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Surgical Treatment of Complex Malignant Anterior Mediastinal Tumors Invading the Superior Vena Cava

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Abstract

Determining the appropriate surgery-based treatment for complicated anterior mediastinal malignancies (CAMM), especially those invading the superior vena cava (SVC) and its branches, remains a challenge for general thoracic surgeons. In this report, we summarize our experience and lessons regarding this issue in order to discuss a reasonable strategy for diagnosis and treatment of CAMM. Between January 2001 and April 2003, 15 patients with CAMM invading the SVC and/or its branches with or without invasion of other neighboring organs were surgically treated in our institution by a single surgeon team. We collected clinical data from the medical charts and from surgeons' specific notes for complicated cases, and performed a comprehensive analysis. There were 9 patients with malignant thymoma. Thymic carcinoma, teratoma, embryonal carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and mixed teratoma with thymoma were diagnosed in 1 patient each. All procedures were performed via median sternotomy. Some angioplasty techniques were successfully used to resect and reconstruct the SVC. Ten of the 15 patients also underwent pulmonary resection due to involvement of pulmonary parenchyma. Four of the patients underwent perioperative chemotherapy. There were no perioperative deaths. Two patients suffered prolonged ventilation after surgery, and there were no other severe complications related to surgery. One patient died 10 months after surgery. The remaining 14 patients were still living and their progress is still monitored. As of August 2004, the median follow-up duration for all patients was 35 months, and the disease-free survival duration was 10–43 months. CAMM can be safely and completely resected via a median sternotomy, even if it has invaded other mediastinal structures. CAMM should be pathologically identified before initial treatment. A good

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outcome for patients with CAMM is possible if a suitable strategy combining accurate diagnosis and appropriate treatment, especially surgical resection, is established.

The incidence of primary malignant mediastinal tumors remains a relatively uncommon finding. Anterior mediastinal neoplasms include several types of tumors, the most common of which are thymic tumors, germ cell tumors, and lymphomas.[1] Because few symptoms are present in the early stages of development, these tumors are almost always locally advanced at presentation or have even invaded surrounding tissues, including major blood vessels, pericardium, and lung tissue, which may preclude a curative surgical resection. Although recent advances in diagnostic techniques have led to more accurate preoperative delineation and histologic diagnoses, determining the appropriate surgery-based treatment for complicated anterior mediastinal malignancies (CAMM), especially those that invade the superior vena cava (SVC) and its branches, remains a challenge for general thoracic surgeons. Therefore, we retrospectively summarized our experience and lessons from 15 patients with CAMM, specifically tumors that had invaded the SVC, with/without invasion of other organs, who underwent extended radical resection. We discussed the surgery skills, preoperative histologic diagnoses, treatment strategy, and evaluated the safety of the extensive resection including involved vital organs, especially the SVC system, on outcomes in patients with CAMM.

PATIENTS AND METHODS

Between January 2001 and April 2003, 15 patients with CAMM invading the SVC system, with or without invasion of other organs were treated at the Peking University Beijing Cancer Hospital by a single surgeon team. Only patients with tumors located in the anterior mediastinum with macroscopic tumor invasion of the SVC system at the time of operation and that required resection were included in this study. Medical charts were reviewed for demographic data, clinical presentation, diagnostic investigations, operative procedure, tumor invasion (as determined by diagnostic physicians and by the surgeon), histologic diagnosis, postoperative morbidity and mortality, long-term follow-up, and adjuvant therapy. Clinical staging included history and physical examination, posteroanterior and lateral chest roentgenograms, chest and abdominal computed tomography scans, bronchoscopy, and upper venography by bilateral simultaneous upper extremity injection when there was a suggestion of compression of the venous system. Follow-up was performed through outpatient visits and phone calls.

RESULTS

Patient Demographics

Nine men and six women were enrolled. The mean age at diagnosis was 40.6 years (range: 21–71 years). Eight patients presented with cough, three with bloody phlegm, three with chest pain, three with fever, three with SVC syndrome, one with myasthenia gravis (MG), and one with pure red-cell aplasia anemia (PRCAA) (Table 1).

Pathology

Malignant thymoma was diagnosed postoperatively in nine patients. Thymic carcinoma, teratoma, embryonal carcinoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and mixed teratoma with thymoma were diagnosed in one patient each. A preoperative pathologic diagnosis of thymoma was made for two patients by final needle aspiration (FNA). One patient was diagnosed with adenocarcinoma, another with carcinoma but of a hard-to-define histologic type.

Radiographic Analysis

X-ray films showed that the tumor sizes ranged from 4.0 $\times$ 5.0 cm^2 to 10.0 $\times$ 17.0 cm^2. Computed tomography scans showed that the tumor sizes ranged from 4.3 $\times$ 4.0 $\times$ 5.0 cm^3 to 16.9 $\times$ 10.1 $\times$ 9.6 cm^3, that all tumors had invaded the SVC system, and that the tumors did not have well-demarcated borders. In 10 patients, the tumor had invaded lung tissue; in three, enlarged mediastinal lymph nodes; in two, parietal pleura; and in one, the right hydrothorax. Superior vena cava angiography was performed on seven patients to evaluate the involvement of major blood vessels and surrounding organs. The SVC and /or the left or right innominate vein was constricted or obstructed in four patients, and the SVC was displaced in one patient. There were no abnormalities within the arterial system.

Perioperative Chemotherapy

Two patients for whom a preoperative diagnosis was made received preoperative chemotherapy. Patient 10

received two cycles of cisplatin-based chemotherapy; reevaluation showed stable disease. Patient 13 received four cycles of cisplatin-based chemotherapy; the tumor shrank, but the change did not qualify as a partial response.

After surgery, patients 10 and 13 received two additional cycles of cisplatin-based chemotherapy, and patients 14 and 15 received ABVP chemotherapy (Adriamycin, bleomycin sulfate, vinblastine, and prednisone) for 8 cycles and 12 cycles, respectively. No postoperative adjuvant treatment was administered to the remaining subjects.

Surgical Procedures and Outcome

All 15 patients underwent surgery for complete resection of the tumor and any involved tissue, and for repair or reconstruction of the main blood vessels involved. In addition, for patient 10, total resection of the SVC and both innominate veins and reconstruction with a Y-shaped artificial vessel were performed (Fig. 1). For patients 7 and 15, total resection of the SVC and both innominate veins plus interposition with a single-lumen artificial vessel were performed (Fig. 2). The prosthetic SVC conduits we used were Dacron grafts. For patients 4, 5, and 9, partial resection of the SVC and innominate veins and angioplasty with a pericardial patch were performed. All 6 of these patients were operated on using total SVC clamping. In patients 6 and 13, the tumor was resected, the left innominate vein was removed, and its distal end was ligated. In the remaining seven patients, the tumor was resected and the partial lateral wall of the SVC and/or innominate vein were directly resected and sutured under lateral SVC clamping (Fig. 3). Ten patients also underwent pulmonary resection: right pneumonectomy, right extrapleural pneumonectomy, right upper-middle bilobectomy, left upper lobectomy, and right upper lobectomy (one patient each) or wedge resection of the left upper lobe (five patients). In this group of patient, we performed anatomic pulmonary resection instead of wedge resection in five patients because, clinically, wedge resection could not reach the radical resection due to extensive tumor invasion.

After surgery, patient 10 was supported by a breathing apparatus for 25 days due to respiratory failure, and patient 15 was supported for 15 days due to myasthenia gravis (MG). In patient 1, the PRCAA did not resolve, even after postoperative administration of glucocorticoid and several blood transfusions, but the patient's condition had improved compared with preoperation situation. There were no other severe complications or surgery-related deaths.

Patient 13 died because of recurrent embryonal carcinoma 10 months after surgery. The remaining 14 patients were still alive as of August 2004, and their follow-up will continue. The median follow-up duration for all patients is 35 months, and disease-free survival time ranges from 10 months to 43 months.

DISCUSSION

Preoperative Biopsy

Some investigators have suggested that preoperative biopsy should be avoided when the anterior mediastinal tumor has well-demarcated borders and could easily be resected completely.[2–4] That assessment seems reasonable because a biopsy could increase the possibility of tumor seeding. But for invasive tumors, biopsy is necessary, because their complete resection necessitates simultaneous resection of involved vital organs, and such procedures carry relatively more severe risks. Examination of tissue obtained using FNA may not always differentiate Hodgkin's lymphoma from non-Hodgkin's lymphoma, or even lymphoma from thymoma, because the tissue samples are often too small to facilitate an accurate diagnosis. This limitation may partially explain why the preoperative and postoperative pathologic diagnoses were inconsistent in our two patients. Yet, because of the minimal trauma and the overall accuracy associated with it, FNA is used extensively.[5] Although FNA did not produce an accurate diagnosis for patients 10 and 13, this procedure provided a general diagnosis that suggested that preoperative chemotherapy would be appropriate. At the same time, although surgery resulted in good outcomes for the two patients with lymphoma, one of them underwent resection of vital organs and artificial vessel replacement, which required more consideration than if there had been a preoperative diagnostic outline. We, therefore, suggest that preoperative biopsy is necessary for CAMM (Fig. 4).

Surgical Resection of Thymic Malignancies

Thymoma and thymic carcinoma were diagnosed in 11 subjects, including one who had mixed teratoma and thymoma. Surgery is the primary therapy for thymic tumors[4,6] however, for stage III or IV (Masaoka's staging system) thymic tumors, which are considered unresectable because they invade vital organs such as the SVC, innominate veins, pericardium, lung, and pleura, radiotherapy is preferred. Radiotherapy achieves good results

Table 1.
Clinical data of 15 patients with complicated anterior mediastinal malignancies.

Case	Age	Sex	Clinical symptoms	Tumor size (mm^3)	SVC angiography results	Preoperative biopsy	Postoperativediagnosis
1	44	M	Pale (PRCAA)	76× 95× 100	–	–	Malignant thymoma
2	50	M	–	45× 50× 60	–	–	Malignant thymoma
3	48	M	–	80× 110× 90	–	–	Malignant thymoma
4	39	F	Cough	65× 40× 35	–	–	Malignant thymoma
5	55	M	Chest pain	43× 40× 50	–	–	Malignant thymoma
6	37	M	Cough	70× 55× 60	–	Thymoma	Malignant thymoma
7	45	M	Cough	50× 80×100	Constriction of SVC, > 1/2	Thymoma	Malignant thymoma
8	29	M	Bloody phlegm	35× 40× 60	Negative	–	Malignant thymoma
9	71	M	Chest pain	55× 35× 40	Displacement of SVC	–	Malignant thymoma
10	39	F	Cough,Chest pain, SVC syndrome	80× 69× 90	SVC complete obstructed, both innominate veins constricted	Carcinoma	Thymic carcinoma
11	38	F	Cough, bloody phlegm	55× 39× 60	Negative	–	Mixed teratoma and thymoma
12	39	M	Cough, bloody phlegm	57× 68× 82	–	–	Teratoma
13	21	F	Fever,SVC syndrome	169× 101×96	Constriction of SVC and left innominate vein, > 1/2	Adeno-carcinoma	Embryonal carcinoma
14	28	F	Cough, fever	40 × 70 × 55	–	–	Hodgkin's disease
15	26	F	Cough, fever, MG, SVC syndrome	60× 90× 88	Constriction of both innominant veins, > 1/2	–	Non-Hodgkin's lymphoma

Chemotherapy		Surgical procedures besides the resection of tumors	Postoperative complications	Survival(M) status
Pre-	Post-			
–	–	Partial lateral wall of SVC was resected and sutured	–	43 Alive
–	–	Partial lateral wall of right innominant vein was resected and sutured	–	38 Alive
–	–	Partial lateral wall of SVC was resected and sutured, wedge resection of left upper lobe	–	26 Alive
–	–	Partial resection of SVC and both innominate veins plus angioplasty with pericardial patch, right upper lobectomy	–	41 Alive
–	–	Partial resection of SVC and both innominate veins plus angioplasty with pericardial patch	–	39 Alive
–	–	Left innominate vein removed and distal end ligated, wedge resection of left upper lobe	–	24 Alive
–	–	Resection of SVC and both innominant veins and interposition with a single-lumen artificial vessel	–	31 Alive
–	–	Partial lateral wall of SVC resected and sutured, right extrapleural pneumonectomy	–	35 Alive
–	–	Partial resection of SVC and both innominate veinsplus angioplasty with pericardial patch, partial resection of right parietal pleural	–	35 Alive
Cisplatin based, 2 cycles	Cisplatin based,2 cycles	Total resection of SVC and both innominate veins, reconstruction with a Y-shaped artificial vessel, right pneumonectomy	Breathing apparatus support for 25 days	27 Alive
–	–	Partial lateral wall of left innominate vein resected and sutured, wedge resection of left upper lobe	–	36 Alive
–	–	Partial lateral wall of SVC resected and sutured, wedge resection of left upper lobe	–	29 Alive
Cisplatin based, 4 cycles	Cisplatin based, 2 cycles	Left innominate vein removed and distal end ligated, wedge resection of left upper lobe	–	10 Dead
–	ABVP8 cycles	Partial lateral wall of left innominate vein resected and sutured, left upper lobectomy	–	28 Alive
–	ABVP12 cycles	Total resection of SVC and both innominant veins and interposition with a single-lumen artificial vessel, right upper-middle bilobectomy	Breathing apparatus support for 15 days	39 Alive

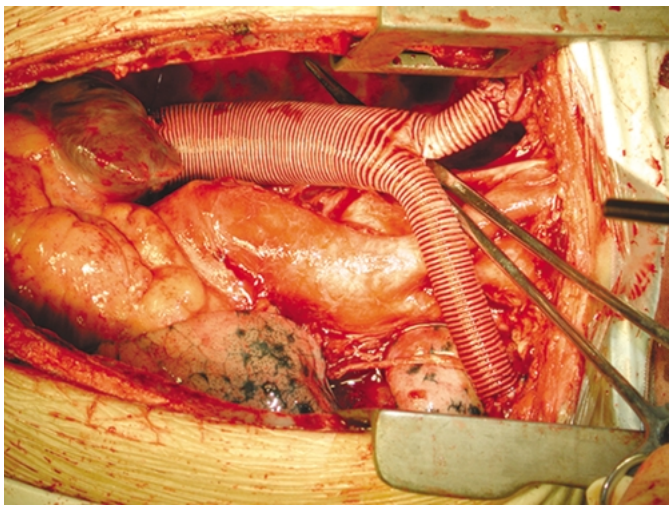

Figure 1. Surgical procedure for patient 10. Tumor resection + right pneumonectomy + total resection of SVC and both of the innominate veins, reconstruction with a Y-shaped artificial vessel.

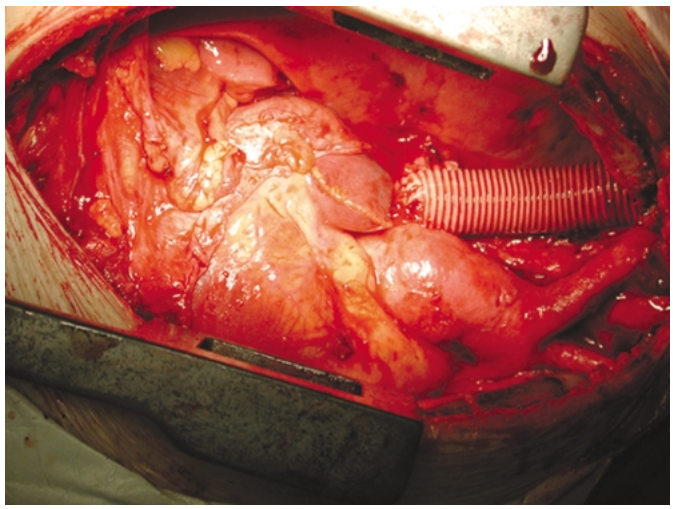

Figure 2. Surgical procedure for patient 15. Tumor resection + right upper lobectomy + total resection of SVC and interposition "single-lumen" artificial vessel.

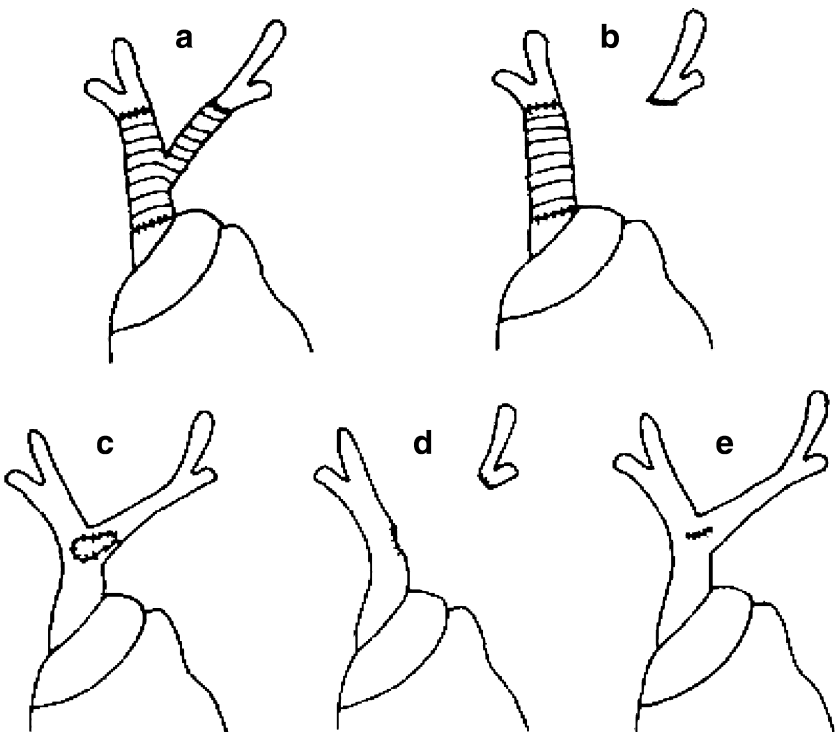

Figure 3. Surgical procedures for complicated anterior mediastinal malignancies. **A.** Total resection of the SVC and both innominate veins and reconstruction with a Y-shaped artificial vessel (patient 10). **B.** Total resection of the SVC and interposition with a single-lumen artificial vessel (patients 7 and 15). **C.** Partial resection of the SVC and/or innominate veins and angioplasty with a pericardial patch (patient 4, 5, and 9). **D.** Left innominate vein was removed and its distal end was ligated (patient 6 and 13). **E.** Partial lateral wall of the SVC, innominate vein, or both were directly resected and sutured (the other 7 patients).

overall, but some patients die of radiotherapy-related complications rather than the tumor itself. Complications include acute pericarditis, secondary primary carcinoma, chronic heart diseases (e.g., chronic constrictive pericarditis, coronary artery disease, etc.) pulmonary fibrosis, hypothyroidism, and poor quality of life[7–13] Furthermore, radiotherapy does not appear to achieve results as effective as complete resection. Among patients with stage III thymoma the 5- and 10-year survival rates for patients who received radiotherapy were only 53% and 44%, respectively.[6] The 10-year survival rate was 45% to 60% for patients who received surgery as primary therapy,[14,15] 75% to 94% for those whose tumors were completely resected, and 31% to 35% for those who had incomplete resections.[6,14] Thus, the survival rate for patients with thymoma appears to depend on the completeness of the original excision. Curran *et al.*[16] suggested avoiding postoperative radiotherapy if complete resection is achieved with primary surgery. All 11 subjects in our series with locally advanced thymic tu-

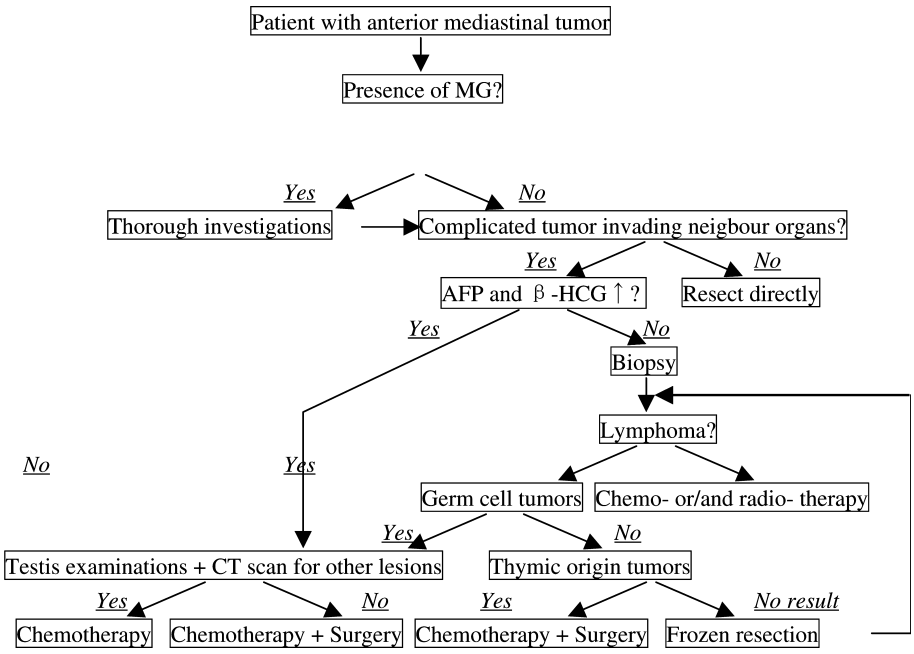

Figure 4. Flow chart for pretreatment decision making in patients with anterior mediastinal tumors. MG: myasthenia gravis; AFP: alpha fetoprotein; β-HCG: β-human chorionic gonadotropin; CT: computed tomography.

mors (all stage IV) received complete resections. Among them, only one patient underwent preoperative and postoperative chemotherapy; unfortunately, the other 10 did not undergo perioperative therapy. As of August 2004, these patients were alive, and all were experiencing good quality of life. We will continue to follow them to determine long-term survival rates.

Diagnosis and Treatment of Germ Cell Tumors

Germ cell tumors include many types of neoplasms, the most common of which are teratoma, seminoma, and nonseminous germ cell tumors (NGCTs).[17] Teratoma, embryonal carcinoma, and mixed teratoma and thymoma were diagnosed in 3 of our subjects. Wood [17] suggested that if a patient with an anterior mediastinal tumor has a high beta-human chorionoc gonadotropin (β-hCG) or alpha-fetoprotein (AFP) concentration, then therapy for germ cell tumors should begin immediately (Fig. 4).

Complete resection should be perfomed as the primary therapy for benign teratomas. As for seminomas and NGCTs, cisplatin-based chemotherapy plus surgery is a preferred strategy than surgery alone due to the highly malignant potential and tendency toward early metastasis.[17,18] In patient 13, embryonal carcinoma was clinically considered to be a thymic carcinoma preoperatively because of the FNA diagnosis of adenocarcinoma. Fortunately, because of the invasion of the SVC, the patient was administered four cycles of cisplatin-based preoperative chemotherapy. The tumor shrank, but the response did not qualify as a partial remission. Then a complete excision was performed, including total resection of the involved left innominate vein. Moreover, another two cycles of the same chemotherapy was given postoperatively. But this patient died of a recurrence 10 months after surgery, which indicates that this tumor was highly malignant.

Role of Surgical Resection in Selected Lymphoma

Lymphoma was diagnosed in two of our subjects. Theoretically, lymphoma tends to be systemic, and its treatment is dominated by radiotherapy and chemotherapy; surgery is regarded as a diagnostic technique only.[19,20] Our two patients with lymphoma were actually presumed post-surgery to have thymic tumors, because they lacked a pathology diagnosis; 1 of them was found to have MG as well. Tumor resection, right upper-middle bilobectomy, and total resection of the SVC and both innominate veins plus interposition with a single-lumen artificial vessel were performed in patient 15; the postoperative pathologic diagnosis was non-Hodgkin's lymphoma. Tumor resection, left upper lobectomy, and resection of part of the lateral wall of the left innominate vein were performed in patient 14; the postoperative diagnosis was Hodgkin's lymphoma. Both of these patients accepted adjuvant ABVP chemotherapy (12 and 8 cycles, respectively), and both are alive and remain on follow-up. From this experience, we realize that some

lymphomas might also be accompanied by MG, and that preoperative biopsy must be undertaken for patients with an invasive tumor so that the appropriate treatment strategy can be determined. If the preoperative biopsy does not lead to a definitive diagnosis, then a frozen-section biopsy should be performed during surgery to prevent unnecessary extensive resection.

Surgical Techniques

The surgical techniques used on the 15 patients included not only tumor resection but also pericardium resection, lung tissue resection through an anterior incision, and angio-techniques. Angio-techniques may be most important, because they allow complete resection in persons who would not otherwise be considered candidates for surgery. The procedures include partial lateral-wall resection of the SVC and simple angioplasty, total resection of the SVC and both innominate veins plus interposition of a single-lumen artificial vessel, and total resection of the SVC and both of the innominate veins plus reconstruction with a Y-shaped artificial vessel. In angio-techniques, median sternotomy can provide the best exposure of an anterior mediastinal tumor and allows exploration of both thoracic cavities. Surgeons should try to perform an en bloc resection, including the involved vessels, to decrease the possibility of tumor seeding, but if it is hard to perform an en bloc resection, a fractional resection can be considered. When exploring the involved vessel, attention should be paid to tumor emboli, which can result in embolism or metastasis. If the tumor invades the right innominate vein or SVC, partial lateral-wall resection plus simple angioplasty or a pericardium patch repair can be performed when the involved vessel's length is less than 2 cm and the circumference is less than half the size of the whole circle; otherwise, artificial vessel replacement should be considered. If total SVC clamping is needed during the operation, the SVC should be clamped at the level above the azygos vein to reserve some lateral-branch circulation to decrease brain damage due to drainage obstruction. Generally, if clamping is at this level, an SVC bypass is not necessary, but if clamping is below the azygos vein and lasts longer time such as more than 60 minutes, a SVC bypass should be considered. Anticoagulant therapy should be given perioperatively, any artificial vessel should be soaked in heparin-salt water, and eversion sutures should be used to smooth the vascular inner wall.

In conclusion, CAMM should be pathologically identified before initial treatment. Extensive tumor resection for thymic malignancies may permit long-term survival with good quality of life. Comprehensive treatment that includes chemotherapy, radiotherapy, and surgery remains the dominant strategy for treating primary malignant germ cell tumors and isolated primary anterior mediastinal malignant lymphomas. Therefore, a good prognosis for patients with CAMM tumors is possible if a suitable strategy combining accurate diagnosis and appropriate treatment especially surgical resection are established.

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