannoma?”. In the initial survey, the articles were evaluated by seven researchers (authors) according to the following inclusion criteria: articles published in Portuguese, English or Spanish using the selected keyword combinations and published between 1969 and 2015 that were readily accessible. After the initial selection of material, articles repeated in different databases and that featured other tumors occurring in intrathoracic organs unrelated to schwannoma were excluded. The final sample included 47 scientific articles.

RESULTS

Epidemiology

Neurogenic tumors account for approximately 20% of all mediastinal neoplasms in adults and approximately 25% in children. Schwannomas and neurofibromas are neurogenic tumors of the posterior mediastinum (Westphal *et al.*, 2002). The majority of neurogenic tumors in the posterior mediastinum originate from intrathoracic organs, while only 5.4% grow on the chest wall (Aruj *et al.*, 2014). Schwannomas most commonly originate from the extremities, head and neck (Dahl, 1977). Though these tumors occur in adults, they are often observed at younger ages (Khanlou *et al.*, 1998). They usually affect people in their thirties and forties, although at present, patient age ranges from six to 78 years old and no predilection for sex or ethnicity has been reported (Westphal *et al.*, 2002).

Pathology

Typically, the intercostal nerve lies between the innermost intercostal and internal intercostal muscles. An additionally, this nerve lies along the subcostal groove together with the intercostal blood vessels. It is known that when the neurilemmoma grows towards the external chest wall, it may be blocked by the bottom edge of the adjacent rib (Jun Ahn *et al.*, 2014). Because of this growth, schwannomas that originate from the intercostal nerve can project lumps into the thoracic cavity. It is worth noting that there are two possible forms of growth: tumors that develop within and those outside the thoracic wall (Jun Ahn *et al.*, 2014; Queiroz, 1999). The first is the neurilemmoma, which arises from the lateral cutaneous branch of the main intercostal nerve. On the chest wall, the

intercostal nerve traverses a subcostal course and provides lateral cutaneous branches around the medial axillary line, passing through the subcutaneous layers prior to and after this line (Jun Ahn *et al.*, 2014; Osborn, 1999). The second possibility is an anatomical variation. The intercostal nerve can trace a path away from the subcostal groove, blocking the growth of external neurilemmoma (Jun Ahn *et al.*, 2014). Schwannoma is a neoplasm originating from the Schwann cells of the nerve sheath that usually affects sensitive fascicles of the cranial and intercostal nerves (Queiroz, 1999). Cranial nerve VIII is the most affected (Osborn, 1999). Schwannomas are encapsulated hard greyish masses that remain in close proximity to the nerve of origin, and areas of cystic changes and xanthomatosis have been reported (Robbins *et al.*, 2005). These tumors present two distinct growth patterns: Antoni A and Antoni B, can present multiple degenerative changes, such as nuclear pleomorphism, xanthomatous change and vascular hyalinization, with no prognostic differentiation (Ortigara *et al.*, 2006). The growth pattern of cells present in Antoni A regions shows elongated fusiform nuclei, with cytoplasmic expansions arranged in bundles in areas of moderate to high cellularity with minimal stroma matrix; “nuclear-free zones” of expansions are situated between the regions of palisaded nuclei associated with Verocay bodies (Queiroz *et al.*, 1999). The Antoni B growth pattern exhibits thinner cells loosely arranged within microcystic spaces and myxoid change. The cells present minimal cytoplasm, within which thin, ill-defined extensions are observed that are not arranged into bundles (Osborn, 1999). The material between the cells is highly hydrated and is matched by the increased T2 signal visualized with MRI (Robbins *et al.*, 2005; Kano *et al.*, 2009). In most cases, a mutation of the tumor suppressor gene NF2 occurs on chromosome 22. There are three types of NF2 that are distinguished according to their clinical presentation and severity: Wishart, Gardner and mosaic type NF2. The Wishart type appears in childhood or late adolescence and consists of bilateral vestibular schwannomas associated with medullary tumours, whereas the Gardner type appears later, is less debilitating, and presents as bilateral vestibular schwannomas, with few meningiomas (Kano *et al.*, 2009). Malignant transformation is extremely rare in this type of tumor, although local recurrence following resection may be incomplete (Robbins *et al.*, 2005).

Clinical presentation and diagnosis

Thoracic schwannoma tumor growth is slow, which results in a poor clinical condition with few or no symptoms, especially in the early stages. However, when the tumor reaches large proportions, commonly presenting as a bulky mediastinal mass, symptoms can arise as a consequence of the compression site, such as superior vena cava syndrome, dyspnea or dysphagia (Ortigara *et al.*, 2006; Behuria *et al.*, 2015). Sometimes schwannomas can develop in the trachea through the intercartilaginous membrane, forming an hourglass shaped tumor. In the presence of bone erosion, severe pain or pathological fractures are common (Osborn, 1999). In approximately about 10% of cases, growth can exceed the intervertebral foramen and compromise the spinal canal by an hourglass shaped growth that causes paresthesia or paralysis. When this type of growth occurs, symptoms of intramedullary extension are present in 60% of cases (Georghiou *et al.*, 2003; Akwari *et al.*, 1978; Shields, 2000). Additionally, patients can present more severe signs, such as hemoptysis when the tracheobronchial tree is affected, or gastrointestinal bleeding,

as in cases involving the esophagus. Dysphonia can occur with vagus nerve involvement prior to the origin of the recurrent nerve (Katoh *et al.*, 1995; DeVault *et al.*, 1992; Dabir *et al.*, 1990). Schwannomas usually occur alone, arising from any cranial or peripheral nerve, and it is very rare to find multiple schwannomas arising from a single intercostal nerve (Chen *et al.*, 2008). The investigation of intrathoracic schwannomas begins with a full medical history and physical examination, followed by imaging tests. The majority of lesions are diagnosed in young adults, with no predominance of sex (Ortigara *et al.*, 2006). Chest radiography in posterior lateral incidence and profile is usually the first test to detect any changes. The visualization of Tumor becomes more evident when it reaches large diameter, which is not common until symptoms arise resulting from the occupation (Figure 1).

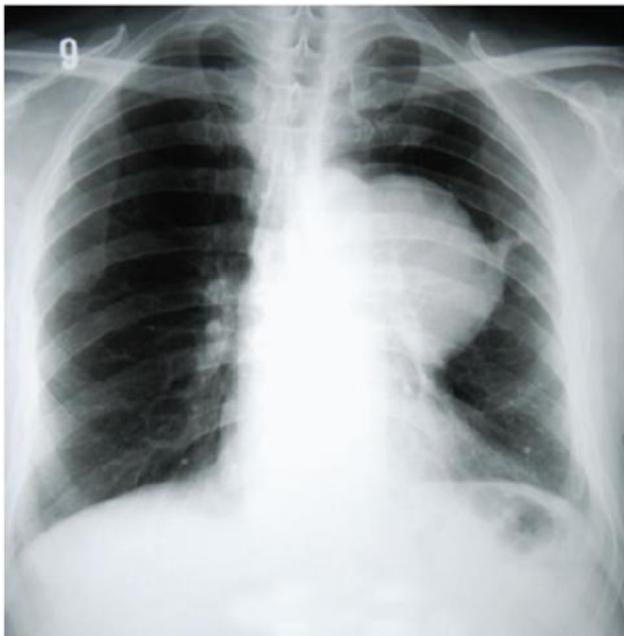


Figure 1. A well-circumscribed mass at the middle lung field. From: Ceberut K, Naseri E, Celik A, Muslehiddinoglu A, Ergin I. One-Stage Combined Thoracic Ancient Schwannomas Total Removal and Coronary Artery Bypass Kadri. Case Reports in Medicine, 2011

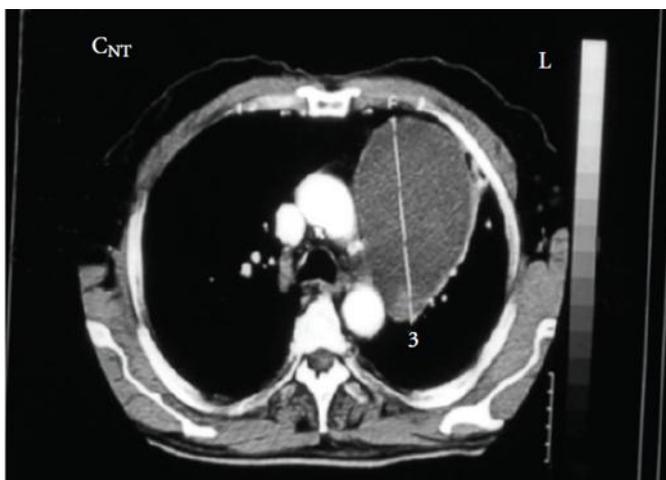


Figure 2. Computed tomography shows homogeneous cystic mass at the costosternal junction. From: Ceberut K, Naseri E, Celik A, Muslehiddinoglu A, Ergin I. One-Stage Combined Thoracic Ancient Schwannomas Total Removal and Coronary Artery Bypass Kadri. Case Reports in Medicine, 2011

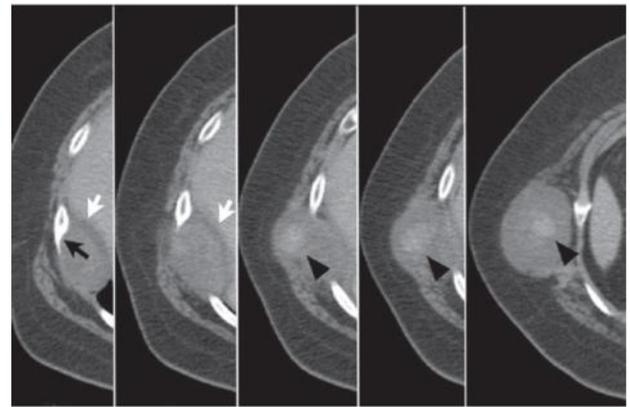


Figure 3. Axial post-contrast CT revealing the inner component of the mass compressing the liver (white arrows) and bulges through the intercostal space into the outer thoracic wall. The tumor erodes the adjacent inferior margin of the 9th rib (black arrow) and shows central enhancement (black arrowheads). From: Ahn SJ, Park KJ, Sun JS, Choi H, Lee YH. Neurilemmoma Showing a Unique Growth Pattern in the Lateral Chest Wall: Both Inside and Outside the Thoracic Cavity. Ann Thorac Cardiovasc Surg, 2014;20:558–60

Generally, this test defines which portion of the mediastinum is involved, but does not reveal tumour density, invasion the medullary canal or adjacent structures (Dabir *et al.*, 1990). Regarding computed tomography (CT) scan, the tumor usually presents itself as a homogeneous mass (Figure 2) with soft tissue density (Chen *et al.*, 2008; Cohen *et al.*, 1986; Hasuo *et al.*, 1993). The presence of hypodense areas corresponds to areas of necrosis or hemorrhage. Neurilemmomas are characterized by several pathological areas: hypocellular areas adjacent to densely cellular areas or proximal to collagen or xanthomatous change (Dabir *et al.*, 1990; Cohen *et al.*, 1986). Although less common, the mass can destroy the bone surrounding regions, resulting in CT images with hypodense areas (Figure 3). In CT, lesion appearance can be highly variable, but is usually well circumscribed (Hasuo *et al.*, 1993). In contrast, magnetic resonance imaging (MRI) shows better definition of the involvement of nerve plexi, vertebrae and the spinal canal. Hyper intense areas in T2 images correspond to cystic degeneration in the tumor (DeCamp *et al.*, 1996). MRI must be performed in patients with suspicion of neurogenic tumors of the posterior mediastinum, to exclude extension of the tumor in the intraspinal region (Chen *et al.*, 2008). As a result, from the moment the tumor develops, typical MRI signals (high intensity) can be observed that enable a very precise diagnosis. Thus, preoperative radiological assessment alone is sufficient, i.e., fine needle aspiration is unnecessary (Sakai *et al.*, 1992). By defining tumor extension more precisely, MRI enables preoperative planning that is more sensitive than CT at delineating the presence or absence of invasion through the neural foramen and the degree of involvement of the vertebral canal (Hasuo *et al.*, 1993). The diagnosis can be confirmed intraoperatively and by histopathological analysis (Cohen *et al.*, 1986). Ancient schwannoma is a rare variant of the tumor that presents degenerative histological changes that can lead to an incorrect diagnosis of malignancy. This rare status can simulate lung neoplasms on chest x-rays and CTs (Petteruti *et al.*, 2008). The radiological features of ancient schwannoma are not well defined due to its rarity. However, the long-term progression of the tumor leads to characteristic degenerative changes, such as cystic formation, calcification, hemorrhage and hyalinization. Its appearance on CT and MRI is typical of this

type of tumor (Dabir *et al.*, 1990; Cohen *et al.*, 1986). Solid components encapsulated with cystic areas, or the presence of cystic masses with marginal growth or with solid nodular components that present calcifications are observed (Isobe *et al.*, 2004; Takeuchi *et al.*, 2008). Some authors suggest that a recommendation for surgical treatment must be considered when a patient has a hyper vascular mass in soft tissues containing amorphous calcification on the simple scan and cystic areas on the MRI (Cohen *et al.*, 1986; Hasuo *et al.*, 1993). The suggestion is that calcification of soft tissue, which is visible in a simple scan, is a characteristic indicative of this pathological entity (Schultz *et al.*, 1994). A definitive diagnosis is only possible after histopathological examination. The most significant histological characteristics of these tumors are the presence of a high degree of nuclear atypia, with the presence of atypical hyperchromatic polymorphic cells and nuclei that frequently contain multiple lobes (Petteruti *et al.*, 2008; Ceberut *et al.*, 2011). Fine needle biopsy can be useful in the diagnosis of anterior and posterior mediastinal tumors, but this technique is difficult to execute in the middle mediastinum because the amount of material is limited; thus it is not recommended for diagnosing these processes (Dabir *et al.*, 1990; Shirakusa *et al.*, 1989). Microscopy reveals two distinct types of tissue, according to the Antoni classification: type A, corresponding to the cellular area, and type B, corresponding to the myxoid area. These two forms are usually associated in the same tumor (Shields, 2000). Benign schwannomas are distinguished by the presence of a biphasic pattern (Antoni A and B) with the presence of Verocay bodies in the type A pattern. These bodies are formed by two parallel lines of nuclei with a space between them that is virtually anuclear (Ahn *et al.*, 1994). Immunohistochemical analysis shows immunoreactivity for the S-100 protein, as reported for neurogenic tumors (Ribet and Cardot, 1994).

Thoracotomy x Thoracoscopy

The treatment of choice for mediastinal schwannomas is resection by videothoracoscopy or open thoracotomy (Strollo *et al.*, 1997). Thus, surgery is the main therapeutic route for neurogenic tumors of the mediastinum, and complete surgical resection is considered the gold standard (Harjula *et al.*, 1986). The management of neurilemmomas located in the mediastinum is determined by the findings of CT or MRI exams. However, these findings only refer to intrathoracic tumors, or those that extend into intervertebral channels due to visualization difficulties (Hasuo *et al.*, 1993; Liu *et al.*, 2014). Benign neurogenic tumors rarely reappear, and simple enucleation is sufficient; no adjuvant therapy is required. The challenge is to preserve nerve function, particularly when the tumor occurs on the phrenic or vagus nerve (Harjula *et al.*, 1986). Preservation of the recurrent laryngeal nerve is essential to prevent paralysis of the same, i.e., postoperative dysphonia. In resections of the vagus nerve below the origin of the recurrent nerve, no cardiac, bronchial or gastrointestinal changes have been observed (Besznyák *et al.*, 1985; Davis *et al.*, 1991). When the tumors originate on the intercostal nerves, if necessary, the nerve root can be sacrificed, resulting in relatively minor deficits (Harjula *et al.*, 1986). It is important to note that episodes of bleeding, cerebrospinal fluid leakage through the intervertebral foramen and paraplegia may be consequences of complete resection attempts of mediastinal neurogenic tumors (Lacreuse *et al.*, 2007; DeCou *et al.*, 2005; Horiuchi *et al.*, 2004). Assuming that the incomplete resection

of the lesion does not affect child's survival, surgeons are encouraged to try resection of these lesions by thoracoscopy (Lacreuse *et al.*, 2007; DeCou *et al.*, 2005; Horiuchi *et al.*, 2004). However, video-assisted thoracoscopy is effective for the removal of mediastinal tumors in children, especially neurogenic tumors as it enables complete resection, histological diagnosis of the lesion and absence of recurrence at the site of placement of the trocars (Guye *et al.*, 2007). In addition to the normal risks of thoracic surgery, such as hemorrhaging, infection and pulmonary morbidity, certain neurological complications can arise due to resection (DeCamp *et al.*, 1996). Among these, those that should be mentioned include deficitssuch as Horner's syndrome, partial sympathectomy, recurrent laryngeal nerve injury and paraplegia (Harjula *et al.*, 1986). Thoracotomy is a viable approach for masses in the middle and posterior mediastinum and is also adequate for the anterior mediastinum if the mass is fully contained within one hemithorax and does not cross the midline (Ortigara *et al.*, 2006). Video-assisted thoracoscopic surgery (VATS) was fully disseminated in the 1980s following technological improvements and consolidation of the laparoscopic technique. Indications for resection by videothoracoscopy include biopsy to exclude malignancy, relief of compressive symptoms, to prevent extension of a tumor into the spinal foramen and to prevent malignancy (Westphal *et al.*, 2002; McClenathan and Bloom, 2004; Aruj *et al.*, 2014). In video-assisted surgery, the patient is positioned as per a lateral thoracotomy, and the camera is introduced into the fifth intercostal space, posteriorly for anterior mediastinal masses and anteriorly for posterior masses. Other accesses depend on the location of the mass. Postoperative recovery of neurological function depends on the type of surgery (Ortigara *et al.*, 2006; McClenathan and Bloom, 2004; Behuria *et al.*, 2015). Among the majority of reported cases that exclusively used the VATS technique to resect mediastinal masses, a high degree of success was obtained, demonstrating the safety of the procedure in the hands of properly trained surgeons. When compared with thoracotomy, VATS requires smaller incisions, which reduces pain, causes fewer and less severe pulmonary complications, shortens hospitalization and promotes earlier return to activities and aesthetic gains. Prognosis after surgery is good, but local recurrence can occur following incomplete resection of the lesion (Ortigara *et al.*, 2006). In some cases, it is possible complete resection of the mass with preservation of important structures, especially if the mass is completely contained within a hemithorax (Figure 4).

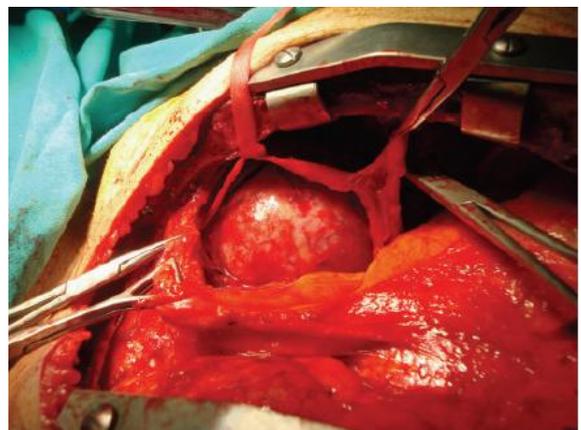


Figure 4. Operative view after sternotomy and preserving nervus vagus; huge mass occupying aortic arch. From: Ceberut K, Naseri E, Celik A, Muslehiddinoglu A, Ergin I. One-Stage Combined Thoracic Ancient Schwannomas Total Removal and Coronary Artery Bypass Kadri. *Case Reports in Medicine*, 2011

If complete resection cannot be performed, a common situation when dealing with malignant tumors, postoperative radiation therapy is the recommended course of action. Occasionally, postoperative chemotherapy can also be effective (Cohen *et al.*, 1986; Hasuo *et al.*, 1993). The majority of mediastinal neurogenic tumors occur in the posterior compartment, and the best surgical approach is a standard thoracotomy. However, VATS is an excellent choice for simple neurogenic tumors (Canvasser and Naunheim, 1996; Bousamra *et al.*, 1996). Tumor excision is curative, since the recurrence of benign schwannomas is unusual (Dabir *et al.*, 1990; Heitmiller *et al.*, 1990). Malignant degeneration of a benign tumor has been described, but it is rare (Das Gupta *et al.*, 1969). Although rare and infrequent, intrathoracic schwannomas of the vagus nerve should be included in the differential diagnosis of mediastinal tumors (Dabir *et al.*, 1990). Conducting a preoperative assessment of intraspinal involvement is essential to decrease the risk of hemorrhaging into the spinal canal and spinal cord damage (Takeuchi *et al.*, 2008; Schultz *et al.*, 1994; Ceberut *et al.*, 2011). When a tumor is identified in this region, the recommended approach is thoracic surgery and neurosurgery. Initially, this process was performed in phases, beginning with a laminectomy and followed by a thoracotomy at a later date (Akwari *et al.*, 1978; Grillo *et al.*, 1983). Currently, the preferred option is performing the procedure in a single operation, in which combined resection is the method of choice. This can be performed through separate incisions or a shared incision (Sawas *et al.*, 2009). A single incision with a vertical component along the spine, and a curvilinear lateral extension, allows access to both specialties. Thus, a laminectomy can be performed to remove the intraspinal component, while the thoracic component can be excised by thoracotomy (Khanlou *et al.*, 1998; Jun Ahn *et al.*, 2014; Queiroz, 1999; Osborn, 1999). This allows for excision of the entire mass and minimizes the risk of undetectable hemorrhage inside the spinal canal, where a hematoma could result in neurological deficit (Akwari *et al.*, 1978; Grillo *et al.*, 1983). More recently, Vallières *et al.* described an approach that uses posterior microneurosurgical techniques and anterior VATS techniques to perform a minimally invasive complete resection (Vallières *et al.*, 1995). A careful preoperative assessment is essential to clarify whether there is any spinal canal or neural foramen involvement, so that the risks of hemorrhage and neurological damage can be significantly reduced (Sawas *et al.*, 2009; McCarthy and Cox, 2014; Westphal *et al.*, 2002). Treatment involves complete surgical resection via thoracotomy or thoracoscopy with neurosurgical exploration to verify whether the tumor has extended into the spinal canal (Sakai *et al.*, 1992; Petteuti *et al.*, 2008). Although recurrence is rare and patients present a good prognosis, since the tumor is benign, when dealing with malignant neurogenic neoplasms, prognosis is poor (Ortigara *et al.*, 2006). Fine needle biopsy can be performed; however, a precise diagnosis may not be possible due to limited cellularity. This raises the possibility of a misdiagnosis of malignancy because the appearance of histological degenerative changes can occur. Surgical excision of the mass is the gold standard for the diagnosis and treatment of these potentially resectable tumors (Tahir *et al.*, 2007).

Conclusion

Intrathoracic schwannoma is often asymptomatic, and the lesion is usually detected in routine imaging tests. Thus, this diagnosis is a challenge and should not be discarded a

diagnostic hypothesis in the presence of mediastinal masses. Magnetic resonance imaging is the preferred imaging technique for preoperative planning because it allows clearer observation of the involvement of nervous plexi, vertebrae and the spinal canal. The recommended treatment remains resection by thoracotomy or VATS, and recurrence of benign neurogenic tumors following the procedure is rare and does not require adjuvant therapy. In addition to the risks common to any thoracic surgery, neurological complications should be taken into consideration when planning the surgical approach. Among the surgical approaches, open surgery continues to be the most commonly used method for treatment. VATS assists in the realization of biopsies to exclude malignancy, to relieve compressive symptoms and to prevent extension of the tumour into the spinal foramen. In cases where VATS is used for tumor resection, prognosis is good, but relapse can occur when the resection is incomplete, and complementary treatment with chemotherapy or radiotherapy is recommended. In the medical literature, few cases of thoracoscopic mediastinal schwannomas exclusively treated by VATS have been reported. However, all the surgical modalities are viable options, and the method should be applied on a case-by-case basis. In this context, doctor and patient should be similarly engaged in choosing the best method to achieve the expected result.

List of abbreviations

CT: Computed Tomography
MRI: Magnetic Resonance Imaging
VATS : Video-Assisted Thoracoscopic Surgery

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Consent for publication

Not applicable

Availability of data and material

Not applicable

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