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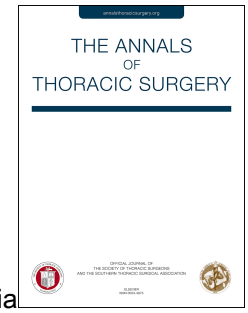

Outcomes and Safety Analysis in Superior Vena Cava Resection for Extended Thymic Epithelial Tumors

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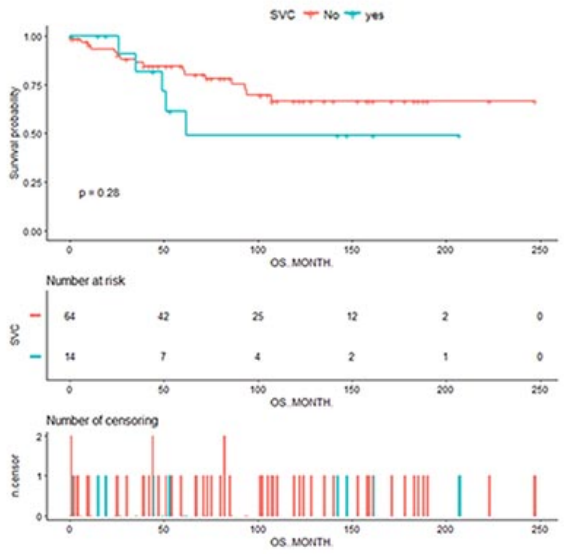
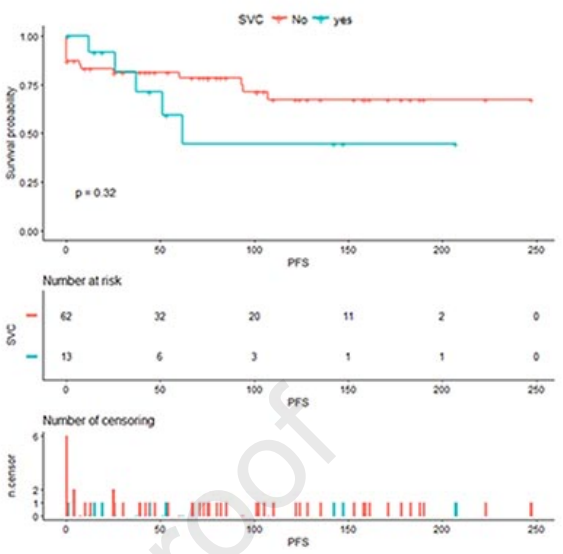


Comparison of overall survival of patients underwent superior vena cava resection (red) or not (green). OS = overall survival, SVC = superior vena cava.



Comparison of progression free survival of patients having undergone superior vena cava resection (red) or not (green) PFS = progression free survival, SVC = superior vena cava.

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Outcomes and Safety Analysis in Superior Vena Cava Resection for Extended Thymic Epithelial Tumors

Running head: SVC resection for thymic tumors

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Classifications: Thymic epithelial tumors; superior vena cava reconstruction; thymectomy; multivariable analysis; Cox analysis.

Total word count: 3,815 words.

Abstract

Background: In stage III–IVa thymic epithelial tumors (TETs), infiltration of superior vena cava (SVC) is not rare. The extent of SVC resection depends on the width of the area of neoplastic invasion. Our paper aims to evaluate the safety and long-term outcomes of extended thymectomy for TETs with SVC resection compared with advanced-stage TETs patients without SVC resection.

Methods: Retrospective review of the experience on patients who underwent extended thymectomy for TETs in the last twenty years, according to STROBE methodology. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan–Meier method. A backward stepwise Cox regression multivariate analysis was performed to determine factors associated with long-term outcomes.

Results: 78 patients underwent surgery for advanced-stage TETs (Masaoka-Koga stages III–IVa) from January 1998 to April 2019. 14 (17.9%) underwent thymectomy with resection of SVC. Presence of ~~a~~ thymic carcinoma (HR=2.26; 95% CI=1.82–6.18; *p*=0.038) and the SVC resection (HR=1.89; 95% CI=1.11–3.96; *p*=0.041) were adverse prognostic factors at multivariate analysis. The median OS and the PFS of all SVC resected patients were 50 (range: 5–207) and 31 months (range: 5–151), respectively. There was no significant difference in OS (*p*=0.28) and PFS (*p*=0.32) between SVC resected and not resected patients.

Conclusions: SVC resection is a safe and effective procedure to restore the venous system continuity and does not seem to affect survival and disease recurrence. This surgical approach allows radical resection of locally advanced TETs, even after neoadjuvant chemotherapy.

Abstract word count: 244 words.

List of Abbreviations

CI = confidence interval

HR = hazard ratio

OS = overall survival

PTFE = polytetrafluoroethylene

PFS = progression-free survival

STROBE = strengthening the reporting of observational studies in epidemiology

SVC = superior vena cava

TET = thymic epithelial tumor

Accounting for 0.2 to 1.5% of all neoplasms (1), Thymic Epithelial Tumors (TETs) include a large variety of rare thoracic malignancies arising in the thymus gland, with a reported incidence of 1.3 – 3.2 per million (2). Since radical resections have been proven to improve the prognosis significantly, therapeutic options depend mainly on the stage and resectability of the disease (3). Despite the employment of a multimodal approach, the management of locally advanced (Masaoka-Koga stages III-IVa) TETs (3) remains controversial. In these patients, thymectomy can be extended *en-bloc* to the lung, pleura, phrenic or vagus nerve, and major vascular structures, resulting in a technically demanding intervention. Even if local or distant relapse could be observed with an average recurrence time of 5 years (4), 5-year survival rates after surgery are encouraging (5), accounting for the choice to perform these challenging operations. In stage III–IVa TETs, the infiltration of the superior vena cava (SVC) and its main branches is not rare and is occasionally associated with SVC syndrome. The extent of SVC resection depends on the width of the area of neoplastic invasion. Complete SVC resection is followed by prosthetic conduit replacement to re-establish the integrity of the venous system. Over the years, several dissimilar materials have been proposed for vascular reconstruction, among which tubularized bovine pericardium and ringed polytetrafluoroethylene (PTFE) are mostly used (6, 7).

Our paper aims to evaluate the safety and the long-term outcomes of extended thymectomy with SVC resection for TETs compared with advanced-stage TETs patients without SVC resection.

Patients and Methods

We retrospectively reviewed, according to the STROBE (Strengthening the reporting of observational studies in epidemiology) statement (8), our single centre experience on patients who underwent extended thymectomy for TET in the last twenty years.

A STROBE checklist was also added in the Supplemental File 1. Clinical data were collected as follows: demographics (age, sex, significant comorbidities); preoperative treatments (chemotherapy, radiotherapy); intervention (type of incision, need for prosthesis implant(s), type of prosthesis, surgical resection of other organs); postoperative treatments (chemotherapy, radiotherapy); recurrences (site, treatment, time to recurrence); outcomes (overall survival (OS)

and progression-free survival (PFS)). Postoperative complications were defined as any adverse event occurring in the hospital or within 30 days from surgery and were classified according to Clavien–Dindo (9). Information on events after discharge and patency of the SVC reconstructed area was collected four months after surgery when the first postoperative enhanced CT scan was performed. Histological classification and subtype were assessed according to the World Health Organization (WHO) Classification of Tumors–IV Edition (1). As regards disease staging, it was assessed according to the Masaoka-Koga staging system (3); inclusion criteria were: stage III tumors (neoplastic invasion into neighboring organs) and stage IVa tumors with neoplastic involvement of the pleura or pericardium limited to one circumscribed area of infiltration.

The rationale behind the inclusion of stage IVa tumors lied on three principles:

a) Stage IV patients included in this series were responsive preoperative chemotherapy, showing a decrease of the tumor size;
b) Surgical resection of the only pleural or pericardial metastasis, along with the en-bloc removal of the tumor would not increase the surgical burden on the patient;
c) Surgery could be followed by adjuvant radiotherapy, as a part a curative-intent sequential strategy (4).

Conversely, patients who presented multiple, diffuse pleural and/or pericardial nodules were excluded.

The Ethical Committee and the Internal Review Board, informed of the database extraction, did not require approval since the retrospective nature of the study.

Statistical Analysis

Quantitative variables were expressed as mean ± standard deviation (SD), whereas nominal variables were expressed binarily as presence or absence of the event. Recurrence was diagnosed based on imaging or pathological examinations found in a review of the case records. Kruskal–Wallis Rank test was used for continuous variables, Fisher Exact test for categorical variables. Progression-free survival (PFS) and overall survival (OS) were calculated based on the

interval between TET resection and detection of recurrence using the Kaplan–Meier method. To determine the Hazard Ratio (HR) of factors associated with long-term outcomes, a backward stepwise Cox regression model was performed using as covariates age (< 50, ≥5 0 years), gender (male, female), clinical response (partial response, stable disease), the postoperative Masaoka-Koga stage, type of pulmonary resection (pneumonectomy vs lesser resections). Variables with a *p*-value < 0.2 were used for multivariate analysis. Significance was defined as a *p*-value < 0.05. Statistical analyses were performed using R software (version 3.6.1, Action of the Toes) with standard, *rcmdr*, and *irr* packages (10).

Results

Our series was composed of 78 patients who underwent surgery for advanced-stage TET (Masaoka III–IVa) from January 1998 to April 2019; 14 (17.9%) underwent thymectomy with resection of the SVC; in 64 (82,1%) patients SVC resection was not deemed necessary, in the absence of neoplastic invasion. Demographics characteristics were described in Table 1. There were no statistically significant differences between the SVC resection group and thymectomy without SVC resection. The mean age at the time of surgery was 56.4 ± 9.6 years and was not statistically significantly different from the leading group (p = 0.794). Pulmonary resections were performed in 49 patients (62.8%). 30-days postoperative mortality was null. 30-day postoperative morbidity rate was not statistically significantly different between the two groups.

In 7 (50%) patients, complete resection with prosthetic reconstruction of SVC was carried out. In 4 (28.6%) patients, a ringed PTFE graft was employed for vascular conduit replacement. Three end-to-end and one end-to-side anastomosis between the SVC and one brachiocephalic vein were performed, with graft interposition. Tubularized bovine pericardium was used in 3 (21.4%) patients for end-to-end anastomosis between the proximal and distal SVC stumps. In the remaining 7 (50%) cases, conduit replacement after SVC resection was not required. In 4 (28.6%) patients, tangential resection was followed by heterologous pericardial patch implant, while in 3 (21.4%) cases tangential resection alone was performed. Two (14.2%) patients had no preoperative chemotherapy. During the postoperative period, 3 (21.4%) patients with a Clavien-Dindo grade II

anemia underwent blood transfusions without reintervention. In one case, a tracheostomy was performed due to massive tumor infiltration of laryngeal nerves (Clavien-Dindo grade IVa). Other 30-day post-operative complications (Table 2) were: unilateral vocal fold palsy (Clavien-Dindo grade I), lobar pneumonia (Clavien-Dindo grade II) and atrial fibrillation (Clavien-Dindo grade I). Graft thrombosis occurred in 1 (14%) patient who had undergone SVC conduit replacement with a ringed PTFE prosthesis seven months earlier. Mediastinal radiotherapy was administered to 8 patients (57.1%). 7 (50%) patients developed a recurrence of disease 23 months after surgery (range: 10 – 37 months). Mediastinal lymph nodes were the most frequently involved site (4 cases). Other sites of metastases were lungs, pleura, vertebrae, brain, and liver. Chemotherapy was administered to 4 patients (29%). One patient underwent mediastinal radiotherapy, and another one received target therapy (tyrosine kinase inhibitor, Sunitinib). Apical segmentectomy of the left lower lobe was performed in one patient with a metastatic lung nodule.

Though stage IVa disease and adjuvant chemotherapy were related to poorer survival, the presence of a thymic carcinoma (HR = 2.26; 95% Confidence Interval (CI) = 1.82 – 6.18; p = 0.038) and the SVC resection (HR = 1.89; 95% CI = 1.11 – 3.96; p = 0.041) were adverse prognostic factors at the Cox multivariate analysis (Table 3).

No patients were lost at follow-up. The median OS and the PFS of all SVC resected patients were 50 (range: 5–207) and 31 months (range: 5-151), respectively. There was no significant difference in OS (p = 0.28, CI 95%) (Figure 1) and PFS (p = 0.32, CI 95%) (Figure 2) between the SVC resected and not resected patients.

Comment

Since SVC replacement is a technically challenging operation, even at a high-volume centre, the management of locally advanced TETs is still a matter of debate among surgeons, oncologists and radiotherapists (11, 12). The assessment of resectability depends mostly on the surgeon's judgement and experience but should be discussed by a multidisciplinary team for a more comprehensive overview. A meticulous preoperative workup allows accurate staging of the disease, functional evaluation of the patient and planning of the surgical strategy. The feasibility of

extended surgical resections of surrounding mediastinal organs (e.g., lungs, pericardium, vessels, pleura) should be accurately assessed, as the achievement of complete *en bloc* removal of all affected structures represents the most consistent and significant predictive factor of long-term survival (4, 13, 14). Over the years, the surgical management of SVC involvement has evolved, along with anesthetic, technical, and technological innovations. Thus, patients previously deemed ineligible for operation have now gained access to potentially curative surgery (7, 15).

The completeness of surgical resection is generally indicated as one of the most significant factors influencing prognosis. Infiltration of SVC not only influences the oncologic severity of the disease but also increases the technical complexity of the surgery, requiring extended resections and demanding reconstructive procedures, to achieve radical tumor removal in selected patients. Completeness of resection represents one of the main factors influencing the long-term outcome of patients. Increasing experience in the last years has contributed to improving the results of such complex operations. However, the spread of these interventions among thoracic surgeons remains limited, due to the concern for higher perioperative complication and mortality rates. Nonetheless, owing to the minimal number of published series in this setting, there is no compelling evidence and no standardised indication in the literature. Most papers show neither the precise number of patients undergoing such vascular reconstructive procedure for invasive thymic malignancies nor the results of this subset, merely reporting cumulative data on different mediastinal histology (16).

The prognostic impact of SVC resection in extended thoracic malignancies has been investigated in several studies (7, 17-20) with attention towards prosthetic conduit replacement (21, 22). Reported 5-year OS after radical surgery with SVC resection for advanced-stage TETs ranges from 45% to 58.1%, while the significant complication rate varies from 11.1% to 65%. Although our study is a retrospective evaluation of a limited number of cases, OS and PFS in the SVC resection group were not statistically different from those of patients who do not undergo SVC resections.

The choice of the prosthetic material is still controversial: ringed PTFE grafts seem to ensure long-term patency and prevent parietal collapse in the presence of a negative central venous pressure (23) but require life-long anticoagulation. Tubularized bovine pericardial conduits, on the other hand, have been related to lower incidence of infections and thrombosis (18). In our experience,

while previously preferring ringed PTFE grafts, the employment of tubularized bovine pericardial conduits has increased over the last 14 years. Only one patient developed venous graft thrombosis with mediastinal syndrome, seven months after surgery. He had undergone right atrial partial resection, and complete SVC resection followed by a 12-mm ringed PTFE prosthesis interposition between the right atrial stump and the right brachiocephalic vein, with the exclusion of the left brachiocephalic vein. This patient had the most extended survival in our series (207 months) and never manifested a relapse of disease.

Multimodality treatment strategies have been changing over time. Recent guidelines (4) have suggested a survival advantage of induction therapy for stage III TETs if compared with adjuvant treatment. Long-term survival results of patients included in this analysis may have been influenced by the small number of cases of stage IVa and thymic carcinoma, which have a poorer prognosis with a reduced response to the adjuvant treatment. Anyway, survival in our series is in line with that of other studies including patients undergoing SVC replacement for stage III and IVa thymomas and thymic carcinomas (16).

Preliminary validation studies have demonstrated the value of the IASLC/ITMIG staging system. The adoption of a TNM staging system for TET requires a change of mindset to the surgeons performing thymectomies since they are now strongly encouraged to perform lymphadenectomy in the resection of TET routinely. TNM staging system of TET, included in the 8th edition of the TNM international staging system of thoracic malignancies, should replace the Masaoka-Koga staging system. Nonetheless, the TNM staging system is still not widely accepted (24). Moreover, our database includes the majority of patients operated before the adoption of the TNM staging system (2017).

Our study presents several limitations. It is a retrospective series of prospectively collected patients, providing weak evidence for the feasibility of SVC resection for extended thymic malignancies. Also, it involves a relatively small number of patients. Hence, our results should be interpreted with caution. The main strength is the homogenous series of interventions performed with unmodified indications for surgery and oncologic management strategy over time. The minor discrepancies concerning the surgical technique (tangential/total SVC resection, use of

PTFE/tubularized bovine pericardium grafts, etc.) reflect the different extent of SVC infiltration among various cases and the evolution of prosthetic materials.

Besides, the presented data derive from a twenty-year experience of a high-volume referral centre and noteworthy implications could be drawn from it.

In conclusion, surgical techniques vary widely, depending on the extent of the SVC infiltration and the challenges of SVC resection for TETs are still ongoing. SVC resection is a safe and effective procedure and does not seem to affect survival and disease recurrence. This surgical approach allows radical resection of locally advanced TETs, even after neoadjuvant chemotherapy.

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Demographic and clinical characteristics	**Not SVC resected patients (No = 64)**	**SVC resected patients (No = 14)**	***p* value**
Age, mean ± SD	57.5 ± 14.6	56.4 ± 9.6	0.79
M/F ratio	0.88	1	0.83
Pulmonary resection			0.90
• No	24 (37.5%)	5 (35.7%)	
• Yes o Pneumonectomy o Lesser than pneumonectomy	40 (62.5%) 7 (10.8%) 33 (51.7%)	9 (64.3%) 1 (7.1%) 8 (57.2%)	
WHO Classification			0.79
• A	4 (6.7%)	2 (15.4%)	
• AB	3 (5.0%)	1 (7.7%)	
• B1	5 (8.3%)	0	
• B2	12 (20.0%)	2 (15.4%)	
• B3	16 (26.7%)	4 (30.8%)	
• C	20 (33.3%)	4 (30.8%)	
Masaoka–Koga Staging			0.12
• III	36 (56.2%)	11 (78.6%)	
• IVa	28 (43.8%)	3 (21.4%)	
Neoadjuvant treatment			0.73
• No	39 (60.9%)	3 (21.4%)	
• Yes	25 (39.1)	11 (78.6%)	
Adjuvant Chemotherapy			0.67

• No	57 (89.1%)	13 (92.9%)	
• Yes	7 (10.9%)	1 (7.1%)	
Postoperative Radiotherapy			0.40
• No	20 (31.2%)	6 (42.9%)	
• Yes	44 (68.8%)	8 (57.1%)	
Length of hospital stay, median (range)	8 (3 – 31)	7 (5 – 22)	0.53
Postoperative Complications	32 (50.0%)	7 (50.0%)	0.41
Recurrence			NA
• Any	32 (50%)	7 (50.0%)	
• None	32 (50%)	7 (50.0%)	
Vital status			
• Dead of disease	16 (25%)	5 (35.7%)	
• Dead of other conditions	6 (9.3%)	3 (21.4%)	
• Not evidence of disease	32 (50%)	6 (42.9%)	
• Alive with disease	10 (15.6%)	0	

Table 1: Patients' demographic and clinical characteristics. NA = not applicable, SD = standard deviation. SVC = superior vena cava.

Post-operative Complications	**Not SVC resected patients (No = 64)**	**SVC resected patients (No = 14)**	***p* value**
Clavien-Dindo grade I	10 (15.6%)	1 (7.1%)	0.16
• Atrial fibrillation and other dysrhythmias	5 (7.8%)	0	
• Chylothorax	2 (3.1%)	0	
• Fever	2 (3.1%)	0	
• Others	1 (1.6%)	1 (7.1%)	
Clavien-Dindo grade II	18 (28.1%)	5 (35.7%)	0.18
• Anemia requiring transfusions	13 (20.3%)	3 (21.4%)	
• Pneumonia	4 (6.3%)	2 (14.3%)	
• Others	1 (1.5%)	0	
Clavien-Dindo grade III	2 (3.1%)	0	0.18
• Hemothorax	1 (1.5%)	0	
• Dehiscent sternal wound	1 (1.5%)	0	
Clavien-Dindo grade IV	2 (3.1%)	1 (7.1%)	0.19
• Respiratory failure requiring tracheostomy	0	1 (7.1%)	
• Ischemic stroke	1 (1.5%)	0	
• Cardiogenic shock	1 (1.5%)	0	

Table 2: Main postoperative complications according to Clavien-Dindo [9]. SVC = superior vena cava.

	Univariate Analysis		Multivariate Analysis	
Variable	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Age (> 50 years)	0.99 (0.94 – 1.06)	0.88		
Sex	0.94 (0.2 – 4.33)	0.94		
Thymic carcinoma histology	2.28 (1.51 – 10.21)	0.094	2.26 (1.82 – 6.18)	0.038
Pulmonary resection	1.03 (0.19 – 5.45)	0.98		
SVC resection	1.34 (1.07 – 4.31)	0.064	1.83 (1.11 – 3.96)	0.041
Masaoka–Koga Stage IVa	2.36 (1.17 – 32.19)	0.13	1.99 (0.42 – 9.42)	0.53
Adjuvant chemotherapy	1.97 (1.14 – 7.41)	0.098	0.86 (0.17 – 4.48)	0.86

Table 3: Multivariate Cox Regression analyses of overall survival. CI = confidence interval, HR = Hazard Ratio. SVC = superior vena cava.

Figure Legends

Figure 1: Comparison of OS of patients having undergone superior vena cava resection (red) or not (green) (*p* = 0.28, 95% CI).

CI = confidence interval, OS = overall survival, SVC = superior vena cava.

Figure 2: Comparison of PFS of patients having undergone superior vena cava resection (red) or not (green) (*p* = 0.32, 95% CI).

CI = Confidence interval, PFS = progression free survival, SVC = superior vena cava.