Perioperative management and postoperative outcomes of locally advanced thymic epithelial tumors: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs) are frequently diagnosed at an advanced stage, highlighting the importance of understanding the treatment strategies for these cases. Surgical intervention after chemotherapy or chemoradiotherapy presents specific challenges and underscores the crucial role of perioperative management. This study aimed to explore the perioperative management and postoperative outcomes in patients with locally advanced TETs.

Methods: Relevant studies published between 2000 and 2022 were identified through PubMed searches using a combination of the following terms: "Locally advanced TETs", "Thymoma", "Thymic cancer", "Surgery", "Induction therapy", and "Postoperative outcomes". We analyzed available data to describe the perioperative management and postoperative outcomes of locally advanced TETs.

Key Content and Findings: Surgical outcomes after induction therapy for locally advanced TETs were analyzed for 18 references (total n=646) between 2000 and 2022. The primary objective of induction therapy for locally advanced TETs is complete tumor resection. In recent years, many medical centers have adopted systemic chemotherapy and chemoradiation for the treatment of thymoma and thymic carcinoma, respectively. During surgical intervention, resecting the surrounding organs, such as the lungs, pericardium, and phrenic nerves, is a common practice. Additionally, there may be cases wherein vascular resection of the superior vena cava (SVC) and innominate veins is necessary. Techniques and strategies for revascularization without complications are crucial in these situations. The incidence of postoperative complications varied significantly, ranging from 4.8% to 42%. However, perioperative mortality is typically reported to be approximately 0%, with only two reports showing mortality rates of 1.8% and 9.0%.

Conclusions: The short-term postoperative outcomes of surgical treatment following induction therapy for locally advanced TETs were generally deemed acceptable. However, incomplete resection may occur, particularly when the tumor invades the pulmonary artery or aorta. Hence, careful evaluation the indications for surgery is crucial, considering the patient's overall condition and treatment response.

Keywords: Locally advanced thymic epithelial tumors (locally advanced TETs); induction therapy; surgery; postoperative outcomes

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Introduction

Thymic epithelial tumors (TETs), predominantly thymomas and thymic carcinomas, are commonly observed in the anterior mediastinum (1). As reported by the International Thymic Malignancy Interest Group, a significant number of patients with TETs are diagnosed at advanced stages (2). As a result, locally advanced TETs are frequently treated in clinical practice. Understanding the treatment strategies for these cases is crucial. In cases wherein R0 resection is feasible, upfront surgery is considered appropriate for locally advanced TETs. However, if R0 resection is anticipated to be challenging, the National Comprehensive Cancer Network (NCCN) guidelines and the European Society of Medical Oncology (ESMO) treatment guidelines recommend a treatment approach involving chemotherapy or chemoradiotherapy followed by surgery (3,4). Surgical intervention after chemotherapy or chemoradiotherapy poses additional challenges, emphasizing the importance of perioperative management. This article discussed the perioperative management and postoperative outcomes in patients with locally advanced TETs. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-24/rc).

Methods

Relevant studies published between 2000 and 2022 were identified through PubMed searches using a combination of the following terms: "locally advanced TETs", "Thymoma", "Thymic cancer", "Surgery", "Induction therapy", and "Postoperative outcomes". The reference lists of the relevant articles were reviewed to identify additional studies. Studies that were considered to have relatively low reliability, such as those with fewer than 10 cases, or those not written in English were excluded from the analysis. Data were extracted based on the relevance of the study to the topic. The initial list of eligible studies was developed by one author and reviewed by other team members until a consensus was reached. Further details regarding the methodology used in this study are presented in *Table 1*.

In light of the introduction of the new Tumor, Node, Metastasis (TNM) classification for staging locally advanced TETs in 2017 (5), this review article adopts the Masaoka classification as a means to establish a comprehensive staging framework. It is crucial to acknowledge that, within the Masaoka classification, locally advanced TETs are

classified as stage III. Nevertheless, it should be noted that the examples of stage IVa and stage IVb in the relevant literature are also included in the scope of this review. Moreover, when transposing these stages to the TNM classification, there is a likelihood that T2–T4 (equivalent to stages II and III) as well as certain stage IVa cases would also be subsumed.

Preoperative management

Only a limited number of prior reports address the preoperative management of TETs. The preoperative considerations for TETs encompass the following (6):

- ❖ Evaluation for respiratory symptoms, including the possibility of airway stricture.
- ❖ Preoperative evaluation by the anesthesiology department.
- ❖ Systematic evaluation of the patient, with a particular focus on potential autoimmune complications.
- ❖ Assessment of pharmacotherapy for myasthenia gravis (MG) if MG is present.

The anesthetic management of patients with TETs undergoing thymectomy encompasses several risks associated with potential airway obstruction, hypoxia, and cardiovascular instability. These complications can manifest during various stages, including positioning the patient in the supine position, anesthesia induction, extubation, the immediate postoperative period, and persisting for several days after extubation (7,8). Notably, the presence of respiratory symptoms, evident airway constriction observed on computed tomography (CT) scans, and deviations from normal pulmonary function have been utilized to assess the likelihood of perioperative complications (9).

The anesthetic management of MG necessitates a personalized approach that considers the intricacies of the disease, its treatment, and the potential effects of surgery, anesthesia, and associated medications. The primary goal is to prevent the exacerbation of muscle weakness and to uphold respiratory function. Whenever feasible, the usage of neuromuscular blocking drugs and agents impeding neuromuscular transmission should be minimized (10). Regarding the preoperative medical management of MG, the administration of anticholinesterase drugs and glucocorticoids should be sustained throughout the perioperative period, as discontinuation might worsen symptoms. On the other hand, nonsteroidal immunosuppressive agents, with their prolonged action

Table 1 The search strategy summary

Items	Specification
Date of search	4/1/2023 to 4/30/2023
Databases and other sources searched	PubMed
Search terms used	"Locally advanced TETs", "Thymoma", "Thymic cancer", "Induction therapy", "Surgery", "Postoperative outcomes"
Timeframe	2000–2022
Inclusion criteria	Prospective studies, retrospective studies, meta-analyses, case studies
Exclusion criteria	Papers which we considered with low reliability and non-English papers
Selection process	The search conducted by M Takenaka and the paper selection was made after discussion with the corresponding author K Kuroda

duration, are less likely to be significantly impacted by perioperative discontinuation (10).

History of induction therapy

In general, early-stage tumors with well-defined borders of the TETs are easily resectable. However, locally advanced TETs classified as Masaoka stage III or higher often show invasion of the pericardium, great vessels, and lungs. This makes complete resection challenging, depending on the tumor location and degree of invasion. Consequently, these tumors have a high risk of incomplete resection, leading to a higher likelihood of recurrence (11). Consequently, when surgery is performed as the initial treatment for Stage III TETs, the rates of complete resection vary and are generally not favorable, ranging from 40% to 90% in the reported series (12-14). Therefore, preoperative treatment is administered for locally advanced TETs to increase the rate of complete resection. Recently, it has been reported that the number of invasive structures is a prognostic predictor of cancer-specific survival in patients undergoing surgery for locally advanced thymoma (15). The number of invasive structures is a factor not expressed in the TNM or Masaoka classification and is interesting from the perspective of defining local advance.

Since the efficacy of induction therapy was first reported by Giaccone *et al.* in the 1980s (16), numerous studies have investigated its use of induction therapy for TETs. However, approaching the existing literature on induction therapy for TETs with caution is important. Many of the available studies were retrospective and heterogeneous, encompassed both thymoma and thymic carcinoma, and often lacked a comparison group of patients who underwent surgery without induction therapy (17). Furthermore, owing to the rarity of this disease, published prospective clinical trials are scarce, with most studies being limited to single-arm phase II studies (18-24).

There is no consensus regarding whether chemotherapy or chemoradiotherapy should be selected as the induction therapy for locally advanced TETs. However, some reports have suggested that the treatment approach should be based on the histology of TETs (25,26). In thymic carcinoma, complete resection is an unequivocally favorable prognostic factor (27-29), and planning the treatment appropriately is crucial to achieve microscopic complete resection. Therefore, the preferred treatment is chemoradiotherapy, which has a high local therapeutic efficacy. Conversely, in thymomas, while complete resection is the primary goal, debulking surgery has shown potential effectiveness (30,31); surgery is typically performed after chemotherapy, and radiation is added postoperatively. A retrospective report from the European Society of Thoracic Surgeons (ESTS) database revealed that 76% of patients with locally advanced thymoma received chemotherapy as induction therapy (32). Furthermore, Wei *et al.* reported that, in the Chinese Alliance for Research in Thymomas (ChART) database, chemotherapy was chosen more frequently as the preferred induction therapy over chemoradiotherapy after 2004, as compared to before 2003 (33). Regimens commonly used as induction therapy to alleviate locally advanced TETs include ADOC (adriamycin, cisplatin, vincristine, cyclophosphamide), PAC (cisplatin, doxorubicin, cyclophosphamide), VIP (cisplatin, etoposide, ifosfamide), CAMP (cyclophosphamide, cisplatin, doxorubicin and prednisolone or cisplatin, doxorubicin and methylprednisolone), CP (carboplatin, paclitaxel), and

CODE (cisplatin, vincristine, doxorubicin, etoposide).

Wang *et al.* (34) highlighted the advantages of induction therapy, including (I) providing objective clinical benefits by reducing tumor size and alleviating symptoms; (II) downstaging tumors, which can potentially convert initially unresectable tumors into resectable ones; (III) enhancing early local and systemic disease control; and (IV) demonstrating the feasibility and effectiveness of specific drugs and therapies. These benefits underscore the value of induction therapy in the management of TETs. However, one must note that chemotherapy or chemoradiotherapy used as induction therapy can lead to the development of dense fibrosis in structures affected by tumor invasion. Fibrosis can pose a challenge for surgical dissection. Consequently, en bloc resection may be necessary, even in cases wherein no definitive tumor invasion is confirmed histologically (18).

Combined resection of surrounding organs and R0 resection

The primary approach for treating TETs is to achieve complete resection of the tumor and its invasive sites (12,35). The ability to successfully perform thorough surgical resection is a crucial factor that significantly influences postoperative recurrence rates and overall survival (OS) outcomes (12,36). Previous reports of locally advanced TETs since 2000 are shown in *Table 2*, though some cases included Masaoka stage IVb. Previous studies reported significant variations in the rates of complete resection following induction therapy for locally advanced TETs, ranging from 15% to 95% (18-25,33,34,37-44). This wide range of outcomes was likely due to the heterogeneous nature of locally advanced TETs. In cases of locally advanced stage III TETs, resection can be relatively easier, and complete resection is feasible when the invasion is limited to structures such as the lungs, pericardium, or phrenic nerves. However, when the invasion involves critical structures, such as the main pulmonary artery or aorta, achieving complete resection becomes more challenging. These cases often require extracorporeal circulation during surgery, which can lead to a higher likelihood of unresectability.

Kunitoh *et al.* attributed the incomplete resection of locally advanced TETs to various factors, including invasion of the pulmonary artery trunk and superior vena cava (SVC) and aortic, myocardial, and sternal invasion (21). In contrast, Mineo *et al.* identified intrathoracic extension of the tumor and significant vascular invasion as contributing factors to incomplete resection (39). These studies highlighted the specific tumor characteristics and anatomical involvement that can hinder complete resection in locally advanced TETs. In most cases, invasion of the SVC can be addressed through resection using an artificial vessel bypass. However, the feasibility of reconstruction depends on the extent of invasion. In some instances, the reconstruction of the SVC can pose challenges due to the extent of the invasion and the complexity of the procedure. In cases wherein the tumor invades the aorta, achieving complete resection is often challenging, and incomplete resection may be the outcome. However, there have been reports wherein combined resection with aortic replacement was performed, which was also reported by Shintani *et al.* (25). Notably, a case of thymic carcinoma with aortic invasion was successfully treated with complete resection, and the patient has remained recurrence-free for a period of 3 years (45). These instances demonstrated that complete resection with aortic involvement is possible in select cases, leading to favorable outcomes. Several reports exist regarding the complete resection of TETs with aortic or cardiac invasion using cardiopulmonary bypass, yielding relatively favorable outcomes (46-48). The risk of systemic dissemination of tumor cells while employing cardiopulmonary bypass is deemed acceptable and seems to be low when juxtaposed with the risk of hematogenous tumor cell dissemination triggered by vascular invasion of malignant thymoma or thymic carcinoma (49,50).

On the other hand, among TETs, the challenge of achieving radical resection whenever feasible while considering the risk of potential postoperative complications from aggressive surgery has been highlighted in the context of locally advanced thymomas. In a study by Mastromarino *et al.*, it was concluded that even in cases of locally advanced thymomas resulting in incomplete resection, there were promising 5- and 10-year cancer-specific survival rates of 88% and 80%, respectively (51). This suggests that failure to achieve radical surgery does not preclude the possibility of a cure.

Surgical approach

The choice of surgical approach is a crucial factor in achieving complete resection of TETs. The selection of an optimal approach should prioritize adequate surgical visualization. Although median sternotomy is considered the gold standard for thymectomy, its efficacy may be limited in cases where the tumor extends beyond the mediastinum

Table 2 Surgical outcomes after induction therapy for locally advanced thymic epithelial tumors

Author	Year	Journal	Country	Study design	Induction treatment	Induction therapy chemo regimens	Histology	Eligibility stage criteria	Masaoka stage	Total (n)
Venuta (18)	2003	*Ann Thorac Surg*	Italy	Prospective	CT	Cisplatin-based regimens, 3	Thymoma: 11, thymic carcinoma: 4	Unresectable III	–	15
Kim (19)	2004	*Lung Cancer*	USA	Prospective	CT	CAMP (Kim) 3 course	Thymoma	Unresectable III, IVa and IVb	III: 11, IVa: 10, IVb: 1	22
Lucchi (20)	2005	*Ann Thorac Surg*	Italy	Prospective	CT	CEE 3 course	Thymoma	III and IVA	III: 25, IV: 11	36
Yokoi (37)	2007	*J Thorac Oncol*	Japan	Retrospective	CT	CAMP (Yokoi)	Thymoma	Unresectable III, IVa and IVb	III: 4, IVa: 6, IVb: 4	14
Wright (38)	2008	*Ann Thorac Surg*	USA	Retrospective	CRT	PE 2 course + RT 45 Gy	Thymoma	Unresectable III and IVa	III: 7, IVa: 3	10
Kunitoh (21)	2010	*Br J Cancer*	Japan	Prospective	CT	CODE	Thymoma	Unresectable III	–	21
Mineo (39)	2010	*Ann Surg Oncol*	Italy	Retrospective	CT	PE 3 course	Thymoma	Unresectable III	–	33
Cardillo (40)	2010	*Eur J Cardiothorac Surg*	Italy	Retrospective	CT	CAMP (Kim) 3–4 course	Thymoma, thymic carcinoma	Unresectable III and IVa	III: 18, IVa: 13	31
Rea (41)	2011	*Lung Cancer*	Italy	Retrospective	CT	ADOC 3–4 course	Thymoma, thymic carcinoma	Unresectable III, IVa and IVb	III: 23, IVa: 12, IVb 3	38
Park (22)	2013	*J Thorac Oncol*	Korea	Prospective	CT	CDDP + TXT, 3 course	Thymoma: 9, thymic carcinoma: 18	III and IV	III: 8, IVa: 17, IVb: 2	27
Korst (23)	2014	*J Thorac Cardiovascular Surgery*	USA	Prospective	CRT	PE 2 course + RT 45 Gy	Thymoma, thymic carcinoma	III, IV and I and II (>5 cm)	I: 2, II: 4, III: 12, IVa: 1, IVb: 2	22
Shintani (25)	2015	*Gen Thorac Cardiovasc Surg*	Japan	Retrospective	CRT or CT	CDDP + TXT, CBDCA + PTX, CODE, PE, ADOC + RT (40–60 Gy) (n=12)	Thymic carcinoma	III and IV	III: 11, IVb: 5	16
Cardillo (42)	2016	*Lung Cancer*	Italy	Retrospective	CRT or CT	ADOC, PAC, CEE	Thymoma, thymic carcinoma	III	–	108
Wei (33)	2016	*J Thorac Dis*	China	Retrospective	CRT or CT	Any	Thymoma, thymic carcinoma NET	III and IV	N/A	68
Kanzaki (43)	2019	*Interact Cardiovasc Thorac Surg*	Japan	Retrospective	CRT or CT	Any	Thymoma	III and IV	III: 12, IVa: 13, IVb: 4	29
Fan (24)	2020	*Int J Radiat Oncol Biol Phys*	China	Prospective	CRT	PE + IMRT 60 Gy	Thymoma: 22, thymic carcinoma: 34	III and IV	III: 8, IVa: 6, IVb: 42	56

Table 2 (*continued*)

Table 2 (*continued*)

Author	Year	Journal	Country	Study design	Induction treatment	Induction therapy chemo regimens	Histology	Eligibility stage criteria	Masaoka stage	Total (n)
Yu (44)	2021	*Thorac Cancer*	China	Retrospective	CRT	Platinum based regimens + RT 40–60 Gy	Thymoma	III and IV	III: 10, IVa: 8, IVb: 1	19
Wang (34)	2021	*Front Oncol*	China	Retrospective	CRT or RT or CT	any	Thymoma, thymic carcinoma	III and IV	N/A	81

CT, chemotherapy; CAMP (Kim), cyclophosphamide + cisplatin + doxorubicin + prednisolone; CEE, cisplatin + epirubicin + etoposide; CAMP (Yokoi), cisplatin + doxorubicin + prednisolone; CRT, chemoradiotherapy; PE, cisplatin + etoposide; RT, radiotherapy; CODE, cisplatin + vincristine + doxorubicin + etoposide; ADOC, adriamycin + cisplatin + vincristine + cyclophosphamide; CDDP, cisplatin; TXT, docetaxel; CBDCA, carboplatin; PTX, paclitaxel; PAC, cisplatin + doxorubicin + cyclophosphamide; IMRT, intensity modulated radiation therapy; NET, neuroendocrine tumor; N/A, not available.

or involves the pulmonary hilum on either side. In such scenarios, alternative approaches are necessary to ensure a clear and comprehensive field of view. For tumors extending cephalad to the mediastinum or towards the cervical or subclavian regions, a transmanubrial approach (TMA) is often employed to gain better access (52). Additionally, for tumors involving the pulmonary hilum, a T-shaped incision or hemiclamshell approach may be required to achieve an optimal visual perspective (53). In particular, the hemiclameshell approach offers a wider field of view and greater exposure. By utilizing these alternative approaches, surgeons can enhance their visualization capabilities, enabling a more thorough evaluation and complete tumor resection in TETs cases with complex anatomical involvement.

Conventional median sternotomy used for the surgical management of early-stage TETs has several alternative approaches. These include:

(I) Anterior chest wall lifting method (54): this method is predominantly employed within a unilateral video-assisted thoracoscopic surgery (VATS) approach. The procedure entails raising the anterior chest wall to facilitate access to the thymus, presenting an alternative avenue to sternotomy. The technique of anterior chest wall elevation has demonstrated particular efficacy in cases involving resection of cephalic thymic tissue via a thoracoscope. Nevertheless, Suda *et al.* (55) have noted that a comparable field of view can be attained through the application of carbon dioxide (CO_2) insufflation.

(II) Bilateral VATS (56): this minimally invasive approach uses small incisions and a thoracoscope to visualize and remove the thymus from both sides of the chest. In comparison to the unilateral VATS approach, this method affords sufficient coverage for both left and right thymectomy; however, a notable drawback is the prolonged duration of the operative procedure.

(III) Subxiphoid single-port thymectomy (57): in this approach, access to the thymus is achieved through a small single incision positioned below the xiphoid process of the sternum, facilitating thymus removal. Given that this single-port thymectomy procedure can be executed via a solitary 3.5-cm incision in the abdominal region, typically concealed beneath clothing, it boasts exceptional aesthetic qualities. Moreover, it ranks among the least invasive thymectomy techniques due to the absence of sternal incision and the avoidance of intercostal nerve injury. Suda *et al.* (58) documented that in comparison to VATS thymectomy, single-port thymectomy exhibited comparable operative duration, reduced blood loss, and expedited cessation of postoperative analgesic requirements. Nonetheless, this technique is not without its limitations. It necessitates the utilization of specialized instruments endowed with tip flexibility and mandates CO_2 insufflation. Additionally, the constrained surgical field accentuates the vulnerability to instrument interference.

(IV) Dual-port thymectomy using subxiphoid approach (59): the dual-port thymectomy, an advancement achieved by incorporating an additional port into the single-port thymectomy setup, significantly streamlines the surgical procedure

by obviating the risk of interference between forceps manipulated by the surgeon's two hands. Furthermore, akin to the subxiphoid single-port thymectomy, insertion of a camera scope through a subxiphoid incision allows for the acquisition of the same operative field as achieved through a median sternotomy with the dual-port technique. Should the complexity of the procedure warrant, the maneuverability can be enhanced by introducing additional ports. Notably, this technique's chief benefit lies in its capacity to deliver a favorable field of vision and elevated maneuvering ease.

(V) Robot-assisted thymectomy (55,60): robotic surgical systems are used to perform thymectomy, providing enhanced precision and dexterity to the surgeon. In robot-assisted thymectomy, the approach employed tends to differ across institutions, encompassing the utilization of both the lateral approach and the subxiphoid approach utilizing the dual-port technique. Irrespective of the chosen approach, the procedures are conducted using three to four robotic arms, thereby enabling the execution of precise and high-quality surgery within a three-dimensional field of view.

These examples demonstrate some alternative approaches available for TETs surgery, with each technique offering unique advantages and considerations. In addition to the aforementioned methods, many institutions have implemented the use of CO_2 insufflation to enhance the surgical field during TETs surgery (61). CO_2 insufflation involves introduction of carbon dioxide gas into the chest cavity, creating a pneumothorax. This technique helps improve visibility by creating a clear working space and reducing bleeding during the procedure.

Recently, sporadic reports have highlighted the effectiveness of minimally invasive approaches in managing locally advanced TETs (62-64). Minimally invasive approaches are expected to play a significant role in the surgical management of locally advanced TETs in the future. Kang *et al.* reported 110 cases of robotic thymectomy via the subxiphoid approach, including 67 cases of thymoma and 7 cases of Masaoka stage III or higher (65). This includes cases of combined resection of the pericardium, brachiocephalic vein, and lungs with robot-assisted thoracic surgery (RATS), and we expect to see more reports of combined resection of surrounding organs and angioplasty with minimally invasive approaches such as VATS and RATS in the future.

As technological advances and surgical techniques continue to evolve, there is a growing trend towards employing minimally invasive procedures in the treatment of various thoracic diseases, including TETs. However, notably, in cases of advanced thymomas classified as Masaoka stage III or above, conventional median sternotomy is still commonly used due to the complexities associated with the resection of the surrounding organs (23). The rationale behind adopting a median sternotomy as the surgical approach for locally advanced TETs could stem from the surgeon's conviction that the paramount objective of the procedure is to achieve radicality through the comprehensive excision of the tumor. Additionally, considering the intricacies of the operation, ensuring safety remains a crucial consideration. One must note that the suitability of a minimally invasive approach for locally advanced TETs depends on various factors, including the extent of tumor invasion, involvement of adjacent structures, surgeon expertise, patient-specific considerations, and safety of surgery. Each case should be evaluated individually, and the selection of the surgical approach should be based on a comprehensive assessment of these factors.

Vascular resection and reconstruction

In recent years, numerous reports have highlighted the surgical technique of combined SVC resection for locally advanced TETs (44,66). This approach involves removal of the thymic tumor along with a portion of the SVC if the tumor invades or compresses a major blood vessel. In the past, patients with SVC lesions were often deemed ineligible for surgery because of their high surgical complexity and associated risks. However, with ongoing innovations in the field, management of SVC lesions has improved remarkably. These advancements have led to the expansion of surgical indications and the ability to offer potentially curative procedures to patients who were previously considered unsuitable for surgery (67,68). The 5-year OS rate after radical surgery with SVC resection for advanced-stage TETs ranges from 45% to 58.1%. However, the rate of major complications ranged from 11.1% to 65% (67,69-71). In contrast, a recent retrospective study suggested that the presence or absence of concomitant SVC resection was not a poor prognostic factor for OS or progression-free survival (PFS) (44).

Generally, patchplasty is recommended when tumor invasion into the SVC or brachiocephalic vein is less than 30% of the vessel wall (72). However, when the

	Clot formation	Occlusion symptoms
(a)	–	+
(b)	+	+
(c)	++	+
(d)	++	–
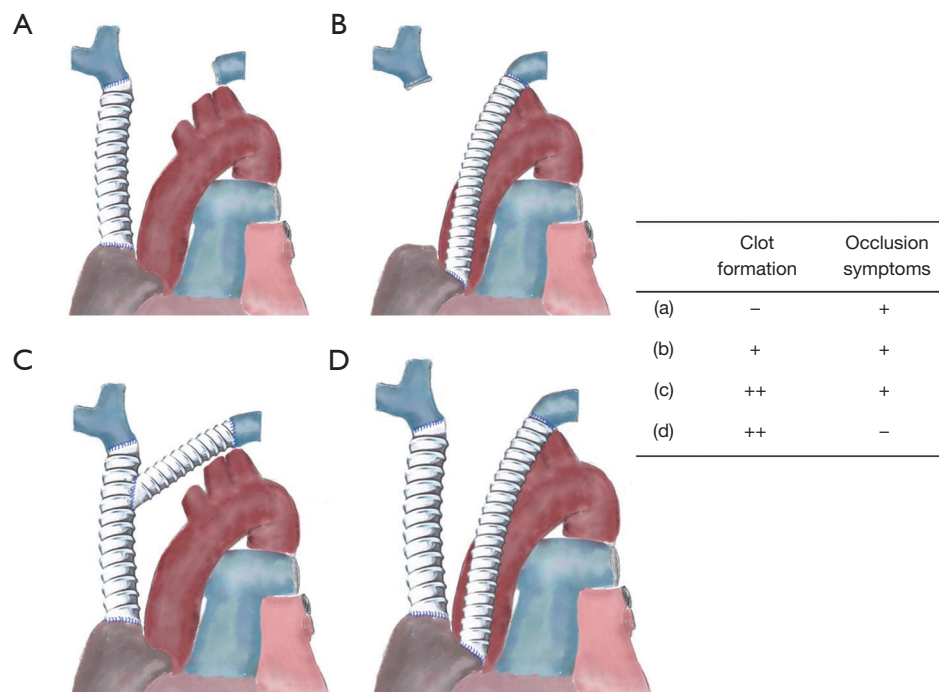
Figure 1 Vascular reconstruction of the SVC, right innominate vein, and left innominate vein using ePTFE graft. (A) Vascular reconstruction of the right innominate vein to the SVC with combined resection of the left innominate vein; (B) vascular reconstruction of the left innominate vein with combined resection of the right innominate vein and SVC; (C) vascular reconstruction of the right innominate vein to the SVC and left innominate vein using a Y-shaped anastomosis; (D) vascular reconstruction of the right innominate vein to the SVC and left innominate vein. The figure has been partially modified from the original source (76). SVC, superior vena cava; ePTFE, expanded polytetrafluoroethylene.

invasion exceeds 50%, complete resection of the vessel and reconstruction with an artificial vessel are recommended (69). If SVC blockage occurs without well-developed collateral vessels or a bypass, it can result in decreased cerebral venous return, reduced cardiac output, increased cerebral venous pressure, and potential complications, such as hemodynamic compromise, brain damage, and airway edema (73). Therefore, additional measures are often necessary to block the SVC. Many centers utilize a technique involving a bypass of the brachiocephalic vein to the right atrium using an artificial blood vessel along with tumor resection (74).

Artificial vessels with inner diameters of 10–14 mm for the brachiocephalic vein and 12–20 mm for the SVC are commonly used in revascularization. However, the risk of thrombus-related obstruction is a natural concern when using artificial vessel replacements because veins are low-pressure systems. Previous reports demonstrated a wide range of graft patency rates after vein replacement, ranging from 62% to 100% (75). This variability is influenced by several factors, including the material and diameter of the artificial vessel, surgical technique employed, and perioperative anticoagulation therapy.

Figure 1 shows the most common revascularization methods for the SVC and brachiocephalic veins (76). However, there is no consensus regarding the preferred reconstruction method, and different institutions have adopted different approaches. Although some reports suggest that using the largest possible vessel and performing reconstruction with a single artificial vessel is preferable (69,70), bypassing the left brachiocephalic vein has notable challenges, which has been linked to a high occlusion rate (77). Shintani *et al.* suggested that left brachiocephalic vein grafts are longer, resulting in a relatively slower blood flow velocity and an increased risk of occlusion. Therefore, they recommended avoiding reconstruction of the left brachiocephalic vein alone (78). They further advised separate reconstruction of each bilateral brachiocephalic vein because anastomosis between Y-shaped grafts is prone to thrombus occlusion. In contrast, Sekine *et al.* emphasized the importance of selecting a relatively thin graft (8–10 mm)

with a wide anastomotic opening to maintain sufficient flow velocity and prevent thrombus formation (79). They also highlighted the importance of avoiding graft torsion (79,80) to ensure successful reconstruction. These differing viewpoints indicate the complexities involved in selecting the optimal approach for SVC and brachiocephalic vein reconstruction, emphasizing the need for individualized decision making based on specific patient factors and surgical expertise.

However, the choice of materials for artificial vessel reconstruction remains debatable. Many centers opt for ring-shaped polytetrafluoroethylene (PTFE) grafts because of their favorable characteristics. PTFE grafts offer good patency, and the rigidity of the ring structure helps prevent graft collapse and withstand compression (69). Compared to other synthetic grafts, PTFE has a lower propensity for thrombus formation, allows for immediate postoperative re-epithelialization, and carries a lower risk of infection and platelet deposition. Natural materials, such as the bovine pericardium, also offer advantages over synthetic options, including a reduced risk of infection and decreased likelihood of thrombosis. In particular, tubed bovine pericardial conduits have a lower incidence of infections and thrombosis (69). Consequently, some facilities have begun to favor the use of tubed bovine pericardial conduits as alternatives to synthetic materials (81). Although Oizumi *et al.* suggested that intraoperative heparin and postoperative anticoagulants may not be necessary for SVC reconstruction (77), many centers still advocate the use of anticoagulation therapy for a certain duration after surgery. Typically, anticoagulation is continued for at least 6 months postoperatively, allowing sufficient time for endothelial formation in the graft. However, even after 6 months, there remains a risk of thrombus formation, and if possible, considering ongoing anticoagulation therapy is advisable to mitigate this risk. Ultimately, the duration and necessity of anticoagulation therapy should be determined on an individual basis, considering the patient's overall condition, risk factors, and surgical outcomes.

Phrenic nerve reconstruction

The phrenic nerve mainly originates from the C4 cervical nerve and descends into the thoracic cavity along the anterior surface of the anterior scalene muscle. It passes between the mediastinal pleura and the pericardium and continues anteriorly into the thoracic cavity until it reaches the diaphragm. Owing to its anatomical position,

the phrenic nerve is susceptible to tumor invasion in cases of locally advanced TETs. Invasive thymomas have been reported to involve the phrenic nerve in approximately 33% of cases (82). Moreover, the occurrence of diaphragmatic paralysis subsequent to concurrent resection of the phrenic nerve leads to a notable 20% to 30% reduction in lung capacity (83). Previous surgical reports have indicated that 21–68% of patients with locally advanced TETs require concomitant resection of the phrenic nerve to achieve complete tumor removal (23,25,39-41).

Unilateral phrenic nerve paralysis is a frequent complication of thoracic surgery that can cause symptoms, particularly in patients with marginal lung function (84,85). Schoeller *et al.* suggested that rapid microsurgical reconstruction of the phrenic nerve might be the optimal treatment for post phrenic nerve complications, especially in cases of nerve transection during surgery (86). The intercostal nerve is commonly used for phrenic nerve reconstruction, but there have been reports of using other nerves, such as the collateral mitral branch of the accessory nerve and the peroneal nerve. Additionally, techniques, such as anastomosis with 8-0 suture and fibrin glue, have been employed for nerve reconstruction (86,87). Nerve reconstruction is generally considered less invasive than diaphragm plication, which involves surgical tightening of the diaphragm muscle. However, nerve reconstruction is typically recommended in cases of short-term paralysis after nerve transection only. This is because prolonged paralysis can lead to the collapse and degeneration of the motor endplates, which are necessary for muscle innervation. The effectiveness of nerve reconstruction diminishes when the motor endplates are irreversibly denervated. Therefore, early intervention with nerve reconstruction is crucial for maximizing the chances of successful reinnervation and functional recovery of the diaphragm. According to Schoeller *et al.*, immediate microsurgical phrenic nerve repair is recommended when phrenic nerve palsy is diagnosed due to complications from resection or surgery. However, certain conditions must be satisfied for this approach (86).

(I)   Sufficient timeframe: nerves regenerate at a rate of approximately 1 mm per day from the proximal nerve junction site to the motor endplate of the diaphragm. Therefore, a timeframe that allows complete reinnervation is required.

(II) Thoracotomy for other reasons: the thoracotomy, a surgical incision into the chest wall, should be performed for reasons unrelated to nerve

reconstruction.

(III) General condition of the patient: the patient should be in a stable general condition that allows at least 30 min of additional operative time for nerve reconstruction without an increased risk to well-being.

By fulfilling these conditions, immediate microsurgical phrenic nerve repair can be considered a treatment option for phrenic nerve palsy in cases of complications related to resection or surgery. Recovery of diaphragmatic motion following nerve reconstruction can take a variable amount of time, typically ranging from 3 to 12 months (88). The success rate of reinnervation using nerve grafts is reported to be 66.7% (88); the success of reinnervation depends on several factors (89), including the interval between nerve resection and reconstruction, the shorter the time between nerve resection and reconstruction, the higher the likelihood of successful reinnervation. Early intervention allows for better nerve regeneration and functional recovery.

(IV) Mechanical tension at the anastomosis: tension applied to the nerve anastomosis plays a role in successful reinnervation. Appropriate tensioning ensures optimal alignment and promotes nerve regeneration.

(V) Sharpness of the injury: the nature and severity of the nerve injury can influence the likelihood of successful reinnervation. Nerves that have been sharply cut or cleanly transected tend to have better regenerative potential than those with more extensive damage.

Aprile *et al.* and Yano *et al.* (90,91) have reported that, for TETs at or beyond the Masaoka III stage, retaining the integrity of the phrenic nerve, even when the nerve is involved, leads to enhanced functional prognosis, without discernible variations in long-term survival rates. Accordingly, the preservation of the phrenic nerve is deemed significant in the context of surgical intervention, even in cases of advanced disease. However, that the surgical management of locally advanced TETs could potentially entail resection of both phrenic nerves. Various methods have been employed to address this complication, including positive pressure ventilation, permanent ventilatory support, diaphragmatic pacing, and diaphragm plication (92). Bilateral diaphragmatic plication for bilateral phrenic nerve palsy may preserve lung capacity in the acute phase.

However, the long-term effects of the procedure remain poorly understood. Diaphragmatic nerve reconstruction may be the only curative treatment for nerve palsy. It aims to restore diaphragmatic functionality and enable normal breathing. Case reports have documented successful outcomes in patients with bilateral diaphragmatic nerve palsy following diaphragmatic nerve reconstruction and diaphragm plication procedures (93).

Surgical outcomes of locally advanced TETs

There is limited literature available on the surgical treatment of locally advanced TETs following induction therapy, particularly regarding short-term postoperative outcomes. This chapter aimed to shed light on short-term postoperative outcomes following induction therapy for locally advanced TETs. *Table 3* lists reports of the surgical treatment of locally advanced TETs after induction therapy since 2000, including the results of postoperative complications. The total number of cases was 466, and the reported incidence of postoperative complications varied widely from 4.8–42% (19-21,23,25,34,38-44). Only few reports have described the grading of complications. However, one must note that locally advanced TETs are a heterogeneous group, and the use of different induction therapy approaches, including radiotherapy and chemotherapy, further complicates direct comparisons between studies. Upon reviewing these reports, it is evident that complications such as pneumonia, atelectasis, atrial fibrillation, other arrhythmias, postoperative bleeding, and postoperative wound infection are relatively common. These complications are expected given the highly invasive nature of the surgery and resection of the surrounding organs, which is often necessary in the treatment of locally advanced TETs. Additionally, the relatively high frequency of respiratory failure and acute respiratory distress syndrome (ARDS) attributed to phrenic or recurrent nerve palsy and potential exacerbation of MG, which may be characteristic of this particular patient population. Mineo *et al.* reported a mild correlation between the incidence of postoperative complications and factors, such as the presence of complications, reconstruction of surrounding organs, and complete tumor resection (39). In contrast, Yu *et al.* found that the group that received preoperative chemoradiotherapy had a significantly higher rate of surgical site infection than the group that did not receive such treatment. However, no significant differences were found in the postoperative chest tube drainage

Table 3 Complications and perioperative mortality in surgery after induction therapy for locally advanced thymic epithelial tumors

Author	Year	Study design	Total (n)	Morbidity rate	Details of complications	Mortality rate
Kim (19)	2004	Prospective	22	1 (4.5%)	ARDS	0%
Lucchi (20)	2005	Prospective	36	> G3: 0%	–	0%
Wright (38)	2008	Retrospective	10	2 (20%)	Cardiac tamponade, ARDS	0%
Kunitoh (21)	2010	Prospective	21	1 (4.8%)	Pulmonary infarction	0%
Mineo (39)	2010	Retrospective	33	14 (42%)	Acute pneumonia (n=6) and respiratory failure requiring tracheal intubation (n=4)	N/A
Cardillo (40)	2010	Retrospective	31	9 (29%)	Pulmonary embolism (n=1), postoperative bleeding (n=1), pulmonary infections (n=2) and wound infections (n=5). One patient experienced adult respiratory distress syndrome after surgical resection and required prolonged hospitalisation	0%
Rea (41)	2011	Retrospective	38	4 (5.3%)	A wound infection with sternal dehiscence, a bronchopleural fistula after pneumonectomy, pneumonia, and respiratory insufficiency in a patient with myasthenia gravis and phrenic nerve resection	0%
Korst (23)	2014	Prospective	22	8 (36.4%)	Pneumonia, pulmonary infiltrate, hemothorax, mucous plugging, aspiration, pleural effusion, intraoperative cardiac arrest, multiple organ failure, neutropenia, dressler syndrome (n=2), atrial fibrillation (n=3)	2 (9%)
Shintani (25)	2015	Retrospective	16	6 (37.5%)	Bleeding, cardiac depolarization, cardiac tamponade, chylothorax, and bilateral recurrent nerve palsy	0%
Cardillo (42)	2016	Retrospective	108	21 (19.4%)	Mostly anemia requiring blood transfusion or atelectasis	2 (1.8%)
Kanzaki (43)	2019	Retrospective	29	6 (21%)	Myasthenic crisis, pneumonia, postoperative bleeding, recurrent nerve palsy, cardiac hernia, chylothorax, wound infection, respiratory failure	0%
Yu (44)	2021	Retrospective	19	–	Arrhythmia, pneumonia, surgical site infection, hoarseness, myasthenic crisis, postoperative bleeding, empyema, pulmonary thromboembolism	0%
Wang (34)	2021	Retrospective	81	12 (14.8%)	Including four cases of bleeding, five cases of hydrothorax, two cases of atelectasis and one case of unhealing wounds	0%

ARDS, acute respiratory distress syndrome; G3, grade 3; N/A, not available.

time, hospitalization time, postoperative arrhythmia, or incidence of pneumonia between the groups that underwent chemoradiotherapy plus surgery and those that underwent surgery alone (44).

Surprisingly, a low perioperative mortality rate has been observed in patients treated with induction therapy followed by surgery for locally advanced TETs. Most studies have reported a perioperative mortality rate of 0%. However, Cardillo *et al.* conducted a retrospective study of 108 patients and reported perioperative mortality in two cases (1.8%) (42). Similarly, Korst *et al.* conducted a prospective study and reported two cases (9%) of perioperative mortality (23). Among the cases reported by Korst *et al.*, one was a patient who experienced respiratory failure due to aspiration pneumonia after combined resection of the phrenic and vagus nerves, and the other was a case of cardiac arrest and multi-organ failure during debulking surgery in a patient with clear infiltration of the ascending aorta (23). As locally advanced TETs often require resection of the surrounding organs, the decision to proceed with surgery should be carefully evaluated, taking into consideration the patient's general condition and other relevant factors.

The postoperative survival outcomes are presented in *Table 2*. The 5-year OS, 5-year recurrence-free survival (RFS), and 10-year OS rates after induction therapy for locally advanced TETs ranged from 44.9% to 100%, 29.5% to 83%, and 19.9% to 90%, respectively (18-25,33,34,37-44). Although there is considerable variation among the reports, the overall results are generally favorable. These outcomes reflect the oncological characteristics of thymomas. Distinguishing between thymomas and thymic carcinomas in TETs can be challenging, particularly when making histological diagnoses prior to treatment. Multiple factors need to be considered, ranging from the initial diagnosis to the implementation of induction therapy and the determination of the appropriate surgical approach.

Limitation

This narrative review has several limitations. Firstly, it should be noted that this is not a comprehensive systematic review encompassing all available research on locally advanced TETs. Furthermore, we did not conduct a specific comparison of the overall quality of the research included in our review. Our focus was on incorporating relevant literature pertaining to induction therapy, combined resection of surrounding organs, surgical approach, revascularization, diaphragmatic nerve reconstruction, and short-term postoperative outcomes, with the aim of providing guidance for perioperative management of locally advanced TETs.

Conclusions

In locally advanced TETs, the short-term postoperative outcomes of surgical treatment after induction therapy are generally acceptable, with a relatively low mortality rate. However, surgical resection of the surrounding organs is often necessary, and effective management of postoperative complications is crucial. In certain cases, incomplete resection occurs, particularly when the tumor invades the pulmonary trunk or aorta. Therefore, the complexities associated with resecting these large vessels must be carefully considered, keeping in mind the patient's overall condition and treatment outcomes. We anticipate future advancements in minimally invasive surgical approaches, surgical techniques, and perioperative pharmacotherapies.

Acknowledgments

Footnote

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