Review Article

Robotic approach for early stage thymic tumors—surgical and oncologic outcomes

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Abstract: Thymoma is a rare tumor with epithelial origin, which represents about 50% of the malignant lesions of the anterior mediastinum. This neoplasm is often associated with myasthenia gravis (MG), in fact, about 30% of the patients with thymoma develops symptoms of myasthenia. The gold standard in the treatment of thymoma is surgical resection and according to ITMIG guidelines is recommended extended thymectomy, particularly in myasthenic patients. For a long time, sternotomy has represented the approach of choice for the exeresis of anterior mediastinal lesions. Nevertheless, nowadays, the advancement of new technologies has allowed the use of minimally invasive methods such as robotic surgery.

Keywords: Robotic surgery; thymectomy; thymic tumors; myasthenia gravis (MG); thoracic surgery

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Thymoma is a rare tumour with epithelial origin, at intermediate malignancy, which represents about 50% of malignant lesions of the anterior mediastinum. The most affected age group is between 50 and 70 years with a higher prevalence in women (1). Due to their anatomical localization, slow growth and poor symptoms, thymic tumours are still diagnosed by chance in only 30 percent of the patients (1). This neoplasm is often associated with paraneoplastic syndromes, particularly with myasthenia gravis (MG), in fact, about 30% of patients with thymoma develops symptoms of myasthenia. Presence of MG is not an independent prognostic factor but it revealed an important role of early diagnosis of thymomas (2). Other syndromes thymoma-associated can be red cell aplasia, pemphigus, immunoglobulin immunodeficiency, Lambert-Eaton. Thymoma has a very slow growth and may be asymptomatic in most cases. At the time of diagnosis, about 40% of patients show signs of irritation of the phrenic nerve or dyspnoea and cough, caused by ab-extrinsic compression of the trachea and symptoms of MG (3). The superior vena cava syndrome, on the other hand, is a much more rare condition associated with the presence of larger lesions that often require an open surgical approach (4).

CT scan and MRI play a fundamental role in the diagnosis of anterior mediastinal tumors. They should be performed on all patients diagnosed with MG or whenever the chest X-ray shows an enlargement of the mediastinum opacity. MRI represents a better choice than CT scan to study the anatomical distance between the lesion and mediastinal structures (5).

When considering the histological staging, according to the data in the literature, 40% of the thymomas presented at stage I, 25% at stage II and III and 1–3% at stage IV. In the case of stages II or III it is often documented an invasion of mediastinal tissue in 50% of patients, with pleural invasion in most cases. In these stages about 30% of the patients have an involvement of innominate vein and 20% of phrenic nerve (6).

Surgical treatment is considered the gold standard treatment in case of early-stage thymomas. Therefore, after a correct diagnostic pathway and an appropriate neurological evaluation for the diagnosis and the treatment of the myasthenic symptoms, patients with early-stage thymoma (Masaoka I, II) may be considered good candidates for surgery (7). As recommended by the ITMIG guidelines, an extended thymectomy should be performed as an early-stage treatment, also in non-myasthenic patients so to avoid the risk of developing MG in the post-operative period (8). The extended thymectomy consists in the complete resection of thymus "*en bloc*" with the anterior mediastinal fat tissue, after the identification of the phrenic nerve bilaterally, from the jugular area to pericardial fat (9).

The surgical treatment is essential to ensure the oncological radicality in thymoma patients and to ensure the remission of neurologic symptoms in patients with MG. To obtain positive oncologic and neurologic results it is mandatory to remove the thymus and all the adipose mediastinal tissue between the two phrenic nerves, as suggested by ITMIG (9). Open sternotomy has represented for a long time the surgical approach of choice for the optimal visualization of the mediastinal lodge, simplifying the complete dissection of the thymic gland *en bloc* with mediastinal adipose tissue, after the identification and isolation of the phrenic nerves sideways and innominate vein in rostral position. In presence of invasion of neighbouring organs, longitudinal median sternotomy also ensures an easy *en bloc* resection of all the structures adherent to the neoplasm (9,10).

After the first thoracoscopic thymectomy reported in 1993 by Sugarbaker, the minimally invasive approach has become, whenever possible, a widespread option for the treatment of thymic disease (11). Video-assisted thoracoscopic surgery (VATS) and robotic surgery, due to the low surgical trauma, the good aesthetic results and positive post-operative results, have proven to be effective (12).

The VATS approach includes unilateral and bilateral access. Some surgeons prefer the left approach due to the fact that the pericardiophrenic angle on this side is not occupied by the superior vena cava. On the other hand, other authors prefer the right approach where the vena cava constitutes a landmark for the identification of the innominate vein (13). In the bilateral VATS approach, some surgeons report a more radical excision due to the better vision of mediastinum (14). In the most recent years, robotic surgery has represented a further evolution in the treatment of thymoma with minimally invasive technique (15).

Robotic surgery represents the latest evolution of minimally invasive surgery. Taking advantages of robotic system features (3D ×10 zoom vision, 7DOF, tremor filtration), the surgeon is able to perform the surgical procedure, respecting all the steps of the extended thymectomy, in safe and efficient manner, similar to the open approach, as suggested by NCCN guidelines (9). Moreover, when compared to open surgery, the robotic approach is associated with shorter hospitalization, lower postoperative complication rate and better quality of life. Also, oncologic outcomes after robotic thymectomy appear to be positive and comparable with open approach. In the last decade, several robotic thymectomy techniques have been described, left or right-side approach, bilateral accesses or single-port sub-xiphoid approach (16).

Some surgeons when performing robotic thymectomy prefer the right-side approach due to the larger space present in right side of the chest cavity and the wider visibility of superior cava and the innominate vein. Other authors use the left side approach for a better management of the whole thymic lodge and the greater easiness to remove the left pericardiophrenic fat tissue of mediastinum. This approach ensures the possibility to obtain a good radicality in the execution of thymectomy, allowing a safe isolation of innominate vein and a great control of the left phrenic nerve which has in a deeper position in the mediastinal fat tissue on this side. However, we have to consider that in case of large lesions or in case of infiltration of mediastinal structures, the surgeon should choose the side of the approach in consideration of the location of neoplasm (17). In case of large thymoma, with potential infiltration of adjacent structures, it is possible to perform a bilateral approach that permits an optimal vision of whole mediastinum and dissection of cancer in a safe manner. Lately, Takashi Suda proposed the sub-xiphoid approach to perform robotic thymectomies, achieving a good visualization of the space included between the two phrenic nerves and a great domain of upper anterior mediastinum (18). All these approaches guarantee a radical exeresis of thymoma, with low risk of dissemination using the no-touch technique, this is possible thanks to wide range of movements of robotic instruments, the three-dimensional vision end use of CO_2 insufflation to enlarge mediastinal working space.

Furthermore, the robotic technique allows the handling of the thymic lesions close to the phrenic nerve with maximum safety, using bipolar instruments to reduce the risk of injury. Moreover, the robot system is provided with

Firefly® Fluorescence Imaging, that after indocyanine green injection during surgery, thanks to a particular system of green light vision, controlled directly by the robotic console, is able to highlight the course of the phrenic nerve on the pericardium with a negative vision.

Furthermore, thanks to the excellent visualization of the operative field and the freedom of movement of the surgical instruments, with robotic surgery, it is also possible to treat neoplasms adherent to the pericardium or infiltrating lung, due to the possibility of executing fine movements in secure way or inserting traditional endoscopic or robotic stapler to perform wedge resection *en bloc* with thymus.

The oncological radicality is closely related to the extension of the surgical excision of thymoma *en bloc* with thymus and next adipose mediastinal tissue, avoiding injury of tumor capsule, according to no-touch technique, and consequently cell dissemination. Moreover, about a third of thymoma patients have MG symptoms and surgical resection has a crucial role in reducing the use of drugs for the treatment of MG in those patients (3).

Several papers in the last decade have described the positive post-operative results associated with the robotic technique compared to open approach. Indeed, in patients who underwent robotic thymectomy is observed lower blood loss, less postoperative complications, shorter tube drainage duration and length of hospital stay (8,9,17).

Studies about oncological results in thymoma after robotic surgical treatment are limited, due to the low incidence of this neoplasm, the indolent behaviour of thymoma requiring long follow-up time and also the recent application of robotic surgery in the mediastinum. Early phase studies about oncologic outcomes have shown good results, for example in 2014 Keijzers reported an overall survival of 100% and tumor recurrence in 2.7% of the patients (19). Later Marulli and colleagues published a multi-institutional European study, with encouraging results. They analyzed the data of 134 patients who underwent robotic thymectomy for thymoma; with 5-year survival rate resulted in 97%, with pleural recurrence in 0.7% of cases (16).

In 2018 Casiraghi has analyzed 48 patients who underwent extended thymectomy (24 by open surgery 24 by robotic-assisted surgery). After a median follow-up of 1.3 years, all patients in the robotic group were alive without recurrences. Furthermore, in this group, they found a shorter mean operating time and a length of hospitalization significantly shorter (20). Moreover, in a recent study, Marulli compared patients subjected to trans-sternal thymectomy with subject underwent robotic approach, finding favorable post-operative results after robotic operation, with similar oncologic results in both groups (15).

Robotic thymectomy could be offered not only for the treatment of small lesions, but as recent studies have demonstrated it is effective and safe to use this technique also in larger thymoma. In 2017 Kneuertz has published an interesting paper regarding the feasibility of robotic surgery in the treatment of big mediastinal lesions (21). Kneuertz has compared 20 patients who underwent robotic thymectomy with 34 patients treated with median sternotomy. The mean diameter of the lesion for the robotic group was 6.0 cm, for open patients 6.7 cm and the combined resection of mediastinal structures (pericardium, phrenic nerve and lung parenchyma) were performed in both groups. Robotic patients presented lower intraoperative blood loss and a shorter hospitalization. The Authors have registered no perioperative deaths and no major vascular injuries, suggesting that this technique could be performed safely and effectively also for large lesions. Another interesting study regarding the treatment of big lesions was published by Wilshire in 2016 (17). They reviewed patients who underwent resection of 3 cm or larger thymoma with robotic or open technique. Both groups were homogeneous for patient characteristics, lesion maximum diameter, adjuvant radiation and postoperative complications. Median chest tube duration and median hospital stay resulted shorter in the robotic group versus open, with a statistically significant difference, with lower morbidity, lower intensive care unit stay and hospitalization in the robotic group compared to open. These studies confirmed that robotic surgery could be effective in the treatment of thymomatous lesions, also in advanced stages.

In our center, robotic thymectomies with a left-side approach to treating thymic hyperplasia or thymoma are performed. From April 2013 to December 2017, 33 patients affected by thymoma underwent robotic thymectomy. Patients were 16 females and 17 males, the mean age resulted in 54.7 years (range, 11–79 years), 22 of them (66.6%) had MG diagnosis The mean diameter of the lesions was 3.53 cm (SD ±2.1). The mean postoperative stay resulted in 4 days (SD ±0.8). The mean chest tube duration was 2.2 days (SD ±1.6). In 2 patients (6%) we found the appearance of postoperative chylothorax that required a surgical robotic review. No other major complications were found in our series. Accordingly, with Masaoka staging of thymoma, we found 11 stage I pts (33.3%), 12 stage II pts (36.3%) and 10 stage III pts (30.4%). At a mean follow up

Figure 1 Video demonstration of a robotic thymectomy with left side approach for a stage II thymoma (22).
Available online: http://www.asvide.com/article/view/29829

of 26.25 months (SD ±11.5) we observed a DFS of 96.9%. The 3-year survival resulted in 100%, also the cancer-related survival was 100% with an OS of 26.25 months. In a patient, after 4 months from the first surgical procedure, were observed pleural relapses treated with surgical excision and intraoperative chemo-hyperthermia (HITHOC). The primary tumor was a big lesion of 7 cm of diameter that resulted in B2/B3 thymoma at Masaoka stage II at histological examination.

To treat thymoma patients with Robotic surgery is safe and effective for its oncological and neurological outcomes. The extended thymectomy in the case of small neoplasm results in a quick and feasible procedure. Thanks to the high technology of the robotic system, a skilled surgeon can perform a safe operation not only in early-stage thymoma, achieving positive short and long terms outcomes. The Results on the application of robotic surgery for the treatment of thymic neoplasm are encouraging, however further comparative studies with longer follow-up and a greater number of patients are necessary.

The attached video shows a robotic thymectomy, for an early stage thymoma, performed in our center (*Figure 1*).

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Footnote

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