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Standardized definitions and concepts of radicality during minimally invasive thymoma resection

Giulia De Iaco#, Debora Brascia#, Alessandro Geronimo, Doroty Sampietro, Angela Fiorella, Marcella Schiavone, Teodora Panza, Francesca Signore, Giuseppe Marulli

Thoracic Surgery Unit, Department of Organ Transplantation and Emergency, University Hospital of Bari, Bari 70124, Italy.
#These two authors equally contributed to the writing of the work.

Correspondence to: Prof. Giuseppe Marulli, Thoracic Surgery Unit, Department of Organ Transplantation and Emergency, University Hospital of Bari, Piazza Giulio Cesare 11, Bari 70124, Italy. E-mail: giuseppe.marulli@uniba.it; beppemarulli@libero.it

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Abstract

Radical thymectomy is the gold standard treatment for thymoma; in particular, completeness of surgical resection of a well-encapsulated thymoma and adequate margins are considered the most important prognostic factors. According to the International Thymic Malignancy Interest Group instructions, in fact, the thymus should be resected *en bloc* with its upper cervical poles and the surrounding mediastinal fat and through a *no-touch* surgical technique. For years, the open approaches have been considered the gold standard treatment for thymic masses, because of technical advantages and proved good oncological results. When applied to properly chosen patients on the basis of the tumor stage, dimension, and histology, minimally invasive approaches could be as effective as open ones in terms of long-term outcomes. To accomplish a minimally invasive thymoma resection, several minimally invasive techniques (transcervical, subxiphoid, thoracoscopic, and robotic) have been described, each presenting advantages and drawbacks. Moreover, when dealing with early stage neoplasms, many authors have proposed to perform the thymomectomy alone, not involving the rest of the thymic gland, but evidence is still imprecise and vague, and some studies have described a higher rate of local recurrence when using this technique. Finally, many studies suggest that surgeons with expertise in minimally invasive lymphadenectomy for lung cancer may easily endorse the idea of nodal dissection, to be performed at least in advanced thymomas involving neighboring structures, large masses, and thymic carcinomas.

Keywords: Thymoma, thymectomy, minimally invasive techniques, radicality

INTRODUCTION

Thymic neoplasms and malignancies are relatively uncommon. Approximately 90% of the tumors of the thymus are thymoma, accounting for about 0.2%-1.5% of all cancers. The remaining 10% are thymic carcinoma, carcinoid tumors, or lymphomas. Indications for thymectomy include suspected thymoma, myasthenia gravis (MG) with and without thymoma, and thymic cists[1-4].

Radical thymectomy is the gold standard treatment for thymoma; in particular, completeness of surgical resection and adequate margins are considered the most important prognostic factors[5,6]. Complete surgical resection of a well-encapsulated and noninvasive thymoma is usually curative, with low risks of local recurrence[7]. Invasive thymoma and thymic carcinoma could be treated with multimodal therapy including induction or adjuvant chemo- or chemoradiotherapy associated with *en-bloc* surgical resection. Surgery is also indicated for treatment of local recurrences and, in some cases, pleural and pericardial implants[8]. To achieve the most complete surgical resection, the International Thymic Malignancy Interest Group (ITMIG) has suggested two surgical procedures for patients with or without MG [Table 1], respectively: extended thymectomy, including the *en bloc* removal of the contiguous right and left mediastinal pleura, mediastinal, and pericardiophrenic fatty tissues, and dissection of aorta-pulmonary window, in addition to complete thymectomy [Figure 1] or complete thymectomy, including the *en bloc* removal of the upper cervical poles and the surrounding mediastinal fat [Figure 2][9].

Along with the *en bloc* resection of thymoma, a no-touch surgical technique should be performed; the thymoma, in fact, should not be grasped or squeezed with retractors because of the possible rupture of the capsule with subsequent pleural dissemination, as Kamel *et al.*[9] demonstrated. Moreover, areas of potential tissue disruption should be marked immediately during dissection on both the specimen and the patient[10]. Completeness of thymectomy should be assessed by macroscopic inspection of the thymic bed, specimen, and subsequent pathological analysis[11]. Complete resection (R0) is defined when there is no evidence of residual tumor (macroscopically and/or microscopically) while incomplete resection is defined when there is evidence of microscopically (R1) or macroscopically (R2) residual tumor. When dealing with thymomas, there is often little tissue surrounding the tumor and quite often the capsule itself constitutes the outer surface of the specimen, leading to misleading interpretations of the margins [Figure 3].

In such cases, only through-and-thorough penetration of the capsule by tumor which reaches the outer surface should be interpreted as a positive margin[12]. After an R0 resection or a complete radiographic response has been previously achieved and an adequate 5-10 years of follow up has been carried out, recurrence can be defined[10]. Given the indolent behavior of many of these tumors, ITMIG has suggested that freedom-from-recurrence (FFR), as calculated from the date of resection to the date of first recurrence, is a better measure than survival in patients who have successfully undergone curative treatment[13]. Average recurrence rates are low for Masaoka Stage I tumors (3%) but increase progressively to 11% and 30% for Stage II and III tumors, respectively[14].

For years, the optimal surgical approach, combining the best degree of resection with minor surgical invasiveness, has been discussed[15-18]. Minimally invasive approaches have become increasingly relevant in the last two decades and a proved alternative to open techniques, which are still considered the gold standard treatment because of technical advantages and proved good oncological results[19]. According to the above-mentioned general principles about radical thymectomies, ITMIG guidelines[10] have been proposed for minimally invasive resections. They should involve no rib spreading or sternal cutting, dissection, and visualization of innominate vein, both phrenic nerves, and pleura in the case of suspected invasion. Moreover, the access incision for retrieval should be large enough to prevent specimen disruption; retrieval should always be done in the bag; and a correct examination of the removed specimen to assess for completeness of the resection is required[10].

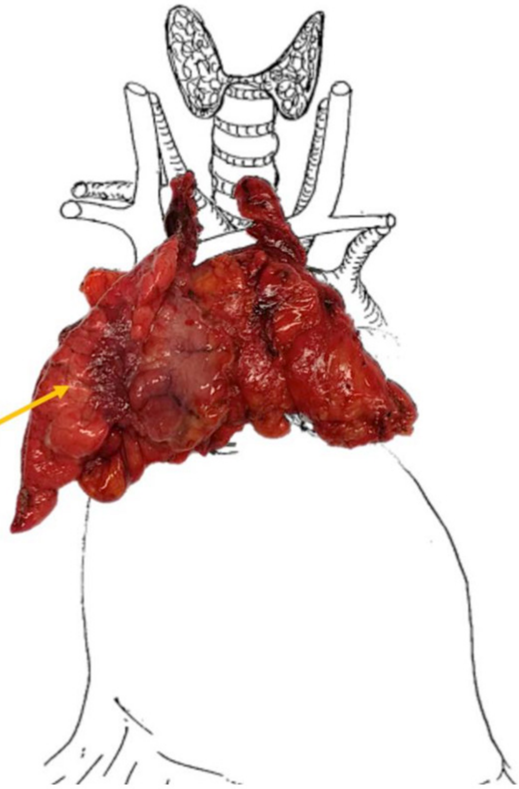

Figure 1. Thymic specimen after *en bloc* resection for locally advanced thymoma invading the lung (indicated with yellow arrow)

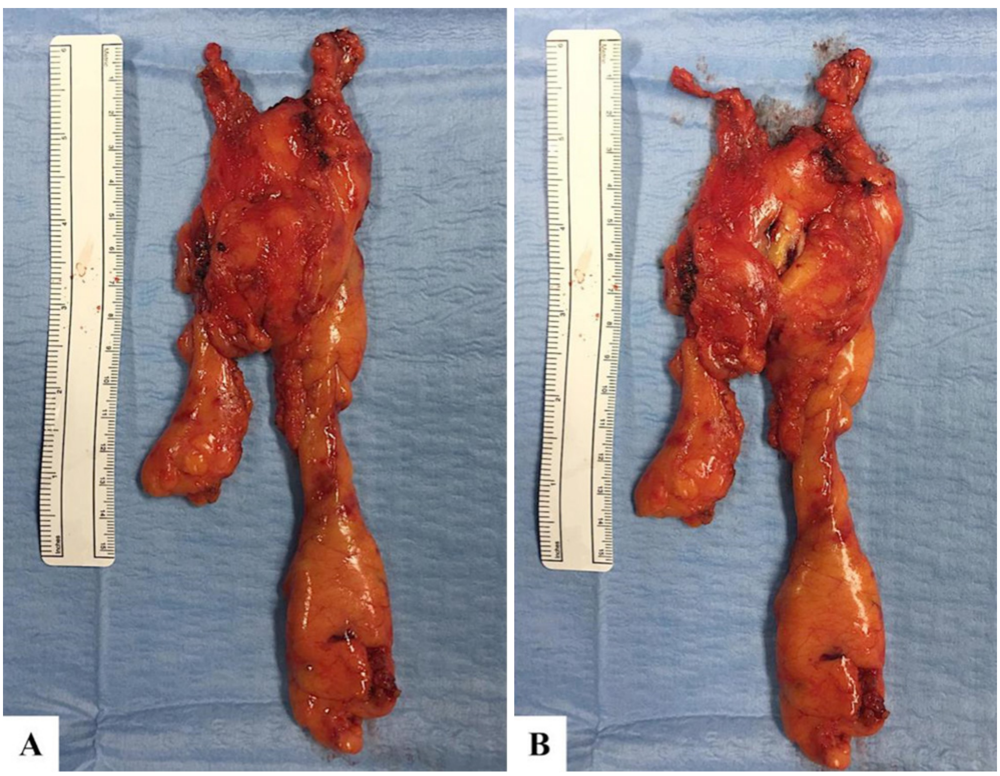

Figure 2. A: Gross specimen after completed video-assisted thoracic surgery thymectomy including all adjacent fat; B: the gross cross section revealed a thymoma 2 cm in size

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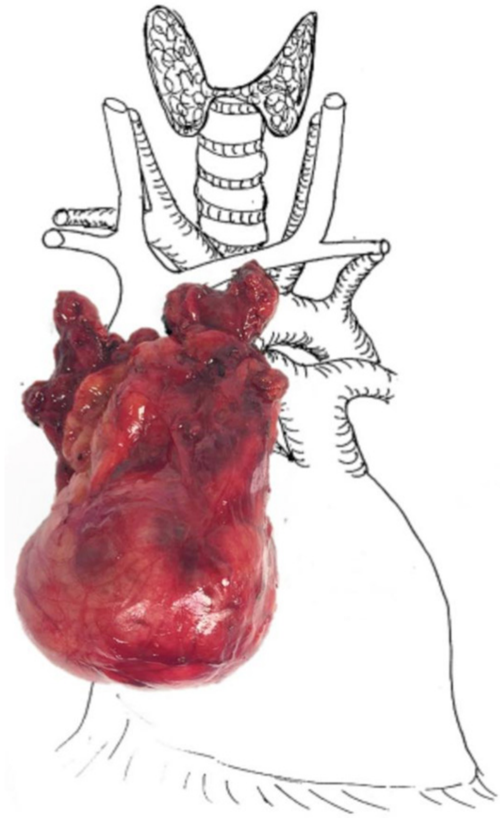

Figure 3. Gross specimen after resection of a well-circumscribed thymoma with a thin fibrous capsule

Table 1. Comparison between extended thymectomy and completed thymectomy

	Extended thymectomy	Completed thymectomy
Indication	Thymic mass MG Both	Thymic mass MG Both
Preoperation preparation	CT/MRI Neurological evaluation for detection of MG Plasmapheresis or immunoglobulins in myasthenic patient	CT/MRI Neurological evaluation for detection of MG Plasmapheresis or immunoglobulins in myasthenic patient
Resection extent	Removal of thymus, thymic fat and other mediastinal structures infiltrated by the mass (pericardium, lung, *etc.*)	Removal of the grossly identifiable thymus and variable amounts of anterior mediastinal fat
Postoperative care	Extubation if good respiratory effort and blood gases Close control of vital signs, especially saturation Aggressive pulmonary toilet Early ambulation Anticholinesterase agents if weakness occurs Plasmapheresis in case of respiratory standpoint worsening Drainage removal in case of patient stability	Extubation if good respiratory effort and blood gases Close control of vital signs, especially saturation Aggressive pulmonary toilet Early ambulation Anticholinesterase agents if weakness occurs Plasmapheresis in case of respiratory standpoint worsening Drainage removal in case of patient stability

MG: Myastenia Gravis; MRI: magnetic resonance imaging; CT: computed tomography

The correct indication of the surgical approach in thymic lesions should be chosen on the basis of the tumor stage, dimension, and histology[20]. Cheng *et al.*[21] suggested that patients would be suitable for minimally invasive thymectomy by fulfilling some radiological criteria: location of the tumor in the anterior mediastinum, tumor encapsulation, presence of a distinct fat plane between the tumor and surrounding structures, existence of residual normal appearing thymic tissue, no mass compression effect, and unilateral tumor predominance, particularly for tumors larger than 3 cm [Figure 4].

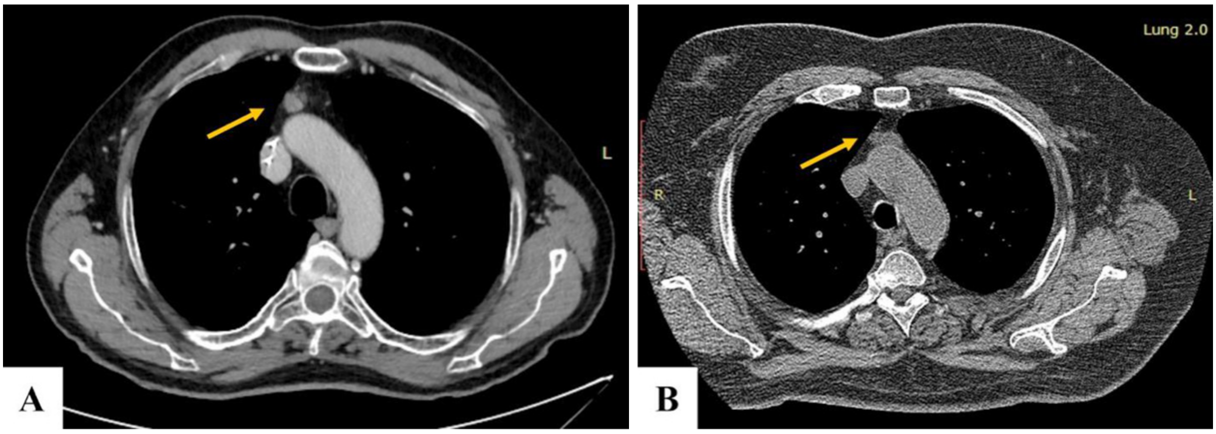

Figure 4. A, B: Computed tomography scan images showing two small thymomas, one (A) with typical calcifications, with regular outlines, amenable to minimally invasive surgery. Histology was positive for type A thymoma (Masaoka-Koga Stage I)

Most published studies agree that thymic lesions larger than 5 cm should be excluded from the minimally invasive approach; to date, dimension is not considered an absolute contraindication, but big lesions may interfere with the thoracoscopic procedure, forcing a conversion, prolonged operative time, and capsule injuries[22]. Kimura *et al.*[23] reported that tumor capsule injury during video-assisted thoracic surgery (VATS) is observed more frequently in patients with thymomas > 5 cm and the recent Japanese Alliance for Research in Thymoma (JART) study found statistically more recurrences in patients with thymomas > 5 cm[24].

Perforation of the capsule, incomplete resection possibility, *en bloc* resection not achievable, and disruption of the tissues exposing the tumor could compromise the complete oncological resection, and they force conversion to open[10,25].

Several minimally invasive techniques (transcervical, subxiphoid, thoracoscopic, and robotic) have been described to accomplish a minimally invasive thymoma resection, each having advantages and drawbacks.

VIDEO-ASSISTED TRANSCERVICAL THYMECTOMY

The transcervical approach for thymectomy was first reported by Sauerbruch in 1912[26] and then performed by Crile in 1966 in a series of patients with myasthenia gravis[27] and by Kirschner and Kark in the 1970s[28,29]. It was only in 1988 that Cooper and colleagues[30] reported a modified approach to perform and extend transcervical thymectomy in contrast with the limited technique reported earlier. Extended thymectomy involved use of a sternum-lifting and a self-retaining retractor to improve mediastinal exposure allowing a more complete removal of mediastinal thymic tissue and extrathymic fat. With the spread of new technologies and minimally invasive approaches, in 1993, the thoracoscopic approach for thymectomy was described for the first time[31]. The advantages of the video-assisted transcervical thymectomy are those of a transcervical route: lower morbidity and pain, shorter hospitalization, faster patient recovery, and reduced cost[32]; moreover, the uniportal transcervical route obviates entry into the pleural spaces, negates the need for chest tubes, provides enhanced exposure in the neck region, and a split-lung anesthesia via a double-lumen endotracheal tube is not mandatory. It is an efficient and inexpensive procedure with a one-night hospital stay and minimal postoperative pain and discomfort to the patient[33]. Relative contraindications to a transcervical approach include prior mediastinal surgery and/or irradiation and cervical spine disorder limiting extension of the neck[33]. The main concerns about this technique are about the narrow surgical field leading to instrument crowding and the not complete visualization of the thymus with the subsequent impossibility to perform a complete clearance of the mediastinal fat compared to an open surgery.

During the years, to surpass these limits, some modified and combined approaches have been described. Ampollini *et al.*[34], for example, described a modified video-assisted transcervical approach, which, using the instruments developed for the minimally invasive thyroidectomy, enable the surgeon to perform the thymectomy without neck hyperextension or permanent sternum elevation, which are mainly responsible for postoperative pain. Yu *et al.*[35], instead, proposed a combined transcervical and unilateral-thoracoscopic thymectomy approach to reach the residual thymic tissue, which might have been left behind in the superior horns or in the upper poles into the base of the neck.

SUBXIPHOID THYMECTOMY

The subxiphoid approach was introduced in 1999 by Kido *et al.*[36], paving the way for Hsu *et al.*[37], who first performed subxiphoid video-assisted thoracoscopic extended thymectomy in 2002. Since then, the subxiphoid approach has been used successfully and many techniques have been described according to the incision design: the uniportal or dual-port subxiphoid approach[38-40], the subxiphoid and subcostal arch approach, subxiphoid robotic thymectomy[41,42], and a combination of the transthoracic and subxiphoid approaches[43].

Each technique should be chosen on the basis of the personal preference of the surgeon along with his experience and of the single case to treat, according to its anatomical peculiarities[44]. Although the uniportal approach seems to be the most minimally invasive approach in existence, it is not an easy technique to learn because of the reduced instrument maneuverability; however, in skilled hands, this limit could be overcome with specially modified instruments and angled thoracoscopes[45,46]. Since the increase in the number of the ports can help obtain a multidirectional view, increasing the safety of the procedure, single-port thymectomy should be started following the training of two- or three-port thymectomy[47]. The subxiphoid robotic approach is the one with the best maneuverability: the left and right robot arms are inserted in the 6th intercostal space. and the entire target/thymus lies between the left and right arms, thereby enabling maximum robot performances[42].

The advantages of the subxiphoid approach are numerous; since the camera is inserted into a subxiphoid incision in the midline of the body, the surgical field is comparable to that in a median sternotomy. This helps identify the location of the bilateral phrenic nerves and confirm the location of the superior pole of the thymus while offering a good visualization in the neck area and a safe dissection of thymic veins[42]. Other advantages include minimal postoperative pain with no occurrence of intercostal neuropathy since intercostal spaces are not traversed and cosmetic outcomes are excellent[43,44,48]. In contrast, when comparing the subxiphoid view to the lateral one in the traditional VATS, it becomes difficult to identify the contralateral phrenic nerve, and there is also the risk of intercostal nerve injury, resulting in postoperative chronic incision pain[43,49]. Zhang *et al.*[43] recently conducted a retrospective analysis comparing 98 patients who underwent a VATS thymectomy through the subxiphoid and subcostal arch approach or the lateral intercostal one. They found statistically significative differences in the length of hospital stay, postoperative pain, and cosmetic satisfaction in favor of the subxiphoid approach.

To deal with larger thymomas and difficult selected cases, some modified approaches have been described. In their experience, Zieliński *et al.*[16] proposed a "maximal" transcervical subxiphoid video-thoracoscopic thymectomy, in which, at the same time, two teams work from above and below the sternum to dissect the thymus while using a double sternal elevator. This technique has the advantage to be more extensive in regard to the removal of fatty tissue from the aorta-caval groove and fatty tissue anterior to the trachea, almost reaching the level of tracheal bifurcation. On the other hand, even if the two-team approach helps to reduce the operative time, it is a far more invasive technique than unilateral VATS affected by more complications than traditional VATS.

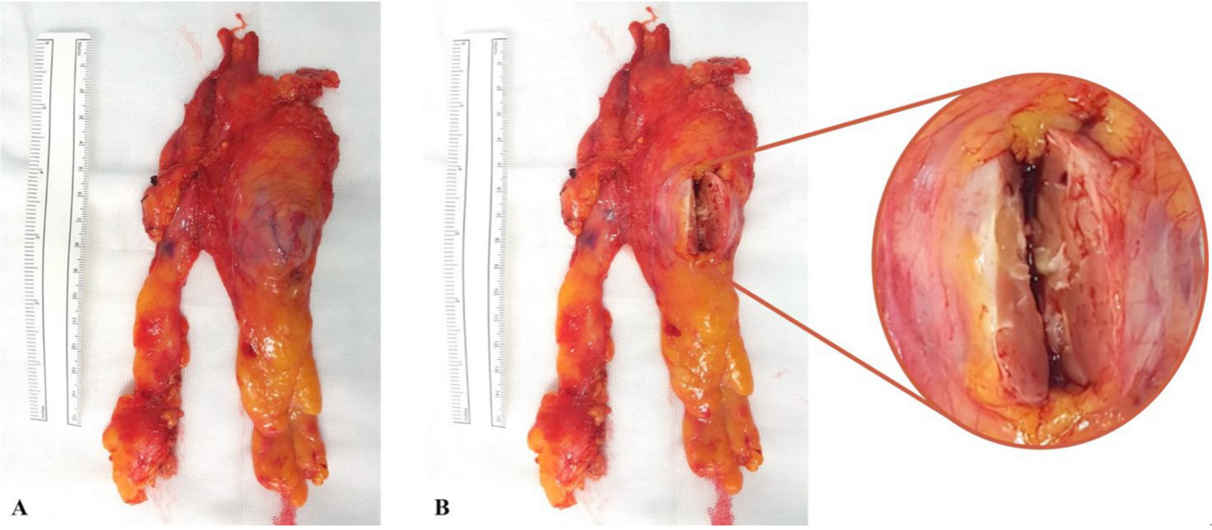

Figure 5. A: Gross specimen after *en bloc* video-assisted thoracic surgery thymectomy; B: gross cross section revealing a thymoma 3.5 cm × 3 cm in size (the zoomed-in nodule is shown in the circle)

Aramini *et al.*[49] described the subxiphoid thymectomy approach aided by a double sternum retractor to better visualize the mass at the level of the anterior mediastinum, particularly in patients with large invasive tumors. The double sternum retractors provide the surgeon with a better view of the tumor, improving the surgical technique and thus preserving the principles of surgical radicality related to the surgical margins.

VATS AND ROBOTIC-ASSISTED THORACOSCOPIC SURGERY THYMECTOMY

VATS was introduced in the 1990s; since then, it has totally changed thoracic surgeons' approach to surgery. The advantages of minimally invasive techniques (MIT) compared with conventional open approaches are well known: shorter hospital stay, quicker recovery, better aesthetic result, lower perioperative morbidity, minor surgical access trauma, postoperative pain, and better preservation of pulmonary function. Despite this, the use of MITs in thymic surgery is still controversial. The main surgeons' concerns relate to the higher risk of rupture of the capsule with the consequent spread of tumoral cells, increased risk of local recurrence, and reduced safety margins [Figure 5].

Although recent studies have reported similar oncological outcomes for early-stage thymoma resections performed both by open and minimally invasive approaches[50-53], the first one remains the gold standard treatment[19]. This is because evidence is sparse and mostly deriving from case reports or retrospective studies due to the low incidence of these tumors. Moreover, given the indolent behavior of many thymic tumors, an adequate 5-10 years of follow-up should be carried out to establish the exact FFR and overall survival. Currently, few data about long-term follow-ups have been published and therefore statistics are still ineffectual.

No tremor filter, two-dimensional view of the operative field, and inability of the instruments to articulate are well-known VATS limitations, and they make it difficult to operate in such a rigid and tiny space as the mediastinum. The development of robotic technologies has solved some of the above-mentioned problems, allowing a better and safer surgical technique. The robotic system, in fact, is endowed by a three-dimensional, high resolution vision camera that enables the best possible view of the operative site; moreover, every endoscopic procedure around anatomic structures is easier and safer because the surgical EndoWrist can articulate and rotate 360 degrees with seven degrees of freedom articulation. These features make robotic surgery extremely appropriate for thymic surgery, enabling the surgeons to do a safe and

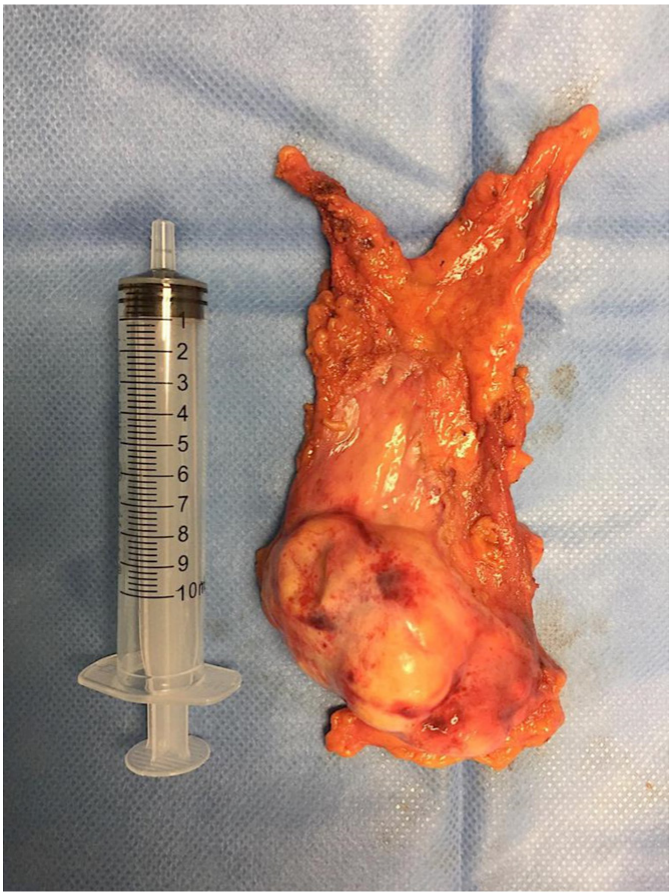

Figure 6. Gross specimen after *en bloc* video-assisted thoracic surgery thymectomy

comfortable dissection of vascular and nervous structures and a better dissection in remote, fixed, and difficult to reach areas of the neck and mediastinum[11,53-57] [Figure 6].

The main limitations of robotic surgery are the high initial costs, the lack of tactile feedback, and the need of a large enough volume of patients to overcome the initial learning curve.

O'Sullivan *et al.*[58] recently published a meta-analysis on robotic versus open and video-assisted thoracoscopic surgery approaches for thymectomy, including 18 articles. When comparing robotic *vs*. open thymectomy, evidence shows no differences in operative time, intraoperative complications, and mortality. On the other hand, significantly lower blood loss, fewer postoperative complications, shorter length of hospital stay, and decreased positive margin rate were reported in the robotic group. When comparing robotic *vs*. VATS thymectomy, instead, the results show no differences in the two groups in terms of operative time, blood loss, length of hospital stay, intraoperative complications, and margin rates. To date, few authors have performed a real comparison between the two techniques, considering not only the perioperative results but also long-term follow-ups [Table 2].

Perioperative parameters were analyzed by Qian *et al.*[68]; when comparing 123 patients with early-stages thymoma who underwent robotic-assisted thoracoscopic surgery (RATS), VATS, or open thymectomy, they found significant differences in blood loss volume, mean postoperative pleural drainage duration, and duration of hospital stay. When comparing two groups for parameters, they found that the outcomes of RATS were more favorable than those of VATS and median sternotomy, while outcomes for VATS

Table 2. Best evidence papers about minimally invasive thymectomy

Ref.	No. of patients	Surgical approach	Thymectomy/ thymomectomy	5-year survival rate (%)	RR (%)	Mean follow up (months)
Roviaro *et al.*[59]	22	uVATS	Thymectomy	95	1.3	51.7
Cheng *et al.*[21]	44	uVATS	Thymectomy	100	0	36.4
Agasthian and Lin[60]	119	uVATS	Thymectomy	100	3.4	58.8
Pennathur *et al.*[61]	18	bVATS	Thymectomy	100	0	27
Takeo *et al.*[51]	35	bVATS	Thymectomy	100	2.8	65
Mussi *et al.*[62]	14	Robotic	Thymectomy	100	0	14.5
Marulli *et al.*[22]	79	Robotic	Thymectomy	97	1.3	51.7
Kimura *et al.*[23]	45	uVATS	Thymectomy	100	6.7	-
Marulli *et al.*[54]	100	Robotic	Thymectomy	100	0	67
Tseng *et al.*[83]	95	VATS (22)	Thymectomy (42) Thymomectomy (53)	100	4.5 1,5	57
Schneiter *et al.*[63]	20	Robotic	Thymectomy	100	11.1	26
Liu *et al.*[64]	76	uVATS	Thymectomy	100	2.6	61.9
Ye *et al.*[65]	125	uVATS	Thymectomy	100	0	16.9
Keijzers *et al.*[66]	37	Robotic	Thymectomy	100	2.7	36
Bae *et al.*[82]	342	VATS (119) Transervical (1) RATS (1)	Thymectomy (239) Thymomectomy (103)	99 100	12.1 9.7	94.5 85.6
Gu *et al.*[80]	1,047	VATS (277)	Thymectomy (220) Thymomectomy (57)	93 96	3.1 5.4	38
Nakagawa *et al.*[81]	1,286	VATS (169)	Thymectomy (276) Thymomectomy (276)	97.3 96.9	4 1.8	53
Narm *et al.*[79]	762	VATS (297)	Thymectomy (76) Thymomectomy (72)	97 96.3	4.1 3.7	49
Marulli *et al.*[11]	134	Robotic	Thymectomy	100	0.7	48
Rusidanmu *et al.*[77]	118	VATS (unspecified)	Thymectomy (43) Thymomectomy (75)	88.4* 98.7*	6.98 2.67	-
Weng *et al.*[67]	358	VATS	Thymectomy	94.5	8	60.5

*10-year survival rate. RR: recurrence rate; RATS: robotic-assisted thoracoscopic surgery; VATS: video-assisted thoracic surgery; uVATS: uniportal VATS; bVATS: biportal VATS

were more favorable than those of sternotomy. Similar findings were reported by Şehitogullari *et al.*[69]. In a recent analysis, they compared 21 *vs.* 24 patients who underwent RATS or VATS thymectomy. They found significant differences in terms of mean operative time, length of hospital-stay, and duration of pleural drainage, while mean operative time, operative pain, and remission rates were superimposable. Rückert *et al.*[70] performed a retrospective analysis on 74 *vs.* 79 patients with MG who underwent robotic or thoracoscopic thymectomy. With a follow-up of 42 months, they found a significant difference in cumulative complete remission rate of MG between the two groups in favor of the robotic one (39.25% *vs.* 20.3%, P = 0.01); no differences were found in terms of conversion rate, operative time, and postoperative complications.

Burt *et al.*[71] recently performed a retrospective multicenter analysis on 943 patients who underwent MIT or open thymectomy by focusing on R0 status as the primary outcome. By comparison, they found a non-significant difference in the R0 resection rate for patients treated with minimally invasive or open approach (83.4% *vs.* 79.4%), stating that the probability of achieving R0 resection for early-stage thymoma is not influenced by a minimally invasive approach, and MIT is equivalent to OT in this regard. Kamel *et al.*[72] published a recent multi-institutional analysis on 2,558 performed thymectomies using an open, VATS, or RATS approach. They found that patients who underwent thymectomy via an open approach were younger, had more advanced tumors, had more incomplete resections (32% *vs.* 30%, and 23%; P = 0.013), less frequently underwent regional lymph node dissection, and had longer hospital stays compared to the VATS and robotic groups. When they performed a matched analysis, all those differences became not statistically significant and the three approaches resulted superimposable.

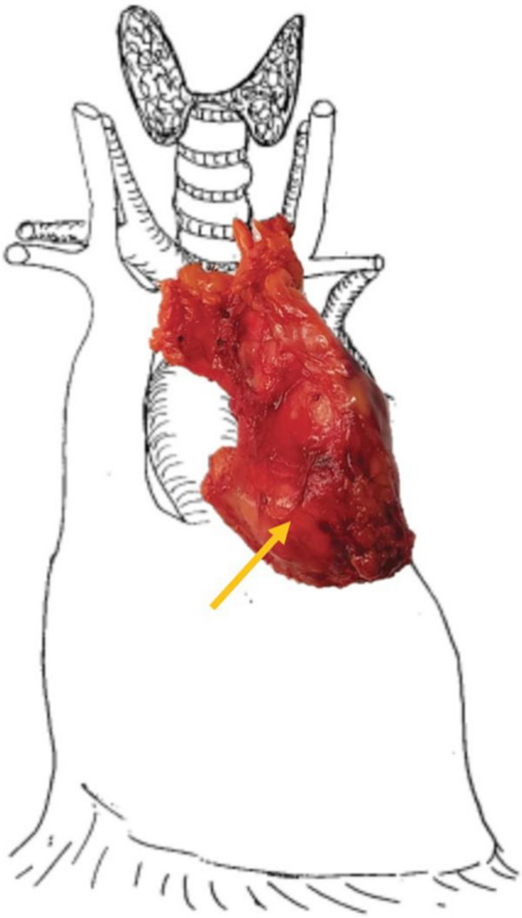

Figure 7. Gross specimen after robotic-assisted thoracoscopic surgery thymomectomy performed for a small intracapsular thymoma (yellow arrow)

Therefore, all published studies do not solve the doubts about which approach should be better among all the available ones and, thus far, no prospective randomized trials have been performed to clear them. For this reason, the choice should be done by the surgeons on the basis of both available evidence and surgeons' personal skills and preferences.

RADICALITY: THYMOMECTOMY OR THYMECTOMY?

All guidelines and large retrospective review studies recommend the complete *en bloc* thymectomy as the current gold standard in all resectable thymic lesions because of the risk of a multicentric thymoma development, the occurrence of MG after the operation, and the prevention of the local recurrences[10,73-76]. However, many authors have proposed the resection of the thymoma without the rest of the thymic gland as a feasible and safe resection in early stage thymomas (Stages I and II) without MG[77-86] [Figure 7].

Fiorelli *et al.*[87] recently published the best evidence about equivalence in terms of oncological outcomes of thymomectomy and thymectomy in patients with early stage thymoma. They found ten papers, and most of which showed no statistical differences in terms of local recurrence, while differences were described in terms of surgical outcomes (operative time, blood loss, drainage duration, and hospital stay) in favor of the thymomectomy.

Among these studies, the largest multicentric ones[80,81] were those with a proved higher rate of local recurrence in the thymomectomy group than in the thymectomy one. Gu *et al.*[80], in their multicenter study from the Chinese Alliance for Research in Thymoma database, retrospectively analyzed 1,047 patients who underwent thymomectomy or thymectomy for early stages thymoma; they found a higher recurrence rate in the thymomectomy group, especially for patients with Stage II thymomas (14.5% *vs.* 2.9%, $P = 0.001$). Similarly, Nakagawa *et al.*[81], in their multicenter study from the JART database, retrospectively analyzed 1286 patients who underwent thymomectomy or thymectomy for early stages thymoma before and after propensity score analysis; they found a higher recurrence rate in the thymomectomy group (2.1% *vs.* 0.41%, $P = 0.06$).

Masaoka[88] published an anecdotal study about his surgical experience in Osaka and Nagoya. In the first experience, most of the 93 patients underwent simple thymomectomies, whereas a majority of patients in the Nagoya series underwent extended thymectomies; in the early 1980s, simple thymomectomy was the procedure of choice, later replaced by extended thymectomy. He found that overall survival rates of the Nagoya series were superior to those of the Osaka one (87.1% *vs.* 66.7% for Stage I; 80.6% *vs.* 60.0% for Stage II).

Voulaz *et al.*[89] published the first study about 157 patients who underwent thymectomy or thymomectomy, comparing for the first time long-term outcomes for advanced-stage thymomas and carcinomas, while previous reports have focused only on early stages. They found that oncologic outcomes in terms of disease-free survival rate of thymomectomy *vs.* thymectomy were superimposable and their median follow-up was 77 months.

To date, there is no prospective study comparing the two approaches and the evidence is still sparse, deriving from retrospective, single-institution, and small studies. The largest published analyses prove that thymomectomy alone is not enough from an oncological point of view for early-stage thymoma. Moreover, given the indolent behavior of these tumors, long-term follow-ups are needed to assess the real rates of recurrence and the superiority of one technique to another.

LYMPHADENECTOMY

For many years, the role of lymphadenectomy of the mediastinum for thymic lesions has not been made clear, and this surgical procedure has long been underperformed. Despite this, lymph node metastases have proven to be a significant, independent, and adverse factor for FFR in patients with thymic carcinoma and thymoma. To date, no clear guidelines are available regarding lymph node dissection and data from the majority of studies show that lymph node sampling is not routinely performed during surgeries, except in Japan where lymphadenectomy has traditionally been a part of the thymic resection.

The Masaoka staging system included N involvement in Stage IVb but made no distinction among the different nodal stations[88]. The eighth edition of tumor, node, and metastasis classification for thymic tumors, instead, has classified nodal stations into anterior (N1) and deep (N2) regional nodes; their involvement stage lesions as IVa or IVb disease[90].

Anterior mediastinal lymph nodes seem to be the primary drainage basin for thymic epithelial tumors and lymphatic diffusion apparently spreads from the anterior to the deep nodes following a right route. This has been determined based on frequency and pattern of metastasis in addition to anatomical location: nodal metastases are located in the anterior mediastinum in 90% of thymomas and carcinoids and 70% of thymic carcinomas[91].

The actual incidence of lymph node metastasis has not been well established. Historically, the prevalence of lymph nodes involvement has been described ranging from 1.8% to 5.1% in thymomas and from 20% to

33.5% in thymic carcinomas and NETs, but these rates could be underestimated because lymphadenectomy is rarely performed by most institutions[91-95].

Two factors have been described to explain lymph node metastasis, namely WHO subtype and tumor size, being both closely related to the biologic aggressiveness of the tumor[96,97]. Hwang *et al.*[92] described lymph node metastasis rate according to WHO histologic types as 5% for Type A, 1.6% for Type AB, 4.8% for Type B1, 9.5% for Type B2, 10.7% for Type B3, and 31.8% for thymic carcinoma. They also found that lymph node metastasis rate was higher in tumor larger than 6 cm. Moreover, most authors have reported lymph node metastasis to be more frequent in tumors invading adjacent organs; these findings suggest lymph node dissection to be performed at least in those patients undergoing *en bloc* resection of thymus and neighboring organs for carcinomas and carcinoids[97,98].

Park *et al.*[98] suggested dissection of more than 10 lymph nodes to be enough for adequate staging. They retrospectively reviewed 45 patients who underwent thymic resection for carcinoma; during the surgery, they performed lymphadenectomy of a mean of 9.4 lymph nodes and divided the patients in four groups according to the extension of lymph node dissection: no lymph node dissection (Nx), node-negative by < 10 nodes dissection (N0a), node-negative by > 10 nodes dissection (N0b), and node metastasis (N1). They found that the five-year FFR rates were 33.3% in N1, 64.1% in N0a, 75% in Nx, and 90% in N0b, while the five-year DFS rates were 33.3% in N1, 48.1% in N0a, 75% in Nx, and 90% in N0b.

Although no evidence has proved it yet, it is possible that surgeons with expertise in minimally invasive lobectomy and lymphadenectomy for lung cancer may easily endorse the idea of nodal dissection, to be performed at least in advanced thymomas involving neighboring structures, large masses, and thymic carcinomas.

CONCLUSION

Radical *en bloc* thymectomy including the upper cervical poles and the surrounding mediastinal fat is the gold standard treatment for non-MG thymoma and adequate margins are considered the most important prognostic factors.

Open approaches remain the gold standard treatment, but minimally invasive techniques could be effectively used in small, early-stages thymic masses, above all because, despite the shortage of studies, the rate of radicality would seem to be slightly higher for minimally invasive techniques. Transcervical, subxiphoid, thoracoscopic, and/or robotic approaches have been described and compared in many studies, each having advantages and drawbacks. However, the lack of prospective randomized trials still gives no answer about which approach should be better among the available ones. Moreover, the concept of radicality should include pathological features of surgical removal (resection must involve the thymoma, thymus, and mediastinal fat) and operation modalities: minimally invasive resection of a thymic neoplasm does not require the use of rib retractor or the execution of sternotomy. The goal is to perform a complete resection using a video monitor, and the service incision to remove the neoplasm must be large enough not to damage the operating piece during extraction. Therefore, minimally invasive surgery is to be preferred to open techniques not only in terms of radicality but also for the best postoperative performance (less pain and aesthetic result).

Although several authors have proposed thymomectomy as a valid limited resection technique, appropriate for patients with small and early-stages thymomas, still little evidence supports its oncological and long-term advantages.

Finally, the role of lymphadenectomy of the mediastinum for thymic lesions has not been clarified, and this surgical procedure has long been underperformed. Since WHO subtype, tumor size, and invasion of neighboring organs have been proved to often be associated with lymph node metastasis, evidence suggests that nodal dissection should be performed at least in advanced thymomas, large masses, and thymic carcinomas.

DECLARATIONS

Authors' contributions

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: De Iaco G, Brascia D, Marulli G

Performed data acquisition, as well as provided administrative, technical, and material support: Geronimo A, Sampietro D, Fiorella A, Schiavone M, Panza T, Signore F

Drafting of the manuscript: De Iaco G, Brascia D, Marulli G

Critical revision: Marulli G

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All authors declared that there are no conflicts of interest.

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Not applicable.

Consent for publication

Not applicable.

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