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ORIGINAL ARTICLE

Superior Vena Cava Resection in Locally Advanced Thymoma—Surgical and Survival Outcomes

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Abstract

This study was aimed at reporting the surgical management of superior vena cava invasion in patients with locally advanced thymoma and to evaluate surgical and survival outcomes. This is a retrospective analysis of 12 patients operated for superior vena cava resection for locally advanced thymoma over 8 years in a thoracic surgery centre in India. An analysis of peri-operative variables including complications was carried out. The influence of various predictors on survival was assessed by log-rank test. Intra-operatively, superior vena cava (SVC) alone was involved in 3 (25%) cases, SVC with BCV involvement was there in 8 cases (66.7%) and in 1 patient, the SVC involvement extended into the right atrium also. In all cases, the tumour was resected en bloc with the involved part of SVC. Repair with primary closure was sufficient in 2 cases (16.6%) in view of < 1/3rd of circumferential involvement. However, in remaining 10 cases, SVC was replaced with PTFE graft (single graft in 6 cases, Y-graft in 2 cases and twin grafts in 2 cases). No peri-operative deaths. Overall survival (OS) at 1, 3 and 5 years was 100%, 91.6% and 83.3%, respectively. Myasthenia gravis and higher Masaoka stage (IV A) of the disease were poor predictors of survival. Superior vena cava resection and reconstruction is a feasible and oncologically superior option in invasive thymoma with SVC involvement. This challenging surgical procedure should only be attempted by an experienced team of thoracic and cardiac surgeons at high-volume centre to achieve best outcomes.

Keywords Locally advanced thymoma · Superior vena cava · SVC reconstruction · Surgical bypass

Introduction

Thymoma is the commonest anterior mediastinal tumour arising from thymic epithelial cells and is usually slow growing [1]. However, some of these tumours exhibit an aggressive behaviour and infiltrate the surrounding structures. In view of the anatomical proximity, superior vena cava (SVC), brachiocephalic veins (BCV) and ascending aorta are affected.

In surgery for thymoma, "completeness of resection" is the main factor which determines the long-term prognosis [2–4]. The optimal surgical strategy in such cases has to include radical resection of the tumour with involved vascular structures and appropriate reconstruction [5]. In patients, where upfront surgical resection of the tumour is not considered feasible, induction chemotherapy should be followed by an attempt at "complete resection", to be followed by adjuvant radiotherapy [6].

Resection and reconstruction of superior vena cava is technically challenging. Majority of patients having invasive thymoma with SVC involvement are considered inoperable by surgeons because of technical complexity, perceived high morbidity and mortality and a false notion of lack of survival benefit following the procedure. Many authors have evaluated the outcomes of SVC resection in advanced lung cancers [7–9]. However, few reports are available regarding its safety and feasibility in invasive thymoma [10, 11]. The extent of circumferential tumour infiltration and the length of SVC involvement decide the mode of reconstruction, i.e. primary

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repair, patch-plasty or resection and replacement with a prosthetic conduit [12]. Herein, we present our experience of SVC resection in patients with invasive thymoma involving SVC and evaluate the surgical as well as survival outcomes.

Material and Methods

Study Population

This is a retrospective analysis of 12 patients of locally advanced thymoma with SVC involvement (with or without BCV involvement) who underwent surgical resection between March 2012 and March 2020 at a tertiary care Thoracic Surgical Centre in New Delhi, India. This study was approved by the institutional ethics committee.

Pre-operative Evaluation

These patients with suspected SVC involvement also underwent computed tomography (CT) angiogram of the chest for better delineation of vascular involvement and anatomy. Histological diagnosis was always confirmed by guided biopsy. Induction chemotherapy was advised in patients where upfront surgical resection was not considered feasible. This consisted of 3–4 cycles of a combination of cyclophosphamide, cisplatin and doxorubicin, repeated every 3 weeks. In this series of 12 cases, 4 patients (33.3%) received induction chemotherapy, whereas the rest 8 patients (66.7%) underwent upfront surgical resection.

Challenges in SVC Resection

Resection of thymoma along with the SVC and reconstruction is challenging and requires a combination of surgical skills and specialised anaesthetic management. The entire surgical and anaesthetic management revolves around mitigating the physiological effects of clamping of SVC, apart from a technically challenging tumour resection and reconstruction with a vascular graft. Cross clamping of SVC leads to sudden stoppage of venous return which reduces cardiac preload and cardiac output leading to precipitous fall in the arterial blood pressure. There is also an increase in the cerebral venous pressure. Rise in cerebral venous pressure to levels approaching the arterial pressure reduces the cerebral perfusion leading to brain oedema and even infarction. These effects are dramatic in patients with minimal or no pre-existing compromise of SVC lumen and modest in patients where the SVC was already partly occluded pre-operatively.

To minimise the deleterious effects of cross clamping of SVC, the anaesthetists have to judiciously use vasoactive drugs and fluids to keep the arterial pressure up. Use of cardio-pulmonary bypass (CPB) or creation of a temporary shunt between one of the internal jugular veins and right atrium has also been suggested [13]. Cardio-pulmonary bypass has its own morbidity and needs heparin, which should be avoided in these patients with extensive dissection. So, we adopted a policy of doing SVC resection and replacement by graft in a manner that the blood flow between one of the innominate veins and right atrium was not interrupted. This was achieved by a unique strategy, described in the "Surgical Details" section.

Anaesthetic Management

The focused peri-operative anaesthetic management includes safe induction, securing airway with double lumen tube and maintaining hemodynamic stability during the entire peri-operative period. These patients require intra-operative monitoring of cerebral venous pressure. We used internal jugular venous pressure (measured through a line there) as a proxy for the cerebral venous pressure. Systemic venous and arterial pressure was monitored by lines at femoral site. Trans-oesophageal echocardiography was used to monitor cardiac filling and hemodynamic changes during clamping of vascular structures. Neuro-protective measures included use of thiopentone, mild hypothermia and monitoring of cerebral oximetry using near Infrared spectroscopy (NIRS) during clamping of SVC. The equipment for cardio-pulmonary bypass should be kept ready beforehand, as it may be needed in case of hemodynamic instability or significant bleeding.

Surgical Details

All procedures were performed through mid-sternotomy. If the tumour was infiltrating either of the BCV (not both) without SVC involvement, the involved BCV was ligated and resected in continuity without any reconstruction. This practice was based on the fact that the opposite patent BCV can take care of the head and upper limb venous drainage. Also, in majority of the thymic tumours, involvement of BCV occurs slowly, giving enough time for development of collateral channels.

However, in case of SVC involvement, the SVC was resected en bloc with the tumour and reconstructed. The type of reconstruction was based on the extent of SVC and BCV involvement:

A. Tumour involves < 1/3rd of total circumference of SVC.

The involved part of SVC was resected after applying side biting vascular clamp and the resultant defect was repaired primarily with 6–0 poly-propylene interrupted sutures (Fig. 1).

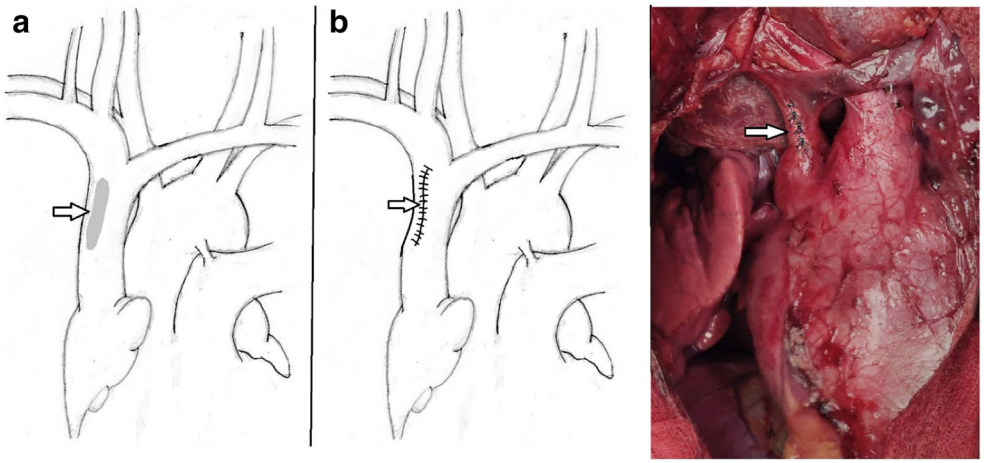

Fig. 1 **a** Tumour involves < 1/3rd of total circumference of SVC. **b** Primary repair. **c** Clinical photograph

B. Tumour involves > 1/3rd of circumference and/or > 2 cm length of SVC.

After resection of involved SVC with the tumour, a prosthetic graft (polytetrafluoroethylene, PTFE) can be used for SVC reconstruction (Fig. 2) (we did not have any case needing this type of repair).

C. Tumour involving SVC + confluence of BCV + adjacent distal segments of both BCV.

In these cases, after complete mobilisation of the tumour with SVC, the same was not resected but reconstruction type was decided and started. We used either a single "Y-graft" or "two separate straight grafts" to restore vascular continuity. The decision of "Y-graft" vs "two separate grafts" was based on the availability of grafts.

a. "Y-graft" technique - The two Y-limbs were anastomosed in an end-to-end fashion with the brachiocephalic veins, and the straight limb of Y-graft was anastomosed to the right atrium. To maintain venous return, cut proximal end of left BCV was anastomosed to one of the Y-limbs first. At this time, the right BCV was draining through involved SVC into the right atrium. The right limb of the Y-graft was kept clamped and an end to side anastomosis of the straight limb of graft was done with the right atrium. Thus, venous drainage was established between left BCV and the right atrium. Now, the tumour with SVC and distal BCVs was resected and proximal cut end of right BCV was anastomosed end to end to the right limb of the Y-graft (Fig. 3).
b. "two separate graft" technique - Here, one end of straight PTFE graft was anastomosed end to end to proximal left BCV and the other end was anastomosed with the right atrium. Then, the tumour with SVC- and distal-involved BCVs was resected and another straight graft used to join proximal cut end of right BCV to the right atrium (Fig. 4).

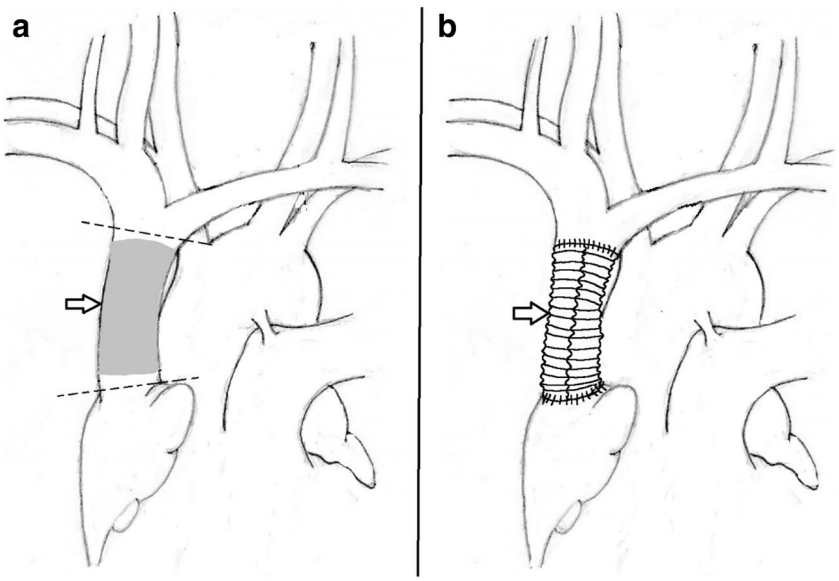

Fig. 2 **a** Tumour involves > 1/3rd of circumference and/or > 2 cm length of SVC. **b** PTFE graft replacing only SVC

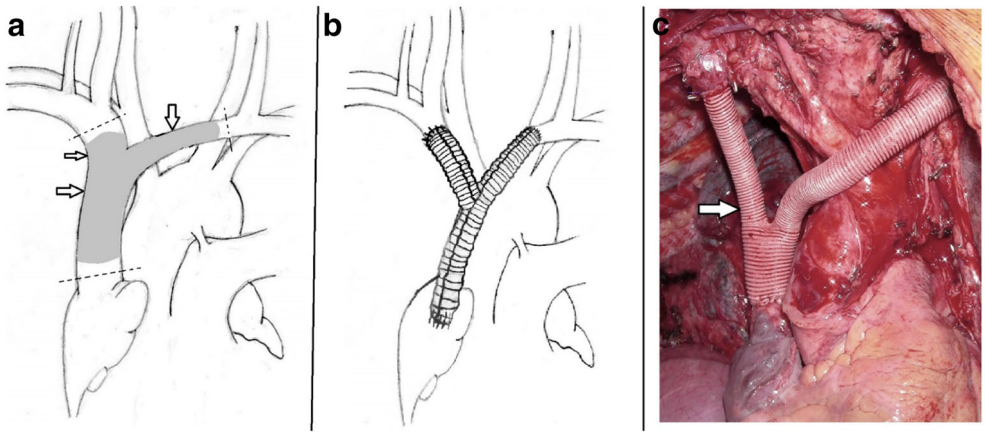

Fig. 3 **a** Tumour involving SVC + confluence of BCV + adjacent distal segments of both BCV. **b** Anastomosis of Y-graft between brachiocephalic veins and right atrium. **c** Clinical photograph

D. Tumour involving SVC + long segment single BCV.

In cases where SVC and long segment of single BCV was involved, after resection, the proximal end of that BCV retracted to a position wherein an anastomosis with the graft was difficult. The same was closed with sutures and the reconstruction was performed by a single straight graft between the un-involved BCV and the right atrium. This method of reconstruction between right BCV and right atrium is illustrated in Fig. 5, and similar anastomosis between left BCV and right atrium in Fig. 6.

Unique feature of our technique was creating an anastomosis between one BCV and right atrium before SVC resection. This alleviated the possibility of cerebral venous hypertension and hemodynamic instability and provided adequate time to perform the rest of anastomosis. In our series, cardiopulmonary bypass was required in only 1 patient, where the tumour extended along the SVC into right atrium also. Here, the right atrium was also resected and closed primarily.

Post-operative Care and Follow-up

Low molecular weight heparin was started from 1st post-operative day which was gradually shifted to oral warfarin therapy to maintain a post-operative international normalised ratio (INR) at 2–2.5. Aggressive chest physiotherapy, oral nutrition and early mobilisation were started as soon as possible. Effective pain relief was achieved by epidural analgesia supplemented with intravenous medications. The chest drains were removed when there was no air leak, the drainage was non-haemorrhagic, and less than 100 ml in 24 h.

Adjuvant Therapy

Adjuvant therapy was decided based on tumour clinical stage (Masaoka-Koga) final histopathology report. Adjuvant radiotherapy was advised to all patients and adjuvant chemotherapy was also given for patients with pleural metastasis.

Follow-up

First follow-up was done at 1 month from discharge on outpatient basis. Graft patency and tumour recurrence were assessed clinically as well as with CECT chest every 6 months for 2 years and then annually thereafter.

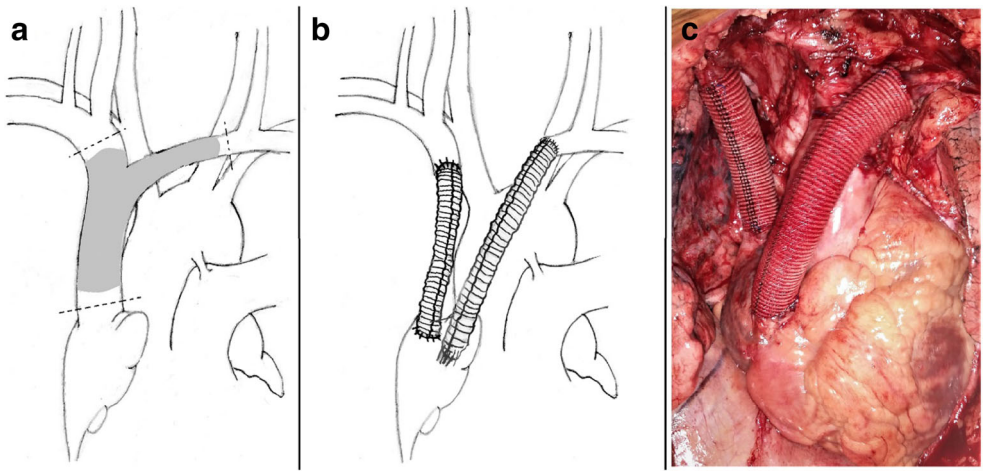

Fig. 4 **a** Tumour involving SVC + confluence of BCV + adjacent distal segments of both BCV. **b** Anastomosis of twin grafts between brachiocephalic veins and right atrium. **c** Clinical photograph

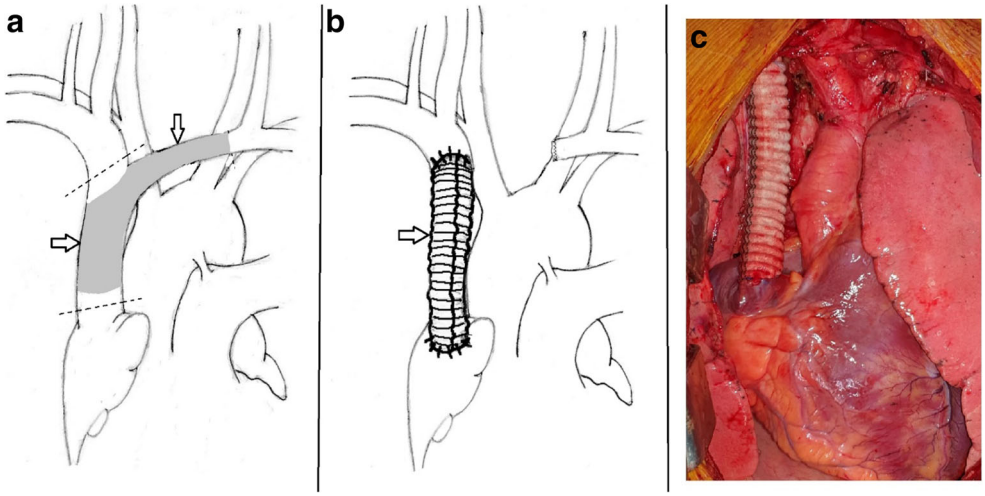

Fig. 5 **a** Tumour involving SVC + long segment of left BCV. **b** Single PTFE graft anastomosed between right BCV and right atrium. **c** Clinical photograph

Statistical Analysis

Statistical analysis was carried out using Stata 14.0 software (StataCorp LLC, Texas, USA). Continuous variables were presented as mean with standard deviation (SD). Categorical variables were expressed as frequencies with percentages. Survival was calculated by the Kaplan-Meier method. Overall survival (OS) was calculated from the date of surgery to the date of death due to any cause. Differences between survival rates were assessed by using log-rank test. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference.

Results

Demographic Characteristics

A total of 12 patients with locally advanced thymoma were included in whom 9 patients (75%) had stage III disease and 3 (25%) had stage IV A disease. There were 10 males (83.3%) and 2 females (16.7%), with a mean age of 51.2 years (range, 29–74 years). Seven patients (58.3%) had myasthenia gravis (MG) associated with thymoma. Based on the pre-operative imaging, 9 (75%) patients underwent upfront surgery, whereas 3 (25%) patients were given NACT (Table 1).

Peri-operative Variables

All the patients underwent surgery through median sternotomy approach. Mean tumour diameter was 7.3 cm. Complete radical resection (R 0) was achieved in all (100%) cases. Intra-operatively, SVC alone was involved in 3 (25%) cases, SVC with BCV involvement was there in 8 cases (66.7%) and in 1 patient, the SVC involvement extended into the right atrium also. The tumour was resected en bloc with the involved part of SVC. Repair with primary closure was sufficient in 2 cases (16.6%) in view of < 1/3rd of circumferential involvement. However, in remaining 10 cases, SVC was replaced with a prosthetic graft (PTFE graft). Single interposition graft was used in 6 cases (50%), Y-graft in 2 cases (16.6%) and twin-straight grafts were used in 2 cases (16.6%) (Figs. 1, 2, 3, 4, 5 and 6).

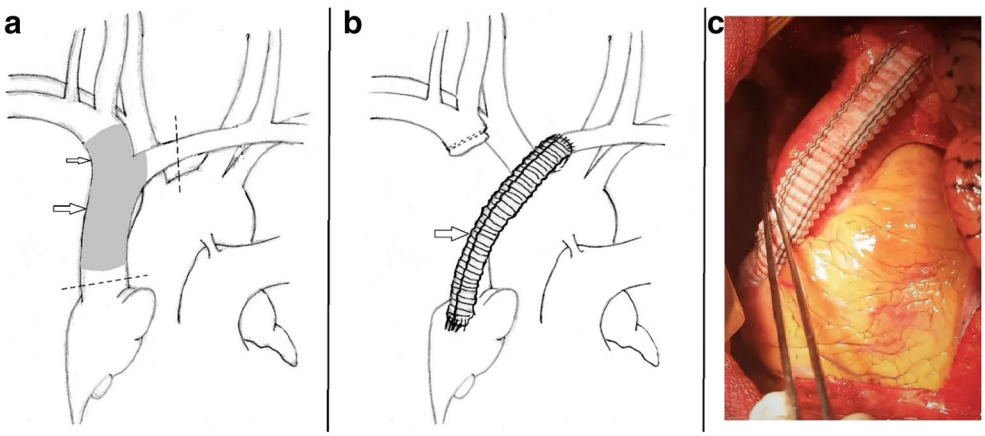

Fig. 6 **a** Tumour involving SVC + long segment of right BCV. **b** Single PTFE graft anastomosed between left BCV and right atrium. **c** Clinical photograph

Table 1 Demography and peri-operative variables of the study group ($n = 12$)

Variables	Number of patients (%)
Male (%)	10 (83.3%)
Female (%)	2 (16.7%)
Age in years (mean ± SD)	51.2 ± 4.6
Patient comorbidities	
Yes	4 (33.3%)
No	8 (66.7%)
Duration of symptoms in months (mean ± SD)	4.5 ± 1.3
Maximum dimension of the lesion in cm (mean ± SD)	7.3 ± 2.4
Myasthenia gravis	7 (58.3%)
Induction chemotherapy	3 (25%)
WHO histology	
Type A (%)	Nil
Type AB (%)	1 (8.3%)
Type B 1 (%)	1 (8.3%)
Type B 2 (%)	2 (16.7%)
Type B 3 (%)	8 (66.7%)
Type of resection	
Only SVC*	3 (25%)
SVC + adjacent BCV**	8 (66.7%)
SVC + adjacent BCV + part of right auricle	1 (8.3%)
Type of repair	
Primary repair	2 (16.6%)
SVC replacement	10 (83.4%)
Single graft	6 (50%)
"Y-graft" technique	2 (16.6%)
"Twin-graft" technique	2 (16.6%)
Completeness of resection	
R 0 (%)	12 (100%)
Masaoka stage	
III (%)	9 (75%)
IV A (%)	3 (25%)
Post-operative radiotherapy	12 (100%)
Post-op ICD duration (in days) (mean ± SD)	7.4 ± 2.1
Hospital stay (in days) (mean ± SD)	12.3 ± 2.4
Post-operative complications (%)	4 (33.3%)
Bleeding	1 (8.3%)
Post-operative chylothorax	1 (8.3%)
Pleural re-collection	2 (16.6%)
Deaths	
< 90 days (peri-operative mortality)	Nil
< 1 year	Nil
< 3 years	1
< 5 years	2

*Superior vena cava

**Brachiocephalic veins

Post-operative complications occurred in 4 patients (33.3%). There was post-operative bleeding in 1 patient which necessitated re-exploration, iatrogenic chylothorax in 1 patient which required thoracoscopic thoracic duct ligation and

pleural re-collection in 2 patients which was managed successfully by ultrasound-guided pig tail chest drain insertion (Table 1).

Survival Analysis

There were no peri-operative deaths (< 90 days) in the study population. The median follow-up duration was 52 months. During this follow-up, there were 2 deaths (16.6%), one patient expired due to dengue shock syndrome 20 months after primary surgery and another patient died of myasthenic crisis at 44 months from surgery. None of the patients had local/systemic recurrence. Overall survival (OS) at 1, 3 and 5 years was 100%, 91.6% and 83.3%, respectively. On testing the equality of survival functions by log-rank test, presence of myasthenia gravis and higher Masaoka stage (IV A) of the disease were poor predictors of survival, whereas administration of neo-adjuvant chemotherapy did not affect the overall survival (Fig. 7).

Discussion

Locally advanced thymoma is characterised by infiltration into surrounding structures like pleura, pericardium, lung, phrenic nerve and mediastinal great vessels [14]. Historically, malignant tumours of thorax infiltrating the mediastinal great vessels were considered unresectable in view of poor surgical and survival outcomes and low graft patency rates. However, with the advancements in the surgical techniques, peri-operative monitoring and care and the availability of newer prosthetic grafts, the surgical and survival outcomes and graft patency rates have improved (Table 2) [15–17].

Most commonly used investigation to assess the stage of thymoma is contrast-enhanced CT chest. However, due to its inherent limitation, CT chest may not always differentiate between tumour infiltration of vessel and abutting the vessel. So, whenever there is suspicion of vascular involvement, CT angiography of the chest should also be performed. In CT scan, the criteria used to evaluate vascular invasion are presence or absence of "Intervening fat planes" between tumour and the vessels [18]. In 11 out of 12 cases (91.6%), the involvement of SVC was accurately assessed by pre-operative CT angiogram. In the remaining 1 case (8.4%), SVC infiltration of the tumour was an intra-operative surprise as CT angiogram showed no evidence of vascular infiltration. On the contrary, we had other cases where CT scan revealed doubtful or obliterated planes and at surgery, the tumour was only abutting and not infiltrating the great vessels and was completely resected. We strongly feel that no such case should be condemned as unresectable only based on absence of fat planes between the tumour and the great vessels and an opportunity at resection by an experienced team should be offered to all patients. In a tumour like thymoma, where "complete resection" is the key issue even in locally advanced tumours, leading to significantly better survival rates [19, 20], this chance must be offered to all the patients.

Even in patients with SVC involvement specifically, complete resection has been reported to have better survival outcomes compared with incomplete resection [21]. However, for patients in whom complete resection is not considered possible upfront, induction therapy (chemotherapy and/or radiotherapy) is advocated [22]. These modalities are proven to

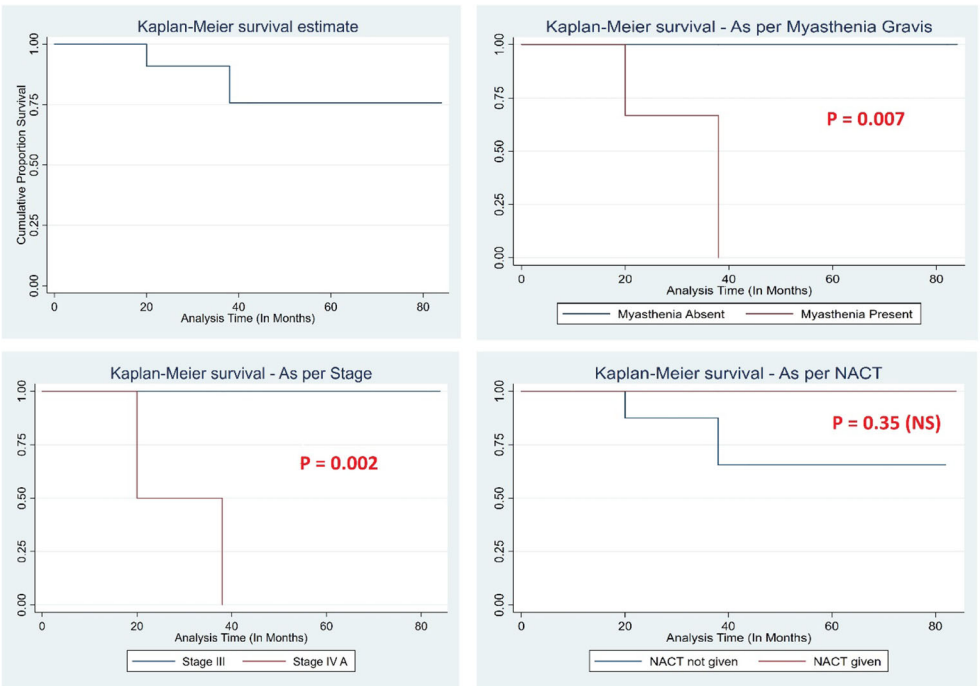

Fig. 7 Kaplan-Meier graphs. Analysis of overall survival

Table 2 Previously published series with superior vena cava resection for locally advanced thymoma

Author and year	Country	No. of patients	Type of graft	Graft patency rate	Survival rates
Bacha et al. (1998)	France	11	PTFE	-	-
Okereke et al. (2010)	USA	10	PTFE	100%	100% (5-year)
Leo et al. (2010)	Italy	11	PTFE	-	-
Sun et al. (2017)	China	25	PTFE	80% (5-year)	79.6% (3-year) and 59.1% (5-year)
Kaba et al. (2018)	Turkey	10	Pericardium, Dacron, PTFE	-	80% (median follow-up - 40 months
Present study (2020)	India	12	PTFE	100%	91.6% (3-year) and 83.3% (5-year)

improve the resectability rates and offer a chance for prolonged disease-free survival [23]. Therefore, an aggressive surgical approach with attempt at radical resection and vascular reconstruction is justified in cases of SVC involvement. This should only be attempted by a joint team of thoracic and cardiac surgeons, with the necessary expertise and experience. A close coordination between thoracic and cardiac surgeons, anaesthetist and medical and radiation oncologist is necessary for successful outcome in these challenging cases. The results justify the efforts.

The type of SVC reconstruction depends on the extent of involvement. Few authors have proposed tangential resection and patch repair if the tumour involvement is < 20% of circumference whereas complete replacement in cases of > 30% circumferential involvement. Our protocol was partial resection and repair using PTFE patch/pericardial patch in cases with < 1/3rd of circumferential involvement and replacement of the SVC by graft in case of > 1/3rd involvement. Many techniques have been described for SVC resection and reconstruction. Initial studies reported total clamping of SVC followed by resection and reconstruction. However, intra-operative hypotension and cerebral venous hypertension were issues which increased the in-hospital mortality up to 14% [24]. To avoid this, a temporary bypass technique using a bypass tube™ between patent brachiocephalic vein and the right atrium was proposed [13]. We circumvented the above challenge by our original technique of anastomosis between one patent BCV and right atrium first, thereby establishing one venous return channel before SVC resection. The only pre-requisite for this technique is patency of at least one of the BCVs. This approach bypasses the venous blood flow from head and upper limbs to the right heart after which the SVC could be safely clamped above and below the area of involvement and resected followed by remaining reconstruction as described earlier. This approach offers three major advantages, firstly, it prevents hemodynamic instability and cerebral venous hypertension secondary to SVC clamping; secondly, it saves time by avoiding the need for a temporary SVC bypass (Anthron bypass tube ™); and lastly, it obviates the need for cardio-pulmonary bypass.

Various materials have been used for the reconstruction of superior vena cava. They include autologous materials such as pericardium or great saphenous vein, bovine jugular vein and synthetic Dacron and PTFE grafts [25, 26]. Autologous veins such as saphenous vein and bovine jugular vein consume a lot of time for the preparation and are prone to similar graft thrombosis [27, 28]. Synthetic Dacron grafts were also used by several authors and with promising results [29, 30]. However, PTFE grafts are currently considered the best option with advantages of durability, long-term patency and excellent clinical outcomes [31, 32]. In all of our cases, ringed PTFE graft was used. During the follow-up, all patients (100%) had graft patency. Maintaining the post-operative INR at the recommended levels is the critical concern to prevent graft thrombosis. In our practice, we start low molecular weight heparin in therapeutic doses to achieve target aPTT (activated partial thromboplastin time) twice the normal values and they were gradually shifted to oral anticoagulation for lifetime.

This study is limited by its retrospective nature which carries many inherent biases. Second drawback is the small number of patients, which limits the strength of the study. Third limitation is short follow-up period. To evaluate the effect of any therapeutic option, at least 10 years' follow-up is required in thymomas due to their indolent nature. So, more prospective studies with larger numbers and longer follow-up are strongly recommended.

Since the prognosis of locally invasive thymoma is mainly determined by complete surgical resection, it is recommended to perform radical surgical resection even when major vessels are involved. Our study emphasises that superior vena cava resection and reconstruction is feasible and safe with improved survival rates in invasive thymoma with SVC involvement. However, these cases are surgically challenging and should only be attempted at high-volume centres with availability of an experienced team of thoracic and cardiac surgeons.

Compliance with Ethical Standards

This study was approved by the institutional ethics committee.

Conflict of Interest The authors declare that they have no conflict of interest.

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