Review Article

Surgical outcomes of patients with locally advanced thymic epithelial tumor undergoing induction therapy followed by surgery: a narrative review

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Background and Objective: Thymic epithelial tumors (TETs), including thymomas and thymic cancers, are relatively rare malignancies originating from the thymus. Although complete surgical resection is the cornerstone of treatment for these tumors, the optimal management strategy for locally advanced cases remains uncertain. Neoadjuvant therapies, with their potential to improve the likelihood of complete resection, are promising, particularly in marginally operable cases. However, the current evidence supporting this approach is lacking. This review of the existing literature on the efficacy of induction therapy followed by surgical resection for stage III or IV locally advanced TETs aimed to provide an up-to-date perspective and highlighting directions for future clinical research.

Methods: PubMed was searched using the keywords "surgery," "survival", "thymoma", "thymic cancer", and "induction therapy". Relevant articles including case series, retrospective studies, prospective studies, and review articles were reviewed and selected for this comprehensive narrative review.

Key Content and Findings: This review included primarily revealed retrospective studies and a limited number of prospective phase II trials on induction therapy followed by surgery for stage III or IV locally advanced TETs. No randomized phase III studies were identified, indicating that a comprehensive evaluation of the benefits of induction therapy on overall survival (OS) has not yet been conducted. Induction therapies for both invasive thymoma and thymic cancer included chemotherapy, radiotherapy, and chemoradiotherapy, with anthracycline-based combination chemotherapies being the primary option. For exclusively invasive thymomas, the median rate of complete surgical resection and the 5-year OS rate were reported as 76% and 85%, respectively. Literature focusing on induction therapy for TETs, which includes both thymoma and thymic cancers, indicates that the rates of complete resection and 5-year OS are 76% and 70%, respectively.

Conclusions: Our narrative review of retrospective and prospective studies highlighted promising long-term OS rates in patients with advanced TETs who underwent induction therapy followed by surgical resection. These findings support this multimodal treatment strategy in selected patients with stage III and IV TETs.

Keywords: Thymoma; thymic cancer; survival; induction therapy; surgery

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Introduction

Thymic epithelial tumors (TETs), including thymomas and thymic carcinomas, are relatively rare, with an annual incidence of approximately 3.2 cases per million (1). Although complete surgical resection remains the gold standard treatment for TETs, achieving this is generally easier in the early stages. Based on the Masaoka (-Koga) staging system, invasion into neighboring structures or the presence of diffuse pleural or pericardial disseminations can hinder radical resection in stage III or IV locally advanced TETs. Patients with locally advanced TETs have poorer outcomes than those with early stages, highlighting the clinical need for multimodal approaches (2-5). For patients with marginally resectable TETs, the neoadjuvant approach can decrease the tumor burden to allow for successful resection. In advanced cases deemed inoperable during preoperative evaluations, the preference leans toward induction therapy, as it may increase the resection rate and decreases the incidence of systemic relapse. However, published data of the managing of locally advanced TETs is lacking, indicating that no standardized management guidelines exist. Given the paucity of robust evidence and the small sample sizes in published studies, we aimed to conduct a narrative review to thoroughly characterize the long-term survival outcomes of patients who underwent induction therapy followed by surgical resection for 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-23-57/rc).

Methods

The search strategy is summarized in *Table 1*. Briefly, we searched PubMed without date restrictions up to January 31, 2024. We only considered manuscripts written in English. The search strategy included the terms “surgery”, “survival”, “thymoma”, “thymic cancer”, and “induction therapy”. This strategy allowed for a selection of representative studies emphasizing tumor characteristics, types of induction therapy, adjuvant therapy, surgical outcomes, recurrences, and overall survival (OS) for stage III to IV TETs. As there is no definitive definition for locally advanced TETs, most studies addressing this topic include stage III (macroscopic invasion into neighboring organ) and IVa (pleural and pericardial metastases) TETs, however, treatment strategies involving preoperatively determined induction therapy, followed by surgical resection, have been employed even for stage IVb diseases (lymphogenous or hematogenous metastasis). This prompted us to collect reports on stage III and IV diseases, with the inclusion of invasive thymomas and thymic carcinoma and the exclusion of thymic neuroendocrine tumors. The article types included retrospective studies, prospective studies, and review articles. Articles without full texts or those with incomplete or irrelevant data were excluded.

Literature review method

We identified 37 studies that met our inclusion criteria. *Table 2* enumerates the studies related to thymoma, *Table 3* details studies concerning thymic cancer, and *Table 4* compiles studies addressing both thymoma and thymic cancers. We also referred to a meta-analysis on induction therapy for locally advanced TETs written by Hamaji *et al.* and a systematic review on overall treatment for TETs published by Falkson *et al.* (2,4). To date, no randomized trials have addressed the management of locally advanced TETs.

Patient and disease characteristics

The mean age at TET diagnosis is typically 50–60 years; however, these tumors can be diagnosed in both children and older individuals. A consistent sex bias for thymomas is generally not seen, although a mild female predominance is observed for type A, AB, and B1 subtypes, whereas carcinomas tend to show male predominance (5,43-46). In the 11 retrospective and two prospective studies addressing locally advanced thymoma, patient numbers varied between 7 and 370, as detailed in *Table 2*. For thymic cancer, the seven retrospective studies included patient counts ranging from 7 to 31, as shown in *Table 3*. A total of 14 retrospective and 3 prospective studies encompassing both invasive thymoma and thymic cancer reported patient numbers ranging from 6 to 301, as detailed in *Table 4*. Among the 37 studies, all but two reported an average patient age within the 40s and 50s. Specifically, the age range was 43.5–58 years for thymoma (*Table 2*), 47.3–60.8 years for thymic cancer (*Table 3*), and 41.8–65.2 years for studies including both thymoma and thymic cancer (*Table 4*). In the studies focusing on patients with thymoma, four studies targeted stage III disease, four studies examined stage IV disease, and the remaining studies included both stage III and IV diseases (*Table 2*). For thymic cancers, all studies encompassed stage III and IV diseases (*Table 3*). Specifically,

Table 1 The search strategy summary

Items	Specification
Date of search	January 30, 2024
Databases and other sources searched	PubMed
Search terms used	"Surgery", "survival", "thymoma", "thymic cancer", and "induction therapy"
Timeframe	Date unrestricted to January 30, 2024
Inclusion and exclusion criteria	Inclusion: English language, case series, retrospective study, prospective study, review article
	Exclusion: case report, no surgical cases
Selection process	Y.S. selected literature, and chose those for inclusion
Any additional considerations, if applicable	References of selected studies were reviewed for inclusion

Table 2 Summary of studies on induction therapy followed by surgery for locally advanced thymomas

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT (%)	Study type	Stage, n
Leuzzi *et al.* (2016 Italy) (6)	1990–2010	370	195	54	24.9	Retrospective	III
Yamada *et al.* (2015 Japan) (7)	1991–2010	310	140	58	13.5	Retrospective	III
Mineo *et al.* (2010 Italy) (8)	1989–2008	33	13	55.5	100	Retrospective	III
Kunitoh *et al.* (2010 Japan) (9)	1997–2005	23	6	56	100	Prospective (phase II)	III
Rena *et al.* (2012 Italy) (10)	1998–2008	18	8	54.5	100	Retrospective	IVa
Yang *et al.* (2011 Korea) (11)	1994–2009	7	3	49	57	Retrospective	IVa
Nakamura *et al.* (2019 Japan) (12)	2003–2017	19	8	49	100	Retrospective	IV
Huang *et al.* (2007 USA) (13)	1996–2006	18	10	43.5	100	Retrospective	IV
Jalil *et al.* (2023 Jordan) (14)	2015–2021	15	5	46.3	52	Retrospective	III, 3
							IV, 12
Yokoi *et al.* (2007 Japan) (15)	1998–2003	17	8	50.6	82	Retrospective	III, 4
							IVa, 9
							IVb, 4
Lucchi *et al.* (2006 Italy) (16)	1989–2004	30	17	53.7	100	Retrospective	III, 20
							IVa, 10
Kim *et al.* (2004 USA) (17)	1990–2000	22	13	47	100	Prospective (phase II)	III, 11
							IVa, 10
							IVb, 1
Bretti *et al.* (2004 Italy) (18)	1989–2000	63	26	51	52	Retrospective	III, 43
							IVa, 20

InT, induction therapy; Stage, Clinical Masaoka (-Koga) stage.

Table 3 Summary of studies on induction therapy followed by surgery for locally advanced thymic cancers

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT or PrT (%)	Study type	Stage, n
Shintani *et al.* (2015 Japan) (19)	1998–2014	16	5	52	100	Retrospective	III, 11
							IVb, 5
Kawasaki *et al.* (2014 Japan) (20)	2001–2010	7	1	47.3	100	Retrospective	III, 5
							IV, 2
Filosso *et al.* (2014 Italy) (21)	2000–2011	31 (40*)	15*	54.5*	35	Retrospective	III, 24
							IVa, 7
Okereke *et al.* (2012 USA) (22)	1990–2011	9 (16*)	7*	52*	56	Retrospective	III, 8
							IVa, 1
Yano *et al.* (2008 Japan) (23)	1983–2006	28 (30*)	14*	59*	18	Retrospective	III, 13
							IVa, 7
							IVb, 8
Suzuki *et al.* (2005 Japan) (24)	1997–2003	11	7	49	36	Retrospective	III, 4
							IVa, 1
							IVb, 6
Takeda *et al.* (2004 Japan) (25)	1983–2003	13 (15*)	5*	60.8*	31	Retrospective	III, 5
							IVa, 4
							IVb, 4

*, including stage I or II patients. InT, induction therapy; PrT, preceding treatment; Stage, Clinical Masaoka (-Koga) stage.

three studies concentrated on stage III disease, one study was exclusive to stage IV disease, and the remaining studies investigated both stage III and IV diseases (*Table 4*). Stage IV diseases could not be classified based on disease status, such as local invasion or dissemination, due to a lack of information in some studies. However, many studies involved cases of stage IV diseases that were initially considered unresectable. Despite these initial assessments, the primary therapeutic goal remained to achieve complete surgical resection, aiming for long-term survival.

Two prospective phase II studies specifically targeted locally advanced thymoma (*Table 2*). Kunitoh *et al.* demonstrated that a weekly dose-dense chemotherapy regimen with cisplatin, vincristine, doxorubicin, and etoposide, followed by surgical resection, was safely administered to 21 patients with stage III thymomas (9). This approach resulted in an 82% complete surgical resection rate (9). Conversely, Kim *et al.* found that induction chemotherapy using cyclophosphamide, doxorubicin, cisplatin, and prednisone, followed by surgical resection, achieved response rates of 80% and complete resection rates of 76% among 22 patients with stage III or IV thymomas (17). Shintani *et al.* reported the outcomes of a multimodal treatment approach for stage III and IV thymic carcinomas (19). Their study included 13 squamous cell carcinomas, two neuroendocrine carcinomas, and one undifferentiated carcinoma, and all patients underwent neoadjuvant chemotherapy. This study found that incomplete surgical resection and pathological vessel invasion were significant unfavorable factors for OS (19). In contrast, Kawasaki *et al.* administered weekly chemotherapy using a combination of cisplatin, vincristine, doxorubicin, and etoposide (CODE), followed by surgery, in seven cases of thymic cancers (20). These included six squamous cell carcinomas and one adenosquamous cell carcinoma. Notably, 4 of the 7 patients achieved an extended OS, surpassing 100 months after surgical resection (20).

The median percentages for each histologic subtype, based on the World Health Organization classification, were as follows: type A, 5% (range, 2–15%); type AB, 11%

Table 4 Summary of studies on induction therapy followed by surgery for locally advanced thymomas or thymic cancers

Studies	Study period	No. of patients	Sex (female), n	Mean age (years)	Rate of InT (%)	Study type	Diagnosis	Stage, n
Kirzinger *et al.* (2016 Germany) (26)	2005–2010	17	13	65.2	100	Prospective (phase II)	IT, 15	III, 17
							TC, 2	
Cardillo *et al.* (2016 Italy) (27)	1990–2010	108	47	51.5	100	Retrospective	IT, 88	III, 108
							TC, 20	
Marulli *et al.* (2011 Italy) (28)	1980–2009	249	112	50	37.8	Retrospective	IT, 221	III, 249
							TC, 28	
Kaba *et al.* (2018 Tarkey) (29)	2002–2015	39	17	41.8	64	Retrospective	IT, 30	IVa, 39
							TC, 9	
Guan *et al.* (2023 China) (30)	2008–2019	31	16	51.7	100	Retrospective	IT, 16	III, 20
							TC, 15	IVb, 11
Park *et al.* (2019 Korea) (31)	2000–2013	102	43	50	100	Retrospective	IT, 51	III, 38
							TC, 51	IV, 64
Ma *et al.* (2019 Taiwan region) (32)	2005–2013	45	24	59	100	Retrospective	IT, 15	III, 15
							TC, 30	IVa, 13
								IVb, 17
Suh *et al.* (2019 Korea) (33)	2000–2013	18	7	48.3	100	Retrospective	IT, 10	III, 13
							TC, 8	IVa, 3
								IVb, 2
Wei *et al.* (2016 China) (34)	1994–2012	68	25	44.8	100	Retrospective	IT, 32	III, 55
							TC, 36	IV, 13
Filosso *et al.* (2015 Italy) (35)	1990–2012	301 (797*)	388*	58*	15*	Retrospective	IT, 745*	III, 223
							TC, 52*	IV, 78
Ried *et al.* (2015 Germany) (36)	2010–2014	6	1	46	83	Retrospective	IT, 4	III, 4
							TC, 2	IVa, 2
Korst *et al.* (2014 USA) (37)	2007–2012	15 (21[#])	4	51	100	Prospective (phase II)	IT, 14	III, 12
							TC, 7	IVa, 1
								IVb, 2
Park *et al.* (2013 Korea) (38)	2007–2011	27	11	54	100	Prospective (phase II)	IT, 9	III, 8
							TC, 18	IVa, 17
								IVb, 2
Rea *et al.* (2011 Italy) (39)	1980–2008	75	43	53	51	Retrospective	IT, 68	III, 51
							TC, 7	IVa, 18
								IVb, 6
Wright *et al.* (2008 USA) (40)	1997–2006	10	7	51.4	100	Retrospective	IT, 9	III, 7
							TC, 1	IVa, 3
Lucchi *et al.* (2005 Italy) (41)	1976–2003	56	21	53.3	64.2	Retrospective	IT, 42	III, 40
							TC, 14	IVa, 16
Jacot *et al.* (2005 France) (42)	1995–2001	8	4	53.8	100	Retrospective	IT, 5	III, 3
							TC, 3	IV, 5

*, including stage I or II patients; [#], including stages I to IV patients. InT, induction therapy; Stage, Clinical Masaoka (-Koga) stage; IT, invasive thymoma; TC, thymic cancer.

(2–18%); type B1, 15% (1–30%); type B2, 28% (2–88%); type B3, 22% (5–50%); type B1+2, 9% (6–11%); type B1+3, 9% (6–11%); type B2+3, 11%; and type C, 25% (12–67%). The predominant histologic subtype was type B, and approximately 15% of cases exhibited a type A element. Studies have indicated that approximately 30% of patients with thymoma have myasthenia gravis (MG), and approximately 20% of patients with MG are diagnosed with thymoma (5). In this review, 13 retrospective studies referred to the presence of MG preoperatively, with a median prevalence of 22% (range, 0–46%).

Induction therapy

One of the standard treatment approaches for locally advanced TETs preoperative induction therapy followed by radical resection. Induction therapy is thought to diminish tumor size and surgical complexity, facilitating more comprehensive surgical resections, reducing local recurrence rates, and improving long-term survival in a subset of patients with locally advanced TETs. However, the efficacy of induction therapies, such as chemotherapy, radiotherapy (RT), and chemo-radiotherapy (CRT) remains uncertain. Falkson *et al.* found no significant difference in OS among patient with thymoma who received neoadjuvant therapy compared to those who did not (hazard ratio =1.53, 95% confidence interval: 0.77–3.33, P=0.29) (2). Very few studies have been conducted on induction therapy for thymic carcinomas and none have demonstrated significant differences in survival between patients who received neoadjuvant therapy and those who did not. Questions persist regarding the combination of modalities that is most effective and whether postoperative therapy is necessary for patients who have undergone induction treatment.

Table 5 presents the types, detailed regimens, and response rates of induction therapy followed by surgical resection for patients with invasive thymoma. Of the 13 studies analyzed, 9 (69%) used chemotherapy as an induction option; 2 (15%) employed either chemotherapy, RT, or CRT, 1 (8%) opted for chemotherapy or CRT, and 1 (8%) used chemotherapy or RT. The 13 studies featured a total of 9 types of chemotherapeutic regimens: CAP (cyclophosphamide + doxorubicin + cisplatin), CAMP (cisplatin + doxorubicin + methylprednisolone), ADOC (cyclophosphamide + doxorubicin + cisplatin + vincristine), PE (cisplatin + etoposide), CP (cisplatin + docetaxel), CAV, cyclophosphamide + doxorubicin + vincristine, VIP (cisplatin + vincristine + ifosfamide), CODE (doxorubicin + cisplatin + vincristine + etoposide), and CAP + prednisolone. Generally, chemotherapeutic regimens that include adriamycin and/or platinum-based multi-agent combinations are recommended unless patients are ineligible for anthracycline. In terms of therapeutic response, induction chemotherapy had a complete response (CR) of 0–14%, a partial response (PR) of 4–86%, and an overall response rate of 4–93%. Falkson *et al.* reported that anemia (39%) and leukopenia (30%) were the predominant chemotherapeutic side effects in patients with stage III or IV thymomas who received induction chemotherapy prior to surgery (2).

For the studies focusing on thymic cancer, the types, regimens, and response rates of induction therapy are shown in *Table 6*. Of the four studies, all used chemotherapy as induction treatment. The observed response rates only in two studies were CR of 0% and PR of 71% and 75%, respectively. Regimens used for thymic cancer included CP, TP (paclitaxel + carboplatin), CODE, PE, and ADOC. Furthermore, adverse events exceeding grade 3 included neutropenia (10–61%), leukopenia (7–57%), diarrhea (11%), alopecia (4%), and anemia (8%).

Among the 16 studies involving both thymoma and thymic cancer, chemotherapy was the induction treatment in 11 studies (69%), while CRT was utilized in three studies (19%), shown in *Table 7*. One study (6%) allowed a choice between chemotherapy, RT, or CRT, and another study provided an option between chemotherapy or CRT. Regimens used in the studies included CAP, CP, TP, ADOC, CAP, PE, octreotide + prednisolone, and CEE (cisplatin + epirubicin + etoposide). Guan *et al.* compared concurrent and sequential CRT for the induction treatment of stage III or IV TETs (30). Their findings indicated no statistically significant differences in the response rate, radical surgical resection rate, or survival between the two treatments; however, sequential CRT was associated with a lower likelihood of adverse events. Across the studies, the observed adverse events from induction chemotherapy included neutropenia (27–71%) and vomiting (5–72%), with variations based on the specific regimens. In a phase II study conducted by Korst *et al.*, induction CRT (PE and concurrent 45 Gy radiation) was administered to patients with stage III or IV TETs and 21 of 22 patients successfully completed the induction regimen (37).

Surgery and complication

Complete surgical resection is a critical determinant of

Table 5 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymomas

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Abdel Jalil *et al.* (2023 Jordan) (14)	CT	CAP	CR, 0; PR, 4	NI	78	115 M (mean)	22
Nakamura *et al.* (2019 Japan) (12)	CT	CAMP	CR, 0; PR, 79	NI	100	76.7 (5Y) 76.7 (10Y)	78 (7 of 9 RPD group)
Leuzzi *et al.* (2016 Italy) (6)	CT/RT/CRT	ADOC/CAP/ others	NI	NI	65	Tri, 86.3 (5Y) 84.9 (10Y)	17.5 (total)
Yamada *et al.* (2015 Japan) (7)	CT/RT/CRT	NI	CR, 2; PR, 37	Lu, PC, CW, V, Ph	80	80.2 (10Y)	27.5
Rena *et al.* (2012 Italy) (10)	CT	ADOC/PE	CR, 6; PR, 61	Lu, PC, Dia, V, Ph	67	85 (5Y) 53 (10Y)	56
Yang *et al.* (2011 Korea) (11)	CT	CP/CAV/VIP	NI	EPP	75	26 M (median)	25
Kunitoh *et al.* (2010 Japan) (9)	CT	CODE	NI	NI	82	91 (5Y)	61.9 (PT, PC, PL)
Mineo *et al.* (2010 Italy) (8)	CT	PE	Good, 37	Lu, PC, Dia, V	51	NI	NI
Yokoi *et al.* (2007 Japan) (15)	CT	CAMP	CR, 7; PR, 86	NI	22	80.7 (5Y) 80.7 (10Y)	100
Huang *et al.* (2007 USA) (13)	CT/CRT	CP/CAP/VIP/PE	CR, 0; PR, 67	Lu, PC, V, CW, Dia	67	78 (5Y) 65 (10Y)	NI
Lucchi *et al.* (2006 Italy) (16)	CT	CAP	CR, 7; PR, 67	NI	77	82.4 (10Y)	NI
Kim *et al.* (2004 USA) (17)	CT	CAP + prednisolone	CR, 14; PR, 64	NI	76	95 (5Y) 79 (7Y)	NI
Bretti *et al.* (2004 Italy) (18)	CT/RT	ADOC/PE	CR, 8; PR, 64	NI	67	Stage III, 142.1 M (median) Stage IVa, 45.9 M (median)	NI

InT, induction therapy; CT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; CAP, cyclophosphamide + doxorubicin + cisplatin; CAMP, cisplatin + doxorubicin + methylprednisolone; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; PE, cisplatin + etoposide; CP, cisplatin + docetaxel; CAV, cyclophosphamide + doxorubicin + vincristine; VIP, cisplatin + vincristine + ifosfamide; CODE, doxorubicin + cisplatin + vincristine + etoposide; CR, complete response; PR, partial response; Lu, lung; PC, pericardia; CW, chest wall; V, vessels; Ph, phrenic nerve; Dia, diaphragm; EPP, extrapleural pneumonectomy; OS, overall survival; M, months; Y, years; Tri, Tri-modality therapies; RPD, resection of pleural dissemination; PT, primary tumor; PL, pleura.

survival for patients with TETs, regardless of the disease stage or histological type. Even for those presenting with locally advanced, initially deemed unresectable TETs, achieving complete surgical resection is the foremost therapeutic objective to secure long-term survival. Surgical outcomes, such as the extent of resection and the rate of complete surgical resection for studies specifically addressing thymoma, are detailed in *Table 5*. Among the five studies, after excluding those lacking detailed information on concomitantly resected organs, the lungs, blood vessels

Table 6 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymic cancers

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Shintani *et al.* (2015 Japan) (19)	CT	CP/TP/CODE/PE/ADOC	NI	Lu, V, Ph	69	71 (5Y)	NI
Kawasaki *et al.* (2014 Japan) (20)	CT	CODE	CR, 0; PR, 71	Lu, PC, V	86	83 M (median)	42.8 (PL, LV, B)
Filosso *et al.* (2014 Italy) (21)	CT	NI	NI	NI	82	NI	NI
Suzuki *et al.* (2005 Japan) (24)	CT	ADOC/PE	CR, 0; PR, 75	V	75	NI	NI

InT, induction therapy; CT, chemotherapy; CP, cisplatin + docetaxel; TP, paclitaxel + carboplatin; CODE, doxorubicin + cisplatin + vincristine + etoposide; PE, cisplatin + etoposide; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; CR, complete response; PR, partial response; Lu, lung; V, vessels; Ph, phrenic nerve; PC, pericardia; OS, overall survival; Y, years; M, months; PL, pleura; LV, liver; B, bone.

(specifically the innominate vein, superior vena cava, and aorta), and pericardium were the organs most frequently resected alongside the thymus, with each being involved in four studies. Other structures commonly resected included the diaphragm in three studies, phrenic nerve in two studies, and chest wall in two studies. The median rate of complete surgical resection was 76% (range, 22–100%). The phrenic nerve is an organ commonly invaded by locally advanced TETs. However, Aprile has reported techniques for sparing the phrenic nerve in the context of locally advanced TETs. These techniques can be applied even in cases undergoing induction therapy, particularly for patients with severe comorbidities or poor performance status (47).

Table 6 details the surgical outcomes, such as the extent of resection and the rate of complete surgical resection, for studies focused on thymic cancer. Among the three studies, after excluding one study that lacked detailed information on concomitantly resected organs, blood vessels were the most frequently resected organ, involved in all the remaining studies. The median rate of complete surgical resection was 79% (range, 69–86%).

Table 7 provides an overview of surgical outcomes, including the extent of resection and the rate of complete surgical resection, across studies that encompass both thymoma and thymic cancer. Among the eight studies, excluding those without detailed information on concomitantly resected organs, the lungs and blood vessels emerged as the most frequently resected organs, each being involved in all the analyzed studies. The pericardium was another structure commonly resected, being involved in seven of the studies. The median rate of complete surgical resection was 76% (range, 52–82%). Korst *et al.* detailed the extent of resection, indicating that the lungs, vessels, pericardium, and phrenic nerve were resected in addition to the thymus (37).

Postoperative complications were noted in 20 studies. Only three studies reported postoperative 30-day mortality rates (1.0–9.5%). The median rate of postoperative complications was 26% (range, 19–42%). These adverse events included pneumonitis, bleeding, cardiac failure, atrial fibrillation, sternal dehiscence, pulmonary embolism, pleural effusion, pulmonary infarction, and cardiac arrest. Mineo *et al.* highlighted that, within the same timeframe, postoperative morbidity rates following resection after neoadjuvant therapy were significantly elevated compared with surgery performed on thymomas without preceding neoadjuvant chemotherapy (8).

Adjuvant therapy

In their systematic review, Falkson *et al.* highlighted the relative benefits of postoperative radiation therapy (PORT) in patients with thymomas (2). PORT demonstrated favorable results for OS and disease-free survival compared with the absence of PORT. Furthermore, patients with thymic carcinomas exhibited prolonged survival after PORT compared with those who did not receive it. Although these findings do not conclusively establish the superiority of PORT for locally advanced TETs due to the low certainty of the data, the overall results are promising. In contrast, few studies have compared the outcomes of adjuvant chemotherapy and the absence of such therapy, and their review by Falkson *et al.* found no statistically significant differences in the OS between these two groups (2). However, for patients with thymic carcinomas, there was a slight trend toward improved OS with adjuvant chemotherapy, albeit with very low certainty.

Among the 12 studies focusing on thymoma, seven provided data on adjuvant therapy, with a median 71%

Table 7 Summary of studies on the effect of induction therapy and surgical outcomes in locally advanced thymomas or thymic cancers

Studies	Type of InT	Regimens	Response (%)	Combined resection	Complete resection (%)	OS (%)	The incidence of recurrence (%)
Guan *et al.* (2023 China) (30)	CRT	CAP/CP/TP + RT (36–40 Gy)	CR, 19; PR, 52	PC, Lu, V, Ph	74	58.1 (5Y) 50.9 (10Y)	NI
Park *et al.* (2019 Korea) (31)	CT	ADOC/CAP/CP/ others	CR, 3; PR, 58	Lu, Dia, V, Ph	64	77.4 (5Y)	NI
Ma *et al.* (2019 Taiwan region) (32)	CT	NI	NI	NI	NI	IT 83.3 (5Y) TC 76.2 (10Y)	NI
Suh *et al.* (2019 Korea) (33)	CT/CRT	ADOC/CAP + RT	CR, 0; PR, 72	Lu, PC, Dia, V, Ph	72	69.1 (5Y)	NI
Kaba *et al.* (2018 Tarkey) (29)	CT	NI	NI	NI	NI	93 (5Y) 56 (10Y)	NI
Wei *et al.* (2016 China) (34)	CT/RT/CRT	CAP/PE/others +RT	NI	NI	76	49.7 (5Y) 19.9 (10Y)	44.9 (5Y)
Kirzinger *et al.* (2016 Germany) (26)	CT	Octreotide + prednisolone	ORR, 88	NI	52	NI	NI
Cardillo *et al.* (2016 Italy) (27)	CT	ADOC/CEE/CAP	NI	Lu, PC, CW, V, Ph	81	71 M (median)	35.2
Ried *et al.* (2015 Germany) (36)	CT	Octreotide + prednisolone/CAP	NI	V, PC, Lu, CW	67	14 M (median)	33
Korst *et al.* (2014 USA) (37)	CRT	PE + RT (45 Gy)	CR, 0; PR, 48	PC, Lu, Ph, V, others	77	71 (5Y)	10.5
Park *et al.* (2013 Korea) (38)	CT	CP	CR, 0; PR, 63	NI	79	79.4 (4Y)	NI
Marulli *et al.* (2011 Italy) (28)	CT	ADOC/CAP/CEE	CR, 6; PR, 63	Lu, PC, V, Ph	82	50 (10Y)	21.2 (R0)
Rea *et al.* (2011 Italy) (39)	CT	ADOC	Response (>50%) 66	NI	NI	52 (10Y)	NI
Wright *et al.* (2008 USA) (40)	CRT	PE + RT (33–49 Gy)	CR, 0; PR, 40	Lu, PC, V, Ph	80	69 (5Y)	30
Lucchi *et al.* (2005 Italy) (41)	CT	CEE	MOR, 67	NI	77.8	83 M (median, in both InT and non-InT)	NI
Jacot *et al.* (2005 France) (42)	CT	CAP	CR, 0; PR, 75	NI	38	34 M (median)	NI

InT, induction therapy; CRT, chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; CAP, cyclophosphamide + doxorubicin + cisplatin; CP, cisplatin + docetaxel; TP, paclitaxel + carboplatin; ADOC, cyclophosphamide + doxorubicin + cisplatin + vincristine; NI, no information; PE, cisplatin + etoposide; CEE, cisplatin + epirubicin + etoposide; CR, complete response; PR, partial response; ORR, overall response rate; MOR, major objective response; PC, pericardia; Lu, lung; V, vessels; Ph, phrenic nerve; Dia, diaphragm; CW, chest wall; OS, overall survival; Y, years; IT, invasive thymoma; TC, thymic cancer; M, months.

of patients (range, 22–100%) receiving it. The adjuvant therapies utilized were diverse: two studies offered chemotherapy, RT, or CRT; two used chemotherapy or RT; one opted for CRT or chemotherapy; one exclusively used RT; and one study lacked detailed information. Yokoi *et al.* found that out of 14 patients who received induction chemotherapy (cisplatin, doxorubicin, and prednisolone), nine proceeded to surgical resection. Of these, only two achieved R0 resection, while the others had incomplete resections (15). PORT was administered to eight patients, including seven with incomplete resections. Notably, two of these patients with incomplete resections achieved long-term survival, lasting 72 and 180 months post-surgery (15).

Out of 17 studies addressing both thymoma and thymic cancer, nine offered data on adjuvant therapy, with a median of 66% of patients (range, 25–89%) undergoing treatment. The types of adjuvant therapy varied: two studies included chemotherapy, RT, or CRT; two employed chemotherapy or RT; two chose CRT or chemotherapy; and three studies did not specify the details. Filosso *et al.* noted that 62% of surgically treated patients received adjuvant therapy, which was linked to improved survival in multivariate analysis (35). However, the majority of the studies did not confirm adjuvant therapy's prognostic value for locally advanced TETs, leaving its overall impact still under discussion.

OS and recurrence

The 5-year, 10-year, and median OS rates, calculated from the initiation of induction therapy or at the time of surgery, were analyzed across various studies. For thymoma, OS outcomes were reported in 12 out of 13 studies, as summarized in *Table 5*. The median 5-year OS was 85% (range, 78–95%), and the 10-year OS was 76.7% (range, 53–84.9%). In the case of thymic cancer, OS results were provided by only two studies, detailed in *Table 6*. Shintani *et al.* reported a 5-year OS of 71% following induction chemotherapy and surgery for thymic cancers, while Kawasaki *et al.* observed a median OS of 83 months (19,20). Among 16 studies addressing both thymomas and thymic cancers to evaluate OS, the median 5-year OS was 70% (range, 49.7–93%), and the 10-year OS was 51% (range, 19.9–76.2%).

Throughout the postoperative follow-up period in various studies, the median recurrence rate was observed to be 30%, with a range from 17.5% to 100%. It is important to note that follow-up durations varied among these studies. In a phase II study by Kunitoh *et al.*, focusing on CODE therapy followed by surgery for stage III thymoma, a relapse rate of 61.9% was reported (9). The initial signs of recurrence in these patients were typically regrowth of the primary tumor or pleural or pericardial dissemination. Kawasaki *et al.* reported relapse sites in 3 out of 7 patients experiencing recurrence, identifying the pleura as the most common relapse site, followed by the liver and bones (20). Marulli *et al.* observed that among 203 patients who achieved R0 resection, 43 (21.2%) experienced recurrence, with a median time to relapse of 46 months (28). Intrathoracic relapse was seen in 13.3% of cases, while extrathoracic relapse occurred in 6.4%. Both intra- and extrathoracic relapses were noted in 1.5% of cases. Significantly, the recurrence rate was markedly higher in patients with histologic types B2-3 thymoma and thymic carcinoma compared to types A, AB, and B1 thymomas (28).

Strengths and limitations

The strengths of this narrative review lie in its approach of separately collating reports from retrospective and prospective studies. The prospective studies provided consistent sample sizes, induction treatment modalities, and regimens, enabling a detailed evaluation of therapeutic outcomes. These assessments shed light on the advantages and disadvantages of multimodal therapies for locally advanced TETs. However, enrolling patients proved challenging, resulting in smaller sizes than the retrospective studies. In contrast, the retrospective studies were much more abundant than the prospective ones, although they displayed higher variability in patient characteristics and induction treatments, such as RT, CRT, or chemotherapy. Nevertheless, upon consolidation of the data from both study types, factors such as curative resection rates, adverse events, postoperative complications, and prognosis were found to be comparable. This suggests that the strategy of induction treatment followed by surgical resection for locally advanced TETs with curative intent can be justified to a certain degree. This review emphasized the histological classification of thymoma and thymic cancer during data collection, given the relatively distinct biological nature of these two neoplasms. We analyzed studies that included both histological types and those that focused on one specific histology. Our findings suggested that multimodal strategies are feasible for both type of TETs from both prognostic and safety perspectives.

This narrative review faces multiple limitations. The

inherent rarity of TETs leads to small sample sizes in the reviewed studies, which, along with the extensive time span these studies cover, contributes to the heterogeneity of their populations. Additionally, the positive outcomes observed post-surgery in patients with stage III–IV advanced diseases may be influenced by selection bias. Secondly, the absence of prospective randomized studies leaves the benefit of adding surgical resection for curative intent, as opposed to multimodal treatment without surgery, an open question. Conducting phase III studies is notably challenging given the infrequency of this condition. Finally, the inability to distinguish between stage IV tumors that are locally invaded and those with pleural nodules, due to the limited information available even after reviewing a large corpus of literature, remains a significant constraint. It is our hope that future reviews will differentiate these two statuses, thereby shedding light on the clinical significance of induction treatment for locally advanced TETs.

Conclusions

This narrative review underscored the potential for encouraging curative surgical rates and long-term OS in patients with locally advanced TETs who received induction therapy followed by surgical resection. These results, drawn from both retrospective and prospective studies, support the consideration of an induction regimen before surgical resection in selected patients with stage III and IV TETs. Henceforth, joint efforts are essential for obtaining more extensive data from prospective studies on this topic.

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References

1. de Jong WK, Blaauwgeers JL, Schaapveld M, et al. Thymic epithelial tumours: a population-based study of the incidence, diagnostic procedures and therapy. Eur J Cancer 2008;44:123-30.
2. Falkson CB, Vella ET, Ellis PM, et al. Surgical, Radiation, and Systemic Treatments of Patients With Thymic Epithelial Tumors: A Systematic Review. J Thorac Oncol 2023;18:299-312.
3. Wei ML, Kang D, Gu L, et al. Chemotherapy for thymic carcinoma and advanced thymoma in adults. Cochrane Database Syst Rev 2013;2013:CD008588.
4. Hamaji M, Ali SO, Burt BM. A meta-analysis of induction therapy for advanced thymic epithelial tumors. Ann Thorac Surg 2015;99:1848-56.
5. Rich AL. Epidemiology of thymoma. J Thorac Dis 2020;12:7531-5.
6. Leuzzi G, Rocco G, Ruffini E, et al. Multimodality therapy for locally advanced thymomas: A propensity score-matched cohort study from the European Society of Thoracic Surgeons Database. J Thorac Cardiovasc Surg

2016;151:47-57.e1.
7. Yamada Y, Yoshino I, Nakajima J, et al. Surgical Outcomes of Patients With Stage III Thymoma in the Japanese Nationwide Database. Ann Thorac Surg 2015;100:961-7.
8. Mineo TC, Mineo D, Onorati I, et al. New predictors of response to neoadjuvant chemotherapy and survival for invasive thymoma: a retrospective analysis. Ann Surg Oncol 2010;17:3022-9.
9. Kunitoh H, Tamura T, Shibata T, et al. A phase II trial of dose-dense chemotherapy, followed by surgical resection and/or thoracic radiotherapy, in locally advanced thymoma: report of a Japan Clinical Oncology Group trial (JCOG 9606). Br J Cancer 2010;103:6-11.
10. Rena O, Mineo TC, Casadio C. Multimodal treatment for stage IVA thymoma: a proposable strategy. Lung Cancer 2012;76:89-92.
11. Yang HC, Yoon YS, Kim HK, et al. En bloc extended total thymectomy and extrapleural pneumonectomy in Masaoka stage IVA thymomas. J Cardiothorac Surg 2011;6:28.
12. Nakamura S, Kawaguchi K, Fukui T, et al. Multimodality therapy for thymoma patients with pleural dissemination. Gen Thorac Cardiovasc Surg 2019;67:524-9.
13. Huang J, Rizk NP, Travis WD, et al. Feasibility of multimodality therapy including extended resections in stage IVA thymoma. J Thorac Cardiovasc Surg 2007;134:1477-83; discussion 1483-4.
14. Abdel Jalil R, Abdallah FA, Obeid Z, et al. Locally advanced thymoma; does neoadjuvant chemotherapy make a difference? J Cardiothorac Surg 2023;18:245.
15. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. J Thorac Oncol 2007;2:73-8.
16. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308-13.
17. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369-79.
18. Bretti S, Berruti A, Loddo C, et al. Multimodal management of stages III-IVa malignant thymoma. Lung Cancer 2004;44:69-77.
19. Shintani Y, Inoue M, Kawamura T, et al. Multimodality treatment for advanced thymic carcinoma: outcomes of induction therapy followed by surgical resection in 16 cases at a single institution. Gen Thorac Cardiovasc Surg 2015;63:159-63.
20. Kawasaki H, Taira N, Ichi T, et al. Weekly chemotherapy with cisplatin, vincristine, doxorubicin, and etoposide followed by surgery for thymic carcinoma. Eur J Surg Oncol 2014;40:1151-5.
21. Filosso PL, Guerrera F, Rendina AE, et al. Outcome of surgically resected thymic carcinoma: a multicenter experience. Lung Cancer 2014;83:205-10.
22. Okereke IC, Kesler KA, Freeman RK, et al. Thymic carcinoma: outcomes after surgical resection. Ann Thorac Surg 2012;93:1668-72; discussion 1672-3.
23. Yano M, Sasaki H, Yokoyama T, et al. Thymic carcinoma: 30 cases at a single institution. J Thorac Oncol 2008;3:265-9.
24. Suzuki M, Ando S, Iida T, et al. Multimodality therapy and significance of serum CYFRA21-1 for thymic carcinoma. Oncol Rep 2005;13:1127-31.
25. Takeda S, Sawabata N, Inoue M, et al. Thymic carcinoma. Clinical institutional experience with 15 patients. Eur J Cardiothorac Surg 2004;26:401-6.
26. Kirzinger L, Boy S, Marienhagen J, et al. Octreotide LAR and Prednisone as Neoadjuvant Treatment in Patients with Primary or Locally Recurrent Unresectable Thymic Tumors: A Phase II Study. PLoS One 2016;11:e0168215.
27. Cardillo G, Lucchi M, Marulli G, et al. Induction therapy followed by surgical resection in Stage-III thimic epithelial tumors: Long-term results from a multicentre analysis of 108 cases. Lung Cancer 2016;93:88-94.
28. Marulli G, Lucchi M, Margaritora S, et al. Surgical treatment of stage III thymic tumors: a multi-institutional review from four Italian centers. Eur J Cardiothorac Surg 2011;39:e1-7.
29. Kaba E, Ozkan B, Erus S, et al. Role of Surgery in the Treatment of Masaoka Stage IVa Thymoma. Ann Thorac Cardiovasc Surg 2018;24:6-12.
30. Guan S, Long W, Liu Y, et al. Prognosis of Concurrent Versus Sequential Chemo-Radiotherapy Induction Followed by Surgical Resection in Patients with Advanced Thymic Epithelial Tumors: A Retrospective Study. Ann Surg Oncol 2023;30:6739-47.
31. Park S, Park IK, Kim YT, et al. Comparison of Neoadjuvant Chemotherapy Followed by Surgery to Upfront Surgery for Thymic Malignancy. Ann Thorac Surg 2019;107:355-62.
32. Ma WL, Lin CC, Hsu FM, et al. Clinical Outcomes of Up-front Surgery Versus Surgery After Induction Chemotherapy for Thymoma and Thymic Carcinoma: A

Retrospective Study. Clin Lung Cancer 2019;20:e609-18.
33. Suh JW, Park SY, Lee CY, et al. Neoadjuvant therapy for thymic neoplasms reduces tumor volume per 3D-reconstructed images but does not improve the complete resection rate. PLoS One 2019;14:e0214291.
34. Wei Y, Gu Z, Shen Y, et al. Preoperative induction therapy for locally advanced thymic tumors: a retrospective analysis using the ChART database. J Thorac Dis 2016;8:665-72.
35. Filosso PL, Evangelista A, Ruffini E, et al. Does myasthenia gravis influence overall survival and cumulative incidence of recurrence in thymoma patients? A Retrospective clinicopathological multicentre analysis on 797 patients. Lung Cancer 2015;88:338-43.
36. Ried M, Neu R, Schalke B, et al. Radical surgical resection of advanced thymoma and thymic carcinoma infiltrating the heart or great vessels with cardiopulmonary bypass support. J Cardiothorac Surg 2015;10:137.
37. Korst RJ, Bezjak A, Blackmon S, et al. Neoadjuvant chemoradiotherapy for locally advanced thymic tumors: a phase II, multi-institutional clinical trial. J Thorac Cardiovasc Surg 2014;147:36-44, 46.e1.
38. Park S, Ahn MJ, Ahn JS, et al. A prospective phase II trial of induction chemotherapy with docetaxel/cisplatin for Masaoka stage III/IV thymic epithelial tumors. J Thorac Oncol 2013;8:959-66.
39. Rea F, Marulli G, Di Chiara F, et al. Multidisciplinary approach for advanced stage thymic tumors: long-term outcome. Lung Cancer 2011;72:68-72.
40. Wright CD, Choi NC, Wain JC, et al. Induction chemoradiotherapy followed by resection for locally advanced Masaoka stage III and IVA thymic tumors. Ann Thorac Surg 2008;85:385-9.
41. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. Ann Thorac Surg 2005;79:1840-4.
42. Jacot W, Quantin X, Valette S, et al. Multimodality treatment program in invasive thymic epithelial tumor. Am J Clin Oncol 2005;28:5-7.
43. Kojima Y, Ito H, Hasegawa S, et al. Resected invasive thymoma with multiple endocrine neoplasia type 1. Jpn J Thorac Cardiovasc Surg 2006;54:171-3.
44. Marx A, Ströbel P, Badve SS, et al. ITMIG consensus statement on the use of the WHO histological classification of thymoma and thymic carcinoma: refined definitions, histological criteria, and reporting. J Thorac Oncol 2014;9:596-611.
45. Ruffini E, Detterbeck F, Van Raemdonck D, et al. Tumours of the thymus: a cohort study of prognostic factors from the European Society of Thoracic Surgeons database. Eur J Cardiothorac Surg 2014;46:361-8.
46. Omasa M, Date H, Sozu T, et al. Postoperative radiotherapy is effective for thymic carcinoma but not for thymoma in stage II and III thymic epithelial tumors: the Japanese Association for Research on the Thymus Database Study. Cancer 2015;121:1008-16.
47. Aprile V, Bertoglio P, Korasidis S, et al. Nerve-Sparing Surgery in Advanced Stage Thymomas. Ann Thorac Surg 2019;107:878-84.

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