Clinical Outcomes of Up-front Surgery Versus Surgery After Induction Chemotherapy for Thymoma and Thymic Carcinoma: A Retrospective Study

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Abstract

Results comparing the outcomes of up-front surgery and surgery after induction chemotherapy in thymic neoplasms are inconsistent. We assessed 204 patients undergoing up-front surgery, surgery after induction chemotherapy, and no surgery. Thymic carcinoma patients receiving up-front surgery had better overall survival. Multivariate analysis showed that thymic carcinoma pathology type and American Joint Committee on Cancer stage IVB are poor prognostic factors.

Introduction: Although induction chemotherapy improves the resectability of thymic neoplasms, it is unclear whether surgery after induction chemotherapy can improve outcomes. We compared long-term outcomes of surgery with and without induction chemotherapy in patients with thymic neoplasms. **Patients and Methods:** We retrospectively investigated the clinical information of patients with thymic neoplasms at the National Taiwan University Hospital between 2005 and 2013. **Results:** Of 204 patients, 119 underwent direct surgery (group 1), 45 underwent surgery after induction chemotherapy (group 2), and 40 underwent no surgery (group 3). The 5-year overall survival rates of groups 1, 2, and 3 were as follows: for 204 patients, 96.3%, 76.4%, and 35.5% ($P < .001$); for 119 thymoma patients, 96.6%, 88.9%, and 100.0% ($P = .835$); for 85 thymic carcinoma patients, 94.7%, 69.7%, and 17.7% ($P < .001$); for 36 American Joint Committee on Cancer (AJCC) stage III-IVA thymoma patients, 92.9%, 83.3%, and 100% ($P = .833$); and for 28 stage III-IVA thymic carcinoma patients, 75.0%, 76.2%, and 62.5%, ($P = .160$). Univariate analysis showed that for group 2 ($P = .0208$) and group 3 ($P < .0001$), thymic carcinoma pathology type ($P = .0010$) and stage IVB disease ($P < .0001$) were poor prognostic factors. Multivariate analysis found thymic carcinoma ($P = .0026$) and stage IVB disease ($P = .0449$) to be poor prognostic factors. **Conclusion:** Up-front surgery leads to best overall survival, and induction chemotherapy followed by surgery may improve resectability and outcomes. Only thymic carcinoma and stage IVB disease were poor prognostic factors in multivariate analysis.

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Introduction

Thymoma and thymic carcinoma are rare thymic epithelial malignancies.[1] According to Surveillance, Epidemiology, and End Results data, the annual incidence of thymoma in the United States is 0.13 per 100,000 persons.[2] The primary treatment for thymoma and thymic carcinoma is complete resection,[3-7] followed by postoperative radiotherapy to treat microscopic or gross tumors.[8-12] Thymoma and thymic carcinoma respond to platinum-based chemotherapy regimens, and in locally advanced disease cases, induction chemotherapy can improve resectability.[13-15] However, there are too few studies that directly compare the outcomes of up-front surgery and surgery after induction chemotherapy. In addition, thymoma and thymic carcinoma use the same staging systems, and the outcomes are often not analyzed separately.[16-19]

Clinical staging of cancer is commonly performed using the Masaoka-Koga staging system and the 8th edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis classification system (TNM).[20,21] This study aimed to assess the disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) rates and real-world, long-term outcomes of up-front surgery versus surgery after induction chemotherapy in thymoma and thymic carcinoma patients. We also analyzed thymoma and thymic carcinoma patients separately.

Patients and Methods

Clinicopathologic Features and Treatment Modalities

We retrospectively reviewed 204 patients diagnosed with thymoma or thymic carcinoma at National Taiwan University Hospital, Taipei, Taiwan, between January 2005 and December 2013. Pretreatment assessment included patient history, comprehensive physical examination, complete blood cell count, blood chemistry analysis, and chest computed tomography. The patients were divided into 3 groups. Group 1 included patients who underwent up-front surgery (n = 119), group 2 included patients who underwent surgery after induction chemotherapy (n = 45), and group 3 included patients who did not undergo surgery (n = 40). Because a higher number of thymic carcinoma patients in groups 2 and 3 might indicate worse outcomes, we analyzed thymoma and thymic carcinoma patients separately. In addition, we compared the outcomes of groups 1, 2, and 3 by controlling unfavorable prognostic factors of pathologic types and advanced disease stages in the multivariate analysis.

Surgical procedures included direct total thymectomy and complete excision of gross tumors. After surgery, patients in groups 1 and 2 were administered 45 to 54 Gy of adjuvant radiotherapy, with the dose being as high as 60 Gy in cases of gross residual tumor.[8-12] Induction chemotherapy included platinum-based regimens; the number of therapy cycles ranged from 1 to 6. Group 3 received chemotherapy, radiotherapy, or chemoradiotherapy.

Pathologic diagnosis of thymoma or thymic carcinoma was based on the World Health Organization (WHO) classification.[1] Clinical staging was determined using the Masaoka-Koga staging system and the 8th edition of the AJCC TNM classification of malignant tumors.

Evaluation and Ethics Statements

Follow-up after initial treatment involved chest computed tomography of all patients every 3 to 6 months. DFS refers to the length of time after initial treatment ended that patients survived without any signs or symptoms of cancer. PFS refers to the survival of patients receiving first-line treatment from the date of initiation of first-line treatment to the date of any treatment failure, including disease recurrence, progression, or death. OS refers to the length of time from the date of initial treatment to the date of death due to any cause. DFS was evaluated in group 1 and 2 stage I-IVA patients. PFS was evaluated in group 3 stage I-IVA or stage IVB patients. OS was evaluated for all groups.

The patients' medical data were deidentified before access and analysis. Therefore, the research ethics committee waived the need for written informed consent from the patients.

Statistical Analysis

Long-term PFS and OS rates were calculated by the Kaplan-Meier method. We also evaluated OS using univariate and multivariate Cox proportional hazard models. Variables significantly associated with OS in the univariate analysis were included in the multivariate analysis. $P < .05$ was considered statistically significant.

Results

Patient Characteristics and Treatment Modalities

Of the 204 patients, 119 had thymoma and 85 had thymic carcinoma. The median age of group 1 was 55 years (range, 24-80 years), 72 patients (60%) were female, 97 patients (82%) had thymoma, 84 patients (71%) had AJCC stage I disease, and 31 patients (26%) had myasthenia gravis. The median age of group 2 was 59 years (range, 22-79 years), and the number of male (21, or 47%) and female (24, or 53%) patients was similar. Of the 45 patients, 30 (67%) had thymic carcinoma, 31 (69%) had AJCC stage IV disease, and 2 had thymic tumors that had invaded the pericardium and were classified as Masaoka-Koga stage III but AJCC stage II. The median age of group 3 was 58 years (range, 13-84 years), 25 patients (63%) were female, 33 (83%) had thymic carcinoma, 31 (77%) had AJCC stage IV disease, and 4 (15%) had hemoglobin concentration < 10 g/dL or aplastic anemia. The percentage of patients aged > 60 years was similar between the 3 groups (range, 37-44%). Detailed patient distributions for each characteristic, including different subtypes of thymoma or thymic carcinoma and stages, are listed in Table 1.

Clinical Outcomes for Patients Undergoing Different Treatment Modalities

For thymoma and thymic carcinoma patients, the PFS and OS of group 1 were better than in groups 2 and 3. The 5-year PFS rates of groups 1, 2, and 3 were 82.5%, 31.6%, and 10.4%, respectively ($P < .001$; Supplemental Figure 1A), and their 5-year OS rates were 96.3%, 76.4%, and 35.5%, respectively ($P < .001$; Supplemental Figure 1B).

When thymoma and thymic carcinoma were analyzed separately, for the 119 thymoma patients, the 5-year PFS rate of group 1 was better compared to groups 2 and 3: 82.3% versus 32.3% and 34.3%, respectively ($P = .001$; Figure 1A). The PFS of groups 2 and 3 was similar. Also, the 5-year OS rates of groups 1, 2, and 3 were similar: 96.6%, 88.9%, and 100.0%, respectively ($P = .835$; Figure 1B).

Table 1 Characteristics of 204 Patients With Thymic Epithelial Neoplasms

Characteristic	Group 1: Up-front Surgery (N = 119)	Group 2: Surgery After Chemotherapy (N = 45)	Group 3: No Surgery (Other Treatments) (N = 40)
Age (y), median (range)	55 (24-80)	59 (22-79)	58 (13-84)
Age > 60 years old	44 (37)	20 (44)	17 (43)
Gender			
Male	47 (40)	21 (47)	15 (37)
Female	72 (60)	24 (53)	25 (63)
Hb < 10 g/dL or aplastic anemia	6 (5)	2 (4)	6 (15)
Myasthenia gravis	31 (26)	1 (2)	2 (5)
Pathology			
Thymoma	97 (82)	15 (33)	7 (17)
A	5 (4)	1 (2)	0
AB	13 (11)	1 (2)	0
B1	12 (10)	1 (2)	0
B1/B2	1 (1)	0	0
B2	13 (11)	1 (2)	2 (5)
B2/B3	10 (8)	1 (2)	0
B3	8 (7)	6 (13)	0
Not defined	35 (29)	4 (9)	5 (13)
Thymic carcinoma	22 (18)	30 (67)	33 (83)
Masaoka-Koga Stage			
I	19 (16)	0	0
II	64 (54)	0	0
III	26 (22)	15 (33)	9 (23)
IVA	8 (7)	13 (29)	4 (10)
IVB	2 (2)	17 (38)	27 (67)
AJCC Stage			
I	84 (71)	0	0
II	7 (6)	2 (4)	1 (3)
III	18 (15)	12 (27)	8 (20)
IVA	8 (7)	14 (31)	4 (10)
IVB	2 (2)	17 (38)	27 (68)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: AJCC = American Joint Committee on Cancer; Hb = hemoglobin concentration.

However, the 85 thymic carcinoma patients in group 1 had better PFS and OS compared to groups 2 and 3. The 5-year PFS rates of groups 1, 2, and 3 were 84.3%, 30.7%, and 6.3%, respectively ($P < .001$; Figure 2A), while the 5-year OS rates were 94.7%, 69.7%, and 17.7%, respectively ($P < .001$; Figure 2B).

The 36 AJCC stage III-IVA thymoma patients in group 1 had better DFS but similar OS compared to groups 2 and 3. The 5-year DFS rates of groups 1, 2, and 3 were 81.4%, 22.2%, and 37.5%, respectively ($P = .161$; Figure 3A), while the 5-year OS rates were 92.9%, 83.3%, and 100%, respectively ($P = .833$; Figure 3B).

In 28 AJCC stage III-IV thymic carcinoma patients, the 5-year DFS rates of groups 1, 2, and 3 were 53.3%, 43.5%, and 25.5%, respectively ($P = .077$; Figure 4A), while the 5-year OS rates were 75.0%, 76.2%, and 62.5%, respectively ($P = .160$; Figure 4B).

Univariate and Multivariate Analyses of Prognostic Factors of Poor OS

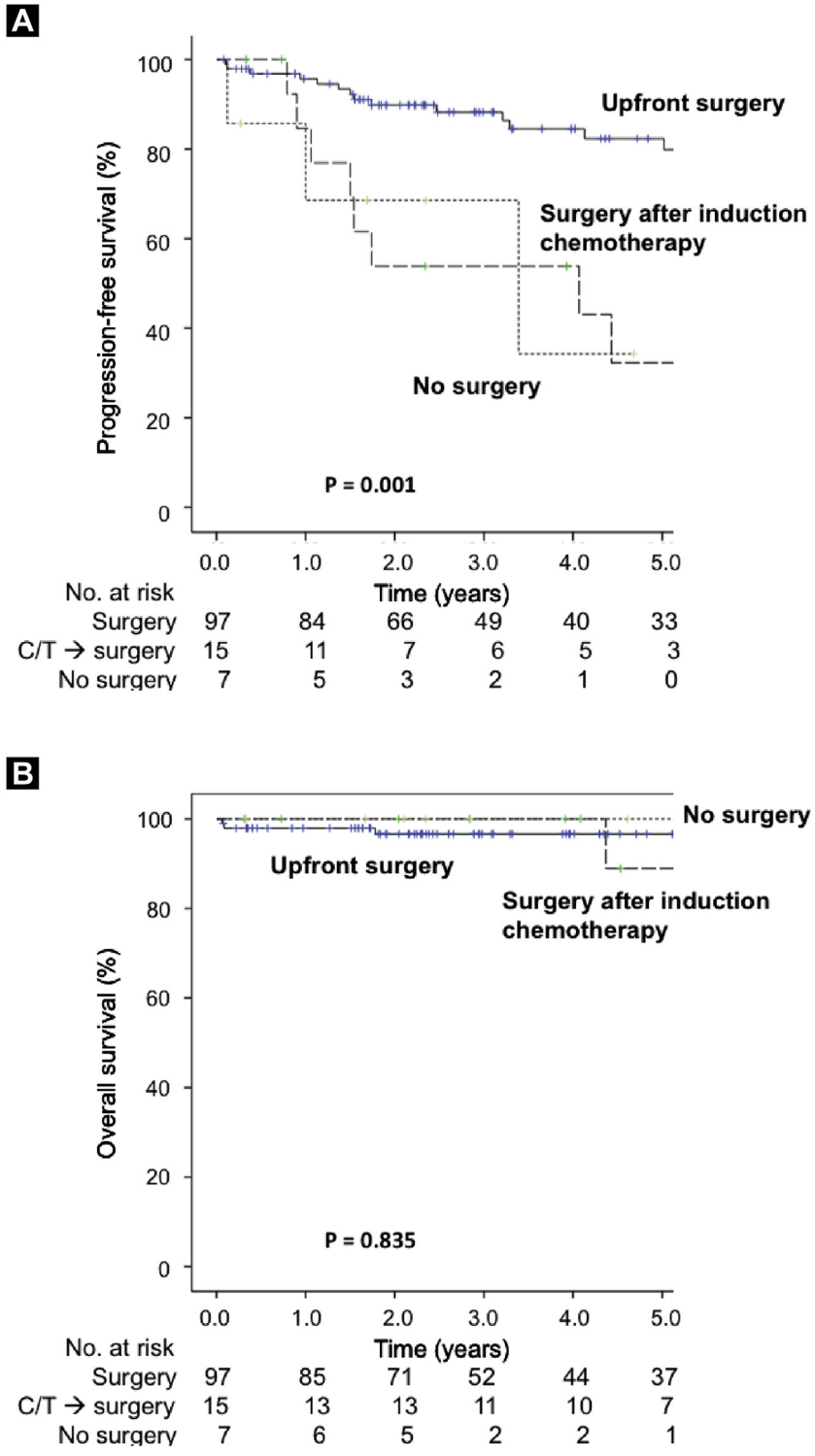
Univariate analysis showed that compared to group 1, group 2 (hazard ratio [HR] = 2.896; 95% confidence interval [CI], 1.175-7.137) and group 3 (HR = 14.280; 95% CI, 6.174-33.031) had a poor prognosis. Thymic carcinoma pathology type (HR = 51.381; 95% CI, 4.965-531.680) and AJCC stage IVB disease (HR = 16.414; 95% CI, 6.360-42.357) were prognostic factors of poor OS, but patient age > 60 years, male sex, hemoglobin concentration < 10 g/dL or aplastic anemia, and myasthenia gravis were not significant prognostic factors of poor OS. In addition, multivariate analysis showed that thymic carcinoma pathology type (HR = 41.341; 95% CI, 3.654-467.739) and AJCC stage IVB disease (HR = 5.805; 95% CI, 1.041-32.287) remained significant prognostic factors of poor OS (Table 2).

Discussion

Although neoadjuvant or induction therapies can increase the complete resection rate of locally advanced thymic epithelial malignancies, their effect on long-term outcomes remains unclear. Bretti et al[22] examined 63 patients with stage IIIA/IV thymoma, including 30 who underwent radical resection and 33 who received neoadjuvant therapy (radiotherapy in 8 patients and cisplatin-based chemotherapy in 25 patients) followed by radical resection. The radical resection rate increased by ~ 20% after neoadjuvant therapy. The PFS (median, 56.9 months) was marginally lower in the latter group than in the former, but OS was similar in both groups. Moreover, the PFS and OS for both groups were better (median, 11.9 and 43.9 months, respectively) compared to patients who did not undergo complete radical resection.[22] Leuzzi et al[23] reported in 28 thymoma or thymic carcinoma patients that surgery after induction chemotherapy (n = 11) and up-front surgery (n = 17) led to similar 3-year DFS (40.5% vs. 53.7%; $P = .67$) and 3-year OS (71.4% vs. 93.3%; $P = .84$). Lucchi et al[24] examined 56 stage III/IVA thymoma or thymic carcinoma patients and reported that 36 patients were provided neoadjuvant chemotherapy followed by surgery and postoperative radiotherapy (n = 25) or chemo-radiotherapy (n = 11), while 20 patients underwent primary surgery followed by adjuvant treatment. The authors also reported that patients receiving neoadjuvant chemotherapy followed by surgery had better OS compared to patients undergoing primary surgery ($P = .004$). In contrast, Wei et al[25] reported that the 5-year OS rate was better for thymoma or thymic carcinoma patients who underwent up-front surgery compared to patients receiving preoperative induction therapies (85.2% vs. 68.1%; $P = .000$). In addition, in patients with downstaged tumors, the 5-year OS rates after preoperative induction therapies (93.8%) and after up-front surgery were similar to each other (85.2%; $P = .438$) but were significantly higher compared to patients without downstaged tumors after preoperative induction therapies (35.6%; $P = .000$).

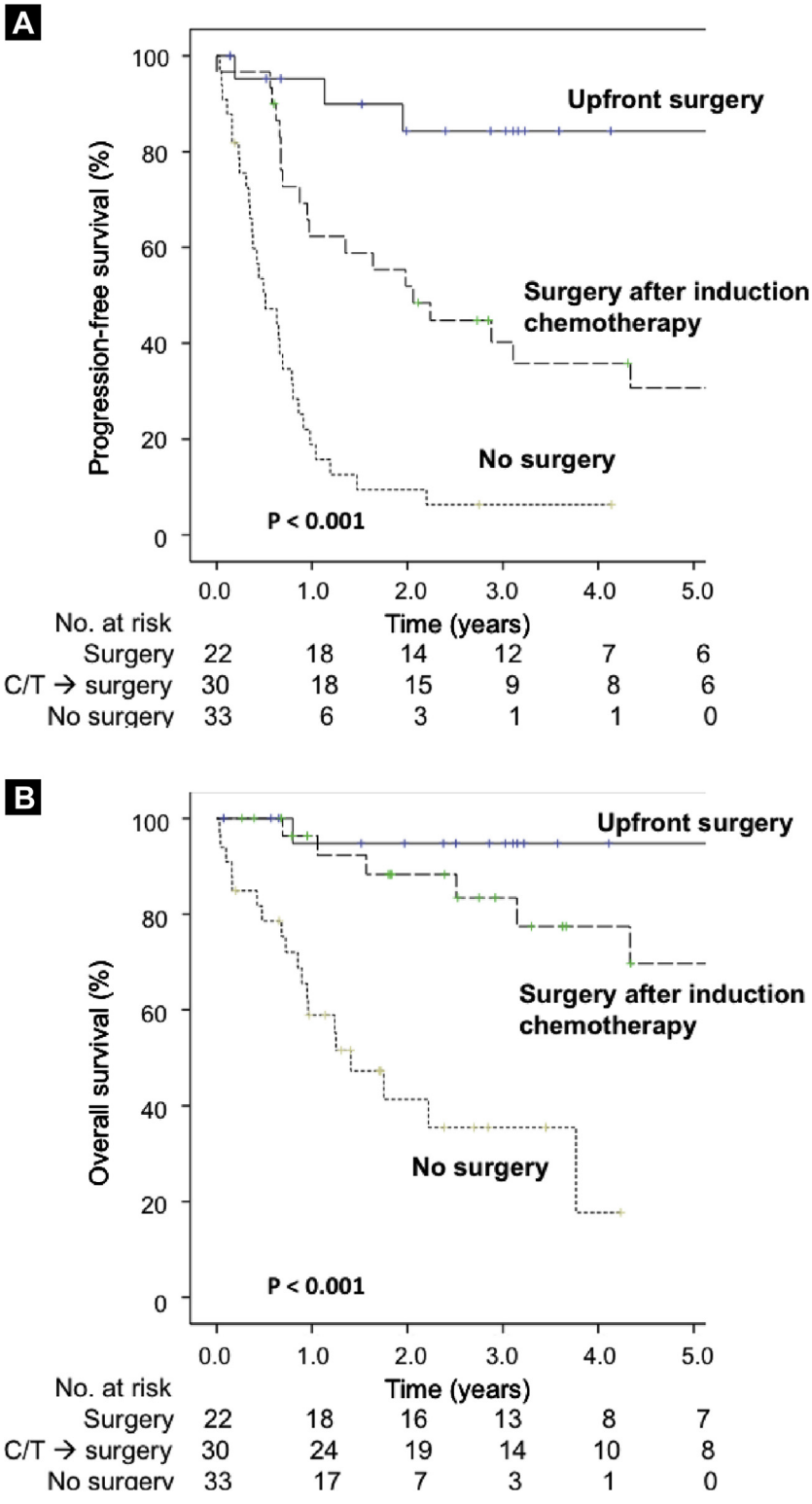
More early-stage thymoma patients in group 1 might have caused better PFS and OS values. As a result of the more indolent course of

Figure 1 PFS and OS Curves for Thymoma Patients Undergoing Up-front Surgery, Surgery After Induction Chemotherapy, and No Surgery. (A) Five-year PFS Rates Were 82.3%, 32.3%, and 34.3%, Respectively ($P = .001$). (B) Five-year OS Rates Were 96.6%, 88.9%, and 100.0%, Respectively ($P = .835$)



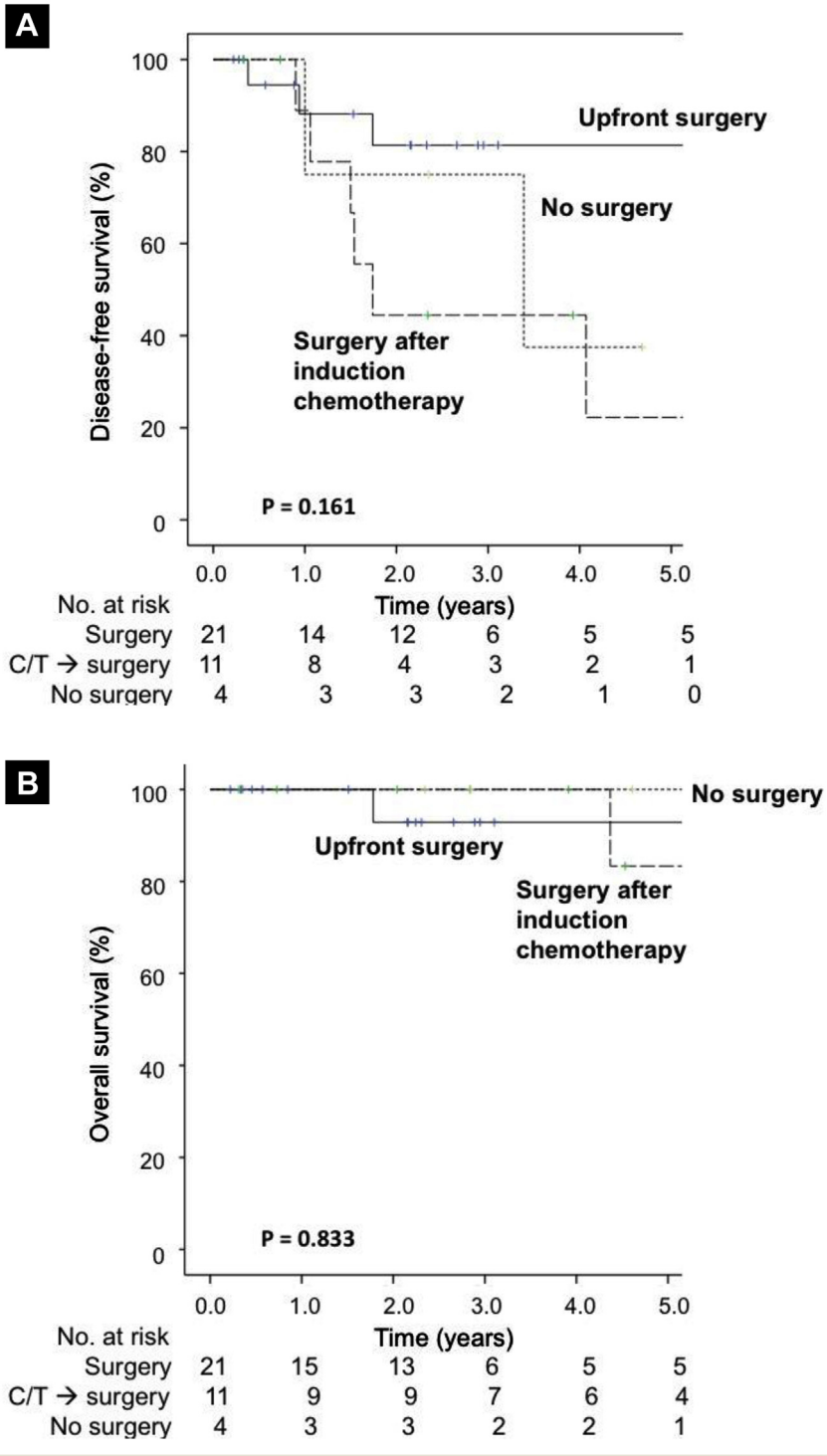
Abbreviations: OS = overall survival; PFS = progression-free survival.

Figure 2 PFS and OS Curves for Thymic Carcinoma Patients Undergoing Up-front Surgery, Surgery After Induction Chemotherapy, and No Surgery. (A) Five-year PFS Rates Were 84.3%, 30.7%, and 6.3%, Respectively ($P < .001$). (B) Five-year OS Rates Were 94.7%, 69.7%, and 17.7%, Respectively ($P < .001$)



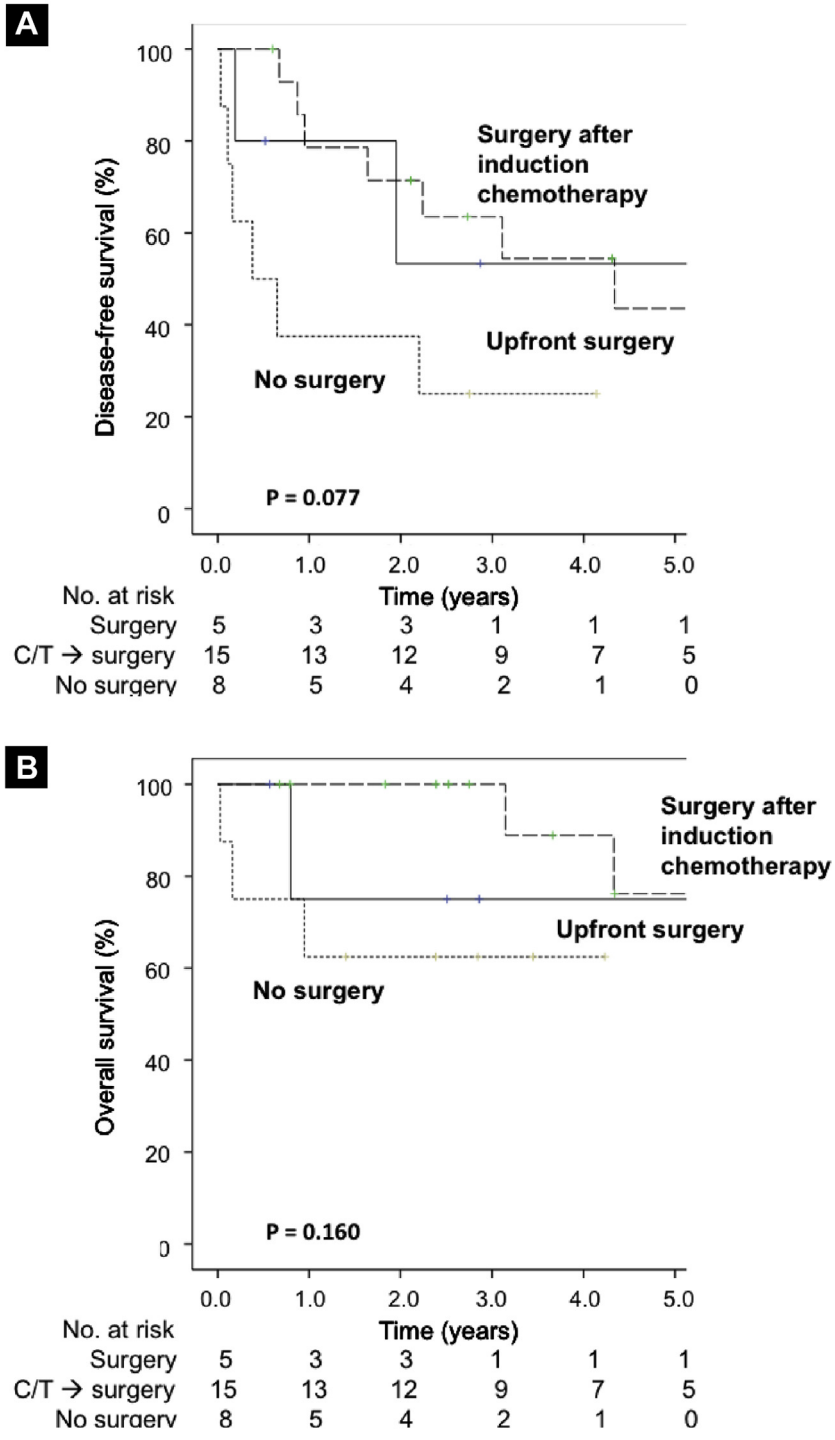
Abbreviations: OS = overall survival; PFS = progression-free survival.

Figure 3 DFS and OS Curves for AJCC Stage III-IVA Thymoma Patients Undergoing Up-front Surgery, Surgery After Induction Chemotherapy, and No Surgery. (A) Five-year DFS Rates Were 81.4%, 22.2%, and 37.5%, Respectively ($P = .161$). (B) Five-year OS Rates Were 92.9%, 83.3%, and 100%, Respectively ($P = .833$)



Abbreviations: AJCC = American Joint Committee on Cancer; DFS = disease-free survival; OS = overall survival.

Figure 4 DFS and OS Curves for AJCC Stage III-IVA Thymic Carcinoma Patients Undergoing Up-front Surgery, Surgery After Induction Chemotherapy, and No Surgery. (A) Five-year DFS Rates Were 53.3%, 43.5%, and 25.5%, Respectively ($P = .077$). (B) Five-year OS Rates Were 75.0%, 76.2%, and 62.5%, Respectively ($P = .160$)



Abbreviations: AJCC = American Joint Committee on Cancer; DFS = disease-free survival; OS = overall survival.

Table 2 Univariate and Multivariate Analyses of Overall Survival

Variable	Hazard Ratio (95% CI)	*P*
Univariate Analysis		
Treatment modality		
Up-front surgery (group 1)	Ref.	Ref.
Surgery after chemotherapy (group 2)	2.896 (1.175-7.137)	.0208[a]
No surgery (group 3)	14.280 (6.174-33.031)	< .0001[a]
Age > 60 vs. age ≤ 60 years	1.571 (0.815-3.028)	.1773
Gender (male vs. female)	1.588 (0.813-3.103)	.1758
Hb < 10 g/dL or aplastic anemia	1.909 (0.669-5.443)	.2268
Myasthenia gravis	0.579 (0.223-1.505)	.2625
Pathology		
Thymoma (non-B3 subtypes)	Ref.	Ref.
Thymoma (B3 subtype)	1.583 (0.130-19.300)	.7188
Thymic carcinoma	51.381 (4.965-531.680)	.0010[a]
AJCC Stage		
I and II	Ref.	Ref.
III and IVA	2.816 (1.036-7.652)	.0424[a]
IVB	16.414 (6.360-42.357)	< .0001[a]
Multivariate Analysis		
Treatment Modality		
Up-front surgery (group 1)	Ref.	Ref.
Surgery after chemotherapy (group 2)	0.364 (0.077-1.717)	.2017
No surgery (group 3)	2.163 (0.439-10.664)	.3432
Pathology		
Thymoma (non-B3 subtypes)	Ref.	Ref.
Thymoma (B3 subtype)	1.345 (0.086-21.165)	.8330
Thymic carcinoma	41.341 (3.654-467.739)	.0026[a]
AJCC Stage		
I and II	Ref.	Ref.
III and IVA	2.143 (0.441-10.421)	.3450
IVB	5.805 (1.041-32.287)	.0449[a]

Abbreviations: AJCC = American Joint Committee on Cancer; CI = confidence interval; Hb = hemoglobin concentration.
[a]$P < .05$.

thymoma, up-front surgery improves only PFS but not OS, suggesting that second-line treatment for patients who do not undergo up-front surgery might still prolong OS. However, because of the otherwise aggressive disease course of thymic carcinoma, up-front surgery improves both PFS and OS. In addition, stage III-IVA thymoma patients undergoing up-front surgery have better DFS but similar OS compared to patients undergoing surgery after induction chemotherapy. In stage III-IVA thymic carcinoma patients, up-front surgery leads to similar DFS and OS compared to surgery after induction chemotherapy. Previous inconsistent results of DFS after up-front surgery and surgery after induction chemotherapy in locally advanced disease might be due to interactions between treatment modalities and thymoma or thymic carcinoma pathology type.

Moser et al[26] and Kondo et al[27] reported that an advanced Masaoka-Koga stage and incomplete resection are two leading prognostic factors of poor OS in thymoma and thymic carcinoma patients. Thymic carcinoma often metastasizes, and it has a worse prognosis than thymoma.[5,28] When compared to other WHO thymoma histology types, the B3 type often presents at later stages and is associated with unfavorable outcomes.[29,30] Some patients with thymoma have myasthenia gravis and pure red cell aplasia, and the outcomes for the latter group are worse.[31,32] We believe that instead of treatment modalities, advanced-stage thymic carcinoma causes poor prognosis.

This study had a few limitations. First, this was a retrospective study, and some patients might not have strictly followed the treatment protocols. Second, we used medical records from 2005 to 2013, and advancements in surgical and radiologic techniques have improved outcomes over the years. However, we believe that it is important to report a real-world comparison of long-term outcomes with and without up-front surgery in patients with different stages and subtypes of thymic epithelial malignancies.

In conclusion, up-front surgery leads to better PFS and OS compared to surgery after induction chemotherapy and no surgery. Up-front surgery in thymoma patients leads to better PFS, while

up-front surgery in thymic carcinoma patients leads to better PFS and OS. In AJCC stage III-IVA thymoma patients, up-front surgery leads to better DFS compared to surgery after induction chemotherapy, while in thymic carcinoma patients, DFS in both groups is similar. The thymic carcinoma pathology type and AJCC stage IVB disease are the two most important prognostic factors of poor OS. Additional studies analyzing the correlation of other tumor biological factors with prognosis are warranted.

Clinical Practice Points

- Complete surgical excision is the main treatment for thymoma and thymic carcinoma, and induction chemotherapy improves resectability.
- This study directly compared outcomes for patients undergoing up-front surgery, surgery after induction chemotherapy, and no surgery.
- Patients undergoing up-front surgery had better PFS and OS compared to patients undergoing surgery after induction chemotherapy.
- Thymoma patients undergoing up-front surgery had better PFS compared to patients undergoing surgery after induction chemotherapy. Thymic carcinoma patients undergoing up-front surgery had better PFS and OS compared to patients undergoing surgery after induction chemotherapy.
- In AJCC stage III-IVA thymoma patients, up-front surgery had a better DFS trend compared to surgery after induction chemotherapy. In thymic carcinoma patients, the DFS of these two groups was similar.
- Instead of treatment modalities, thymic carcinoma pathology type and AJCC stage IVB disease are the two most important prognostic factors of poor OS.

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Disclosure

The authors have stated that they have no conflict of interest.

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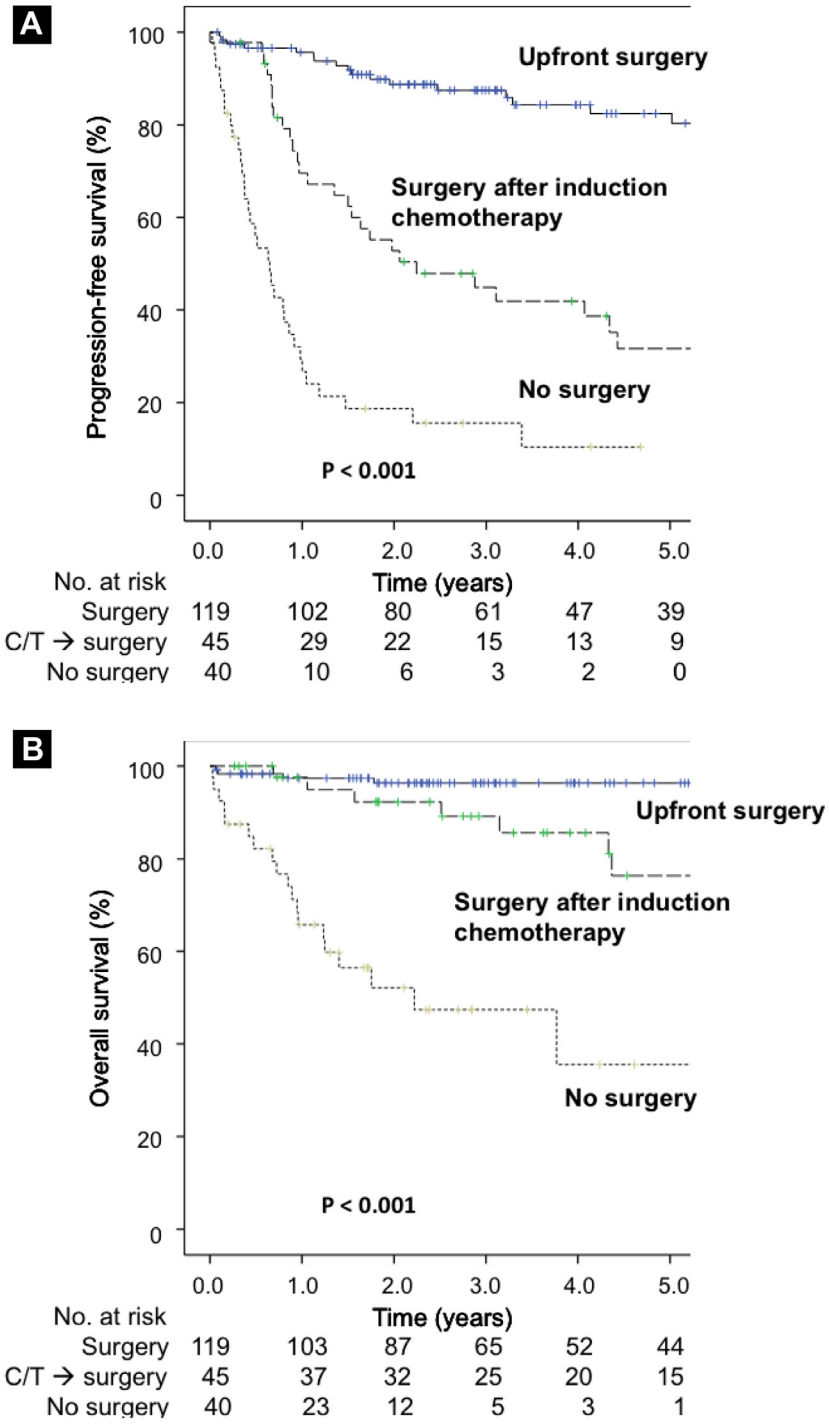
Supplemental Data

Supplemental Figure 1 PFS and OS Curves for Patients Undergoing Up-front Surgery, Surgery After Induction Chemotherapy, and No Surgery. (A) Five-year PFS Rates Were 82.5%, 31.6%, and 10.4%, Respectively ($P < .001$). (B) Five-year OS Rates Were 96.3%, 76.4%, and 35.5%, Respectively ($P < .001$)



Abbreviations: OS = overall survival; PFS = progression-free survival.