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Original Article / Özgün Makale

Surgical treatment of giant mediastinal tumors

Dev mediastinal tümörlerin cerrahi tedavisi

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ABSTRACT

Background: This study aims to evaluate the surgical treatment outcomes of giant mediastinal tumors.

Methods: Between July 2013 and July 2018, medical data of a total of 31 patients (26 males, 5 females; mean age 27.7±8.2 years; range, 18 to 56 years) who underwent radical surgery for a giant mediastinal tumor in our center and 47 cases (26 males, 21 females; mean age 45.4±16.7 years; range, 19 to 62 years) of giant mediastinal tumors retrieved from the National Center for Biotechnology Information database were retrospectively reviewed. Two-year overall survival and disease-free survival rates of the patients were evaluated.

Results: All patients underwent radical surgery (R0 resection). Symptoms caused by giant mediastinal tumors were relieved after radical surgery during follow-up. The two-year overall survival and disease-free survival rates were 100% and 86.7%, respectively, indicating a good prognosis. The surgical procedures for malignancies were more difficult than those for benign pathologies.

Conclusion: Radical surgery is the mainstay for treatment of giant mediastinal tumors to relieve symptoms in a short period of time and to achieve a good prognosis for up to two years, regardless of adjuvant therapy. The surgical route should be cautiously planned before radical surgery to reduce complications.

Keywords: Giant mediastinal tumor, prognosis, radical surgery.

ÖZ

Amaç: Bu çalışmada dev mediastinal tümörlerinin cerrahi tedavi sonuçları değerlendirildi.

Çalışma planı: Temmuz 2013-Temmuz 2018 tarihleri arasında dev mediastinal tümör nedeniyle merkezimizde radikal cerrahi yapılan toplam 31 hastanın (26 erkek, 5 kadın; ort. yaş 27.7±8.2 yıl; dağılım, 18-56 yıl) ve Ulusal Biyoteknoloji Bilgi Merkezi veri tabanından alınan 47 dev mediastinal tümör olgusu (26 erkek, 21 kadın; ort. yaş 45.4±16.7 yıl; dağılım, 19-62 yıl) retrospektif olarak incelendi. Hastaların iki yıllık genel sağkalımları ve hastalıksız sağkalımları değerlendirildi.

Bulgular: Hastaların tümüne radikal cerrahi (R0 rezeksiyon) yapıldı. Dev mediastinal tümörlerin neden olduğu semptomlar, radikal cerrahi sonrasında takip sırasında geriledi. İki yıllık genel sağkalım ve hastalıksız sağkalım oranları sırasıyla %100 ve %86.7 olup, iyi prognozun göstergesi idi. Malignitelerin cerrahi işlemleri, benign patolojilerinkinden daha zor idi.

Sonuç: Radikal cerrahi, adjuvan tedaviden bağımsız olarak, kısa sürede semptomları rahatlatmak ve iki yıla varana kadar iyi bir prognoz elde etmek için, dev mediastinal tümörlerin tedavisinin temelini oluşturur. Komplikasyonları azaltmak için radikal cerrahi öncesinde, cerrahi rol titizlikle planlanmalıdır.

Anahtar sözcükler: Dev mediastinal tümör, prognoz, radikal cerrahi.

A giant mediastinal tumor (GMT), defined as occupying half of the hemithorax or having a diameter >10 cm, is an extremely rare entity characterized by a diversity of symptoms, including chest pain, cough, dyspnea, and dysphagia, as well as potentially lethal respiratory failure and malignant arrhythmias.[1-4] Radical surgery (RS) is recommended for the treatment of a GMT. However, a higher risk of perioperative complications is associated with such large tumors.[3,5]

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Angelopoulos et al.[3] reported an old female with a huge mediastinal malignant schwannoma who suffered from systemic sepsis and multiple organ dysfunction after surgery. A similar case was also reported by Furák et al.[5] in a young female with a large ganglioneuroma suffering from an acute paraplegia with a spinal cord lesion due to vertebral artery injury.

Up to date, there is no similar study including meta-analysis, randomized-controlled trials, and systemic retrospective or observational studies. In this study, we aimed to evaluate the surgical treatment outcomes of GMTs and to develop an evidence-based strategy for the treatment of GMTs.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the First Affiliated Hospital of Chongqing Medical University, Department of Thoracic and Cardiovascular Surgery between July 2013 and July 2018. Medical data of a total of 31 patients (26 males, 5 females; mean age 27.7±8.2 years; range, 18 to 56 years) who underwent radical surgery for a GMT in our center and 47 cases (26 males, 21 females; mean age 45.4±16.7 years; range, 19 to 62 years) of GMTs retrieved from the National Center for Biotechnology Information (NCBI) database were retrospectively reviewed. Inclusion criteria were as follows: age >16 years; having mediastinal tumors involving half of the hemithorax or having a diameter of >10 cm; and previous GMT surgery regardless of radical or palliative. Exclusion criteria were as follows: patients who were unable to tolerate surgery or were unwilling to undergo surgery; and those undergoing exploratory GMT surgery. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No. 00734800). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Forty-seven cases of GMTs reported between January 2008 and December 2018 were retrieved from the NCBI database (https://www.ncbi.nlm.nih.gov/). Among these tumors, 23 were malignant and 24 benign. The malignant tumors consisted of nine liposarcomas,[4-13] five thymomas (Masaoka Stage II-III),[14-18] three schwannomas,[19,20] one gangliocytoma,[21] one angiolipoma,[22] one endodermal sinus tumor,[23] one epithelioid angiosarcoma,[24] one stromal tumor,[25] and one solitary fibrous tumor.[26] The benign tumors included five mature teratomas,[27-31] five schwannomas,[2,32-35] five thymolipomas,[36-40] two leiomyomas,[41,42] two thymomas (Masaoka Stage I),[43,44] one pericardial cyst,[45] one germ cell tumor,[46] one cavernous hemangioma,[47] one lymphangioma,[48] and one pericardial paraganglioma.[49]

Tumor pathology was determined by two pathologists at the Department of Pathology of Chongqing Medical University. Seventeen tumors were reported as malignant (6 thymomas [Masaoka Stage I-III], two liposarcomas, two teratomas, two thymic squamous cell carcinomas, 2 fibrous histiocytomas, 2 spermatocytomas, and 1 non-Hodgkin lymphoma), while 14 were reported as benign (5 mature teratomas, 2 substernal goiters, 2 schwannomas, 2 solitary fibrous tumors, 1 case of Castleman disease, 1 case of fibromatosis, and 1 thymolipoma).

In terms of the tumor location, two tumors originated from the neck and extended toward the anterosuperior mediastinum. One tumor originated from the superior and anterior mediastinum and extended toward the neck. Five tumors originated from the superior mediastinum and extended toward one hemithorax. Twenty-three tumors were located primarily in one hemithorax.

All patients underwent RS. The surgical route was determined based on the tumor location and the invaded structures. Radical surgery (R0 resection) of a malignant tumor was defined as removal of all invaded structures along with the tumor itself, while RS of a benign tumor was defined as removal of the tumor only. Adjuvant therapy (AT) protocols after RS were decided by a multidisciplinary team consisting of physicians, oncologists, and surgeons.

Prognosis was evaluated based on two-year overall survival (OS) and two-year disease-free survival (DFS) rates. Two-year OS was defined as the percentage of patients who survived for at least two years after RS, while two-year DFS was defined as the percentage of patients who survived for at least two years after RS with no relapse or metastasis.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 19.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The Student's t-test was used to analyze significant differences between the groups. The chi-square test was used to analyze differences between the malignant and benign tumor groups. Survival analysis was carried out using the

Kaplan-Meier plot. A *p* value of <0.05 was considered statistically significant.

RESULTS

The symptoms associated with GMTs are listed in Table 1. Although the majority of patients with GMTs treated in our center had no obvious symptoms, nearly half the cases retrieved from the NCBI database had typical clinical symptoms. The discrepancy between these two cohorts was attributed to the different pathological spectrums and tumor size and location. Certain fatal symptoms (e.g., superior vena cava [SVC] syndrome, respiratory failure, and hemoptysis) primarily occurred in patients with malignancies. Hematological disorders (i.e., Cooley anemia in our cohort) occurred in patients with mature teratomas. After RS, the symptoms of dyspnea, dysphagia, cough, chest pain, hemoptysis, and palpitation in both cohorts were relieved or eliminated during a relatively short follow-up period. In addition, SVC syndrome was relieved within two weeks after RS, while hoarseness was eliminated over a period of one month and Cooley anemia had resolved within six months.

The invaded structures, surgical modes, and routes are listed in Table 2. None of the benign tumors involved the surrounding tissues. However, the malignant tumors invaded different tissues in both our cohort and the cases retrieved from the NCBI database. The invaded tissues included vessels (i.e., SVC, innominate vein, subclavian artery, aorta, and pulmonary artery), diaphragm, lung, pericardium, esophagus, nerves, and thoracic wall. The surgical route was determined based on the tumor location and the invaded tissues. A lateral incision was the most common route, as most tumors were primarily located in one hemithorax. A collar incision was added, if the neck was involved. A clamshell or bilateral incision was a more optimal choice, if the tumor extended toward both hemithorax. In our cohort, piecemeal resection was more commonly used for malignancies (p=0.005). However, among the cases retrieved from the NCBI database, there was no significant difference in the use of *en bloc* resection between malignant and benign tumors (p=0.087), as nearly all surgical procedures included *en bloc* resection.

Demographic characteristics of both cohorts and associated complications are summarized in Table 3. In our cohort, patients with malignancies were likely to be younger than those with benign tumors (p=0.019), while there was no significant difference in the age among the cases retrieved from the NCBI

Table 1. Clinical symptoms of GMTs in our cohort and cases retrieved from NCBI database

	Our cohort			NCBI database		
	Total (n=31)	Benign (n=14)	Malignancy (n=17)	Total (n=47)	Benign (n=24)	Malignancy (n=23)
Symptoms						
Dyspnea	4	1	3	24	12	12
Cough	-	-	-	12	7	5
Dysphagia	1	1	-	5	3	2
Chest pain	-	-	-	16	5	11
Fever	-	-	-	2	1	1
Hemoptysis	-	-	-	3	1	2
Hoarseness	1	1	-	-	-	-
Nausea and vomiting	-	-	-	1	1	-
Weight loss	-	-	-	2	1	1
Digital clubbing	-	-	-	1	-	1
Palpitation	-	-	-	4	-	4
Respiratory failure	-	-	-	2	1	1
SVC syndrome	4	-	4	-	-	-
Cooley anemia	1	1	-	-	-	-

GMTs: Giant mediastinal tumors; NCBI: National Center for Biotechnology Information.; SVC: Superior vena cava.

database (p=0.22). The mean maximum diameter of malignant tumors was higher than that of benign tumors in our cohort (p=0.039), while there was no significant difference among the cases retrieved from the NCBI database (p=0.44). Compared to benign tumors, malignancies had a longer mean duration of RS (218.8±57.8 min vs. 162±21.8 min, respectively; p=0.002), chest drainage (5.9±1.6 days vs. 4.5±0.6 days, respectively; p=0.004), hospital stay (7.9±1.6 days vs. 6.5±0.6 days, respectively; p=0.004), and a higher amount of intraoperative blood loss (1,550±828 mL vs. 1,023±147 mL, respectively; p=0.023). There was no mortality during the perioperative period. Arrhythmias after RS were relieved and eliminated during the follow-up period without medical intervention. Chylothorax occurring

Table 2. Clinical data of our cohort and cases retrieved from NCBI database

	Our cohort			NCBI database		
	Total (n=31)	Benign (n=14)	Malignancy (n=17)	Total (n=47)	Benign (n=24)	Malignancy (n=23)
Invaded structure						
Diaphragm	3	-	3	1	-	1
Pulmonary parenchyma	7	-	7	2	-	2
Pericardium	4	-	4	1	-	1
SVC	4	-	4	-	-	-
Esophagus	1	-	1	2	-	2
LIV	3	-	3	2	-	2
Subclavian artery	-	-	-	1	-	1
Phrenic nerve	-	-	-	2	-	2
Thoracic wall	1	-	1	1	-	1
Pulmonary artery trunk	1	-	1	-	-	-
Aorta	-	-	-	1	-	1
Tumor capsule	-	-	-	1	-	1
Surgical mode						
Partial diaphragm resection	3	-	3	1	-	1
Lobectomy	2	-	2	1	-	1
Pulmonary wedge resection	5	-	5	1	-	1
Pneumonectomy	1	-	1	-	-	-
Partial pericardium resection	5	-	5	1	-	1
SVC angioplasty	3	-	3	-	-	-
SVC replacement	1	-	1	-	-	-
Esophagectomy	1	-	1	2	-	2
LIV angioplasty	3	-	3	2	-	2
Thoracic wall resection and reconstruction	1	-	1	1	-	1
Surgical route						
Lateral	23	12	11	29	16	13
Median sternotomy	-	-	-	12	4	8
Neck collar	-	-	-	1	1	-
Neck collar + median sternotomy	3	2	1	-	-	-
Hemi-Clamshell	5	-	5	3	2	1
Clamshell	-	-	-	1	-	1
Bilateral	-	-	-	1	1	-
Radical or palliative						
Radical	31	14	17	45	24	21
Palliative	-	-	-	2	-	2
Surgical strategy						
En bloc	15	12	3	46	24	21
Piecemeal	16	2	14	2	-	2

NCBI: National Center for Biotechnology Information; SVC: Superior vena cava; LIV: Left innominate vein.

Table 3. Demographic and clinical data of GMTs in our cohort and cases retrieved from NCBI database

	Our cohort							NCBI database						
	Total (n=31)		Benign (n=14)		Malignancy (n=17)			Total (n=47)		Benign (n=24)		Malignancy (n=23)		
	n	Mean±SD	n	Mean±SD	n	Mean±SD	*p**	n	Mean±SD	n	Mean±SD	n	Mean±SD	*p**
Age (year)		27.8±8.2		31.1±8.6		24.2±6.4	0.019		45.4±16.7		42.3±15.4		48.4±17.7	0.22
Sex							0.37							0.34
Male	26		12		14			26		13		13		
Female	5		2		3			21		11		10		
Maximum diameter (cm)		18.1±5.1		16.4±4.7		19.5±5.0	0.039		20.8±8.1		19.8±7.5		21.7±8.6	0.44
Adjuvant therapy														
Chemotherapy	10		-		10	-		5		-		5		
Radiotherapy	-		-		-			4		-		4		
Chemoradiotherapy	-		-		-			1		-		1		
Prognosis							-							-
Relapse	3		-		3			1		-		1		
Metastasis	1		-		1			-		-		-		
DFS (year)	-		-			2.3±0.9		-		-			1.9±1.7	
OS (year)	-		-			2.6±0.9		-		-			1.8±1.4	
Complication							-							-
Arrhythmias	2		1		1			-		-		-		
Cholera	1		-		1									
Vocal cord paralysis	-		-		-			1		1		-		
Hemithorax	-		-		-			1		-		1		
Flaccid paralysis	-		-		-			1		-		1		

GMTs: Giant mediastinal tumors; NCBI: National Center for Biotechnology Information; SD: Standard deviation; DFS: Disease-free survival; OS: Overall survival; * Benign vs. malignant tumors; * p<0.05.

after RS was eliminated by fasting and administration of somatostatin for three days. The use of AT after RS is also shown in Table 3. Seven patients refused to receive AT after RS. No neo-AT or radiotherapy was used.

The patients diagnosed with benign tumors survived with no relapse or metastasis since the last follow-up (Table 3). All 17 patients with malignant tumors survived since the last follow-up, of whom 13 remained disease-free. However, one of 17 patients diagnosed with a thymoma (Masaoka Stage III) developed pulmonary metastasis two years after RS, while two others diagnosed with thymic squamous carcinomas and one with a liposarcoma had a relapse at 1.5, 1.2, and two years after RS, respectively. The patients with pulmonary metastasis or relapse refused a second RS and, thus, only received palliative care. The two-year OS rate for malignancies was 100% (17/17), while the two-year DFS was 86.7% (15/17) (Figure 1). Of the cases retrieved from the NCBI database, only one diagnosed with a liposarcoma had a relapse at 1.25 years after RS and underwent a second RS and survived disease-free for another three years. In our cohort, two of 10 patients who received AT had a relapse after RS, while two others who received no AT developed pulmonary metastasis and relapse, respectively. There were no significant differences in the incidences of relapse and metastasis between the patients who receive and did not receive AT (p=0.682). Of the 13 cases retrieved from the NCBI database who received no AT, only one had a relapse, while none developed metastasis. In our cohort, there was no significant difference in the mean DFS duration between the two patients who relapsed after AT and the two patients who relapsed or developed metastasis without AT (1.8±0.4 years vs. 2.1±1.3 years, respectively; p=0.83).

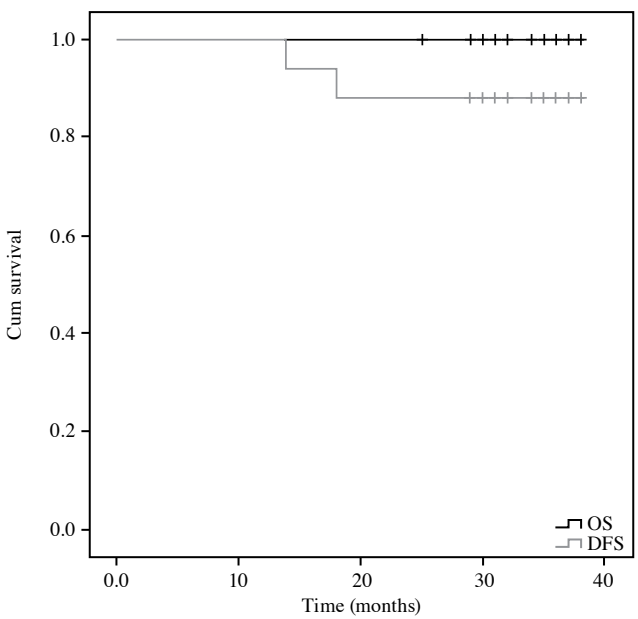

Figure 1. Kaplan-Meier survival analysis.
OS: Overall survival; DFS: Disease-free survival; Cum: Cumulative.

In our cohort, four patients diagnosed with malignancies developed SVC syndrome. The pathology of these patients included one case of thymic squamous cell carcinoma, one thymoma (Masaoka Stage III), and one malignant teratoma. The mean DFS and OS times were 2.3±0.5 and 2.8±1.0 years, respectively. All four of these patients received chemotherapy after RS and survived since the last follow-up. Recurrence occurred in one patient diagnosed with thymic squamous cell carcinoma at two years after RS, while the other three patients remained disease-free.

DISCUSSION

In the literature, most studies of GMTs are published as case reports.[11-15] Our study is, therefore, valuable as it analyzed a series of clinical cases for guiding the treatment of GMTs. Our study results showed a good prognosis in both our cohort and the cases retrieved from the NCBI database using RS. Only four (23.5%) of 17 patients in our cohort with malignancies developed metastasis or relapse, but survived since the last follow-up after RS. The two-year OS and two-year DFS rates of all patients with malignancies were 100% and 86.7%, respectively. Of the cases retrieved from the NCBI database, only one who did not receive AT after RS had a relapse.[25] Therefore, prognosis was better after RS. Nonetheless, it still remains controversial whether AT is required for malignancies after RS.

Radical surgery can relieve or eliminate symptoms during follow-up and improve quality of life of patients. In our cohort and the cases retrieved from the NCBI database, benign tumors primarily caused squeezing symptoms of dyspnea, cough, dysphagia, nausea, and vomiting.[37] Meanwhile, malignancies are associated with invasive and systemic symptoms in addition to squeezing symptoms, such as chest pain, hemoptysis,[21,23] and palpitation.[4,18,20] Under emergent circumstances, such as acute respiratory failure[3] and SVC syndrome, RS can be a life-saving option. In our cohort and the cases retrieved from the NCBI database, the symptoms of squeezing and invasion were relieved during a short-term follow-up after RS. Acute SVC syndrome may also result in sudden death. In our cohort, SVC syndrome of four patients

was relieved within two weeks after RS. The GMTs, regardless of benign or malignant, may accompany endocrinological or hematological disorders such as hyperparathyroidism and chronic dyserythropoietic anemia.[50,51] Cooley anemia in our cohort was gradually rectified by RS during follow-up.

Currently, RS remains the first-choice option for treatment of GMTs. However, the surgical route and strategy are critical for surgical safety and successful R0 resection. A lateral thoracotomy is recommended for tumors primarily located in one hemithorax,[2,3] while median sternotomy is recommended for tumors at the anterosuperior mediastinum.[7,12] The hemi-clamshell procedure should be considered, if the tumor is located at the anterior mediastinum and extends into one hemithorax,[6,15] while the clamshell or bilateral thoracotomy is recommended, if the tumor extends into the bilateral hemithorax.[10,40] A collar incision should be considered, if the tumor involves the neck,[33] while a collar incision plus median sternotomy is recommended, if the tumor is located at the anterosuperior mediastinum and involves the neck.[8] Mini-invasive techniques are not recommended for resection of GMTs, except for cystic lesions or solid lesions located at the posteroinferior mediastinum, which has a larger space.[16,30]

Mediastinal tumors may adhere to or invade the surrounding tissues including the vessels, lung, thoracic wall, diaphragm, and pericardium.[9] To achieve R0 resection, the tumor and the invaded surrounding tissues should be completely removed. Injury to the vital tissues (e.g., great vessels and recurrent laryngeal nerve) should be avoided during RS. Therefore, the surgical route and mode should be cautiously planned. Furthermore, extracorporeal membrane oxygenation or cardiopulmonary bypass is recommended, if angioplasty or prosthesis replacement is required.[10,24] Piecemeal resection is an alternative option, if the tumor cannot be removed *en bloc*, due to the high risk of massive hemorrhage or injury to vital tissues.[30,52]

The main limitations of the present study include its retrospective and single-center design with a small sample size. Therefore, further large-scale, multi-center, prospective studies are needed to confirm these findings.

In conclusion, radical surgery is the paramount strategy for the treatment of giant mediastinal tumors to relieve symptoms within a short period of time and achieve a good prognosis in the long-term. The surgical route and mode should be cautiously planned before RS to reduce the rate of intraoperative complications. We believe that the outcomes of this study provide evidence to guide the treatment of giant mediastinal tumors in clinical practice.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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