

# Cardiopulmonary bypass does not consequentially contribute to postoperative distant metastasis of giant refractory thoracic tumors: A retrospective study with long-term follow-up

Lei Chen<sup>1</sup> | Xuejuan Zhu<sup>1</sup> | Rongying Zhu<sup>1</sup> | Xing Jin<sup>1</sup> | Liping Tan<sup>2</sup> | Yongbing Chen<sup>1</sup> 

<sup>1</sup>Department of Thoracic Surgery, the Second Affiliated Hospital of Soochow University, Suzhou, China

<sup>2</sup>Department of Nursing, the Second Affiliated Hospital of Soochow University, Suzhou, China

## Correspondence

Yongbing Chen, Department of Thoracic Surgery, the Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Gusu District, Suzhou 215004, China.  
Email: chentongt@sina.com

Liping Tan, Department of Nursing, the Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Gusu District, Suzhou 215004, China.  
Email: tlping67@126.com

## Funding information

Discipline Construction Project of the Second Affiliated Hospital of Soochow University, Grant/Award Number: XKTJ-XK202004; Jiangsu Key Research and Development Plan (Social Development) Project, Grant/Award Number: BE2020653; Municipal Program of People's Livelihood Science and Technology in Suzhou, Grant/Award Number: SS2019061; Suzhou Key Discipline for Medicine, Grant/Award Number: SZXK201803; Suzhou Key Laboratory of Thoracic Oncology, Grant/Award Number: SZS201907

## Abstract

**Background:** Few clinical research studies with long-term follow-up have revealed whether cardiopulmonary bypass (CPB) increases the risk of postoperative distant metastasis in patients with giant refractory thoracic tumors. The present study evaluated the risk of distant metastasis after surgery utilizing CPB with long-term follow-up.

**Methods:** Clinical data for patients with giant refractory thoracic tumors who underwent resection with the use of CPB in the Second Affiliated Hospital of Soochow University during the past 11 years were retrospectively reviewed.

**Results:** Of the 14 patients with giant refractory thoracic tumors who had undergone surgery under CPB, 10 patients (71.4%) were completely resected. Twelve patients were followed up for 13–127 months with 10 patients were completely resected and two patients could not be completely resected due to severe tissue invasion. Three patients (25%) suffered from distant metastasis, and four patients (33.3%) experienced local recurrence. Only one patient (1/10) with complete resection suffered from distant metastasis, while two patients (2/10) experienced local recurrence. Two patients (2/2) with major resection suffered from both distant metastasis and local recurrence. Median overall survival for patients who have been regularly followed up was 50 months with 1-, 5-, and 10-year survival of 100%, 75%, and 66.7%. No difference was found between the distant metastasis survival and the local recurrence survival. ( $p = 0.99$ ).

**Conclusions:** CPB is an effective strategy for complete resection of the giant refractory thoracic tumors with an acceptable risk of postoperative distant metastasis for some patients.

## KEYWORDS

cardiopulmonary bypass, distant metastasis, giant refractory thoracic tumors, recurrence

## INTRODUCTION

Giant refractory thoracic tumors do not have a clear diagnostic standard. Their nomenclature mainly emphasizes the

large number of tumors and the difficulty of surgical removal, but does not provide a general description of clinical characteristics. Giant refractory thoracic tumors of various pathological types invade the surrounding tissues and organs with serious consequences. Moreover, completely removing tumors using conventional thoracic surgery is difficult, resulting in poor patient prognosis.<sup>1–4</sup> The surgical

Lei Chen and Xuejuan Zhu authors equally contributed to the work.

Liping Tan and Yongbing Chen authors equally contributed as corresponding authors.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd.

strategy for complete tumor resection is also extremely high-risk, but the adoption of cardiopulmonary bypass (CPB) can ensure the stability of intraoperative respiratory circulation and create favorable conditions for complete tumor resection.<sup>5</sup> Surgeons have been reluctant to use CPB during surgery due to the many complications associated with the procedure and the possibility that it may promote distant metastasis of tumor cells.<sup>5,6</sup> Thus, most patients die due to the lack of effective surgical treatment. However, standardized management can significantly reduce the complications associated with CPB.<sup>7</sup> There are only a few scattered case reports without long-term follow-up, which are not able to confirm definitively whether CPB causes distant metastasis. The present report summarizes the long-term follow-up clinical data for patients with giant refractory thoracic tumors who had undergone surgery under CPB during the past 11 years at the Second Affiliated Hospital of Soochow University (Suzhou, China). It also analyzes the effect of CPB on the distant metastasis of thoracic tumors.

## METHODS

### Patients and data collection

This retrospective cohort study included all patients with giant refractory thoracic tumors who had undergone surgery under CPB during the past 11 years at the Second Affiliated Hospital of Soochow University. The study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (No. JD-HG-2020-18).

The patient characteristics, their surgical treatment, complete resection status, local recurrence, and distant metastasis status were retrospectively reviewed (Table 1). Kaplan–Meier analysis was used for comparison of overall, distant metastasis, and local recurrence survival. The equivalence of the survivor function was tested with the log-rank test. A *p* value of less than 0.05 was considered statistically significant.

### Treatment

All patients were treated with thoracotomy using a median sternal incision and routinely intubated via the ascending aorta. Patients with severe involvement of the ascending aorta were intubated using the femoral artery. The intravenous intubation method through the vena cava, atrial, or femoral vein was selected based on tumor involvement. A SORIN/C5 cardiopulmonary bypass machine (Sorin Group Deutschland GmbH) and a membranous lung (MEDOS Medizintechnik AG) were used during the operation. Heparin (1 mg/kg, flow rate 50–80 ml/kg·min) was added to the CPB pipeline and the activated clotting time of whole blood (480 s) was maintained during the surgery. The intraoperative body temperature was maintained at mild

hypothermia conditions (32–35°C). An extracardiac sucker was used for intraoperative bleeding. Intracardiac sucker was used only in a case of a large amount of bleeding. Tumor suppression therapy was performed with thermodistillation (the body temperature was maintained at 41°C for 1 h) during the heating process of CPB.

The individual surgical treatments are shown in Table 1. At follow-up, patients were recommended to undergo computed tomography (CT), enhanced CT, or positron emission CT to evaluate local recurrence and distant metastasis.

## RESULTS

A total of 14 patients (nine males and five females) with giant refractory thoracic tumors have undergone surgery under CPB during the past 11 years at the Second Affiliated Hospital of Soochow University (Table 1). Among the 14 patients, 10 patients were completely resected (71.4%), while four patients (one case of squamous cell carcinoma of left lung hilus, one case of mediastinal primary T cell lymphoma with pericardial, aortic, and pulmonary artery involvement, one case of giant extraosseous osteosarcoma in the left lung hilus, and one case of thymic squamous cell carcinoma with invasion of the main pulmonary artery and superior vena cava) underwent a major resection due to the large tumor size and severe tumor invasion into the surrounding organs. Twelve patients were regularly followed up for 13–127 months. Two patients were lost to follow-up after returning to their hometown. Median overall survival for patients who have been regularly followed up was 50 months with 1-, 5-, and 10-year survival of 100%, 75%, and 66.7% (Figure 1). No difference was found between the distant metastasis survival and the local recurrence survival. (*p* = 0.99).

Three patients (25%) suffered from distant metastasis, and four patients (33.3%) experienced local recurrence during long-term follow-up. Among the 10 patients who received a complete resection, only one patient (1/10) had distant metastasis 13 months after surgery, and two patients (2/10) suffered from local recurrence. However, the two patients who underwent major resection (2/2) experienced distant metastasis four and 48 months after surgery, and both suffered from local recurrence.

## DISCUSSION

There are several pathological types of giant refractory thoracic tumors that have different prognoses. However, postoperative local recurrence and distant metastasis mean poor prognosis regardless of the nature of the tumor.<sup>8</sup> Complete tumor resection during the operation plays a decisive role in the outcome. In our follow-up cases, only two patients (2/10) with completely removed tumors experienced local recurrence during the long-term follow-up. Notably, previous studies have suggested that complete tumor removal

TABLE 1 Characteristics and perioperative outcomes of the included patients

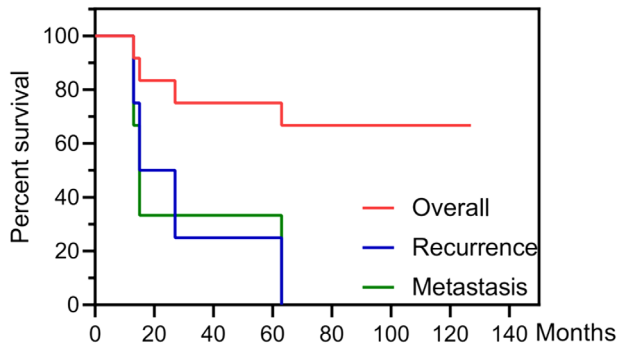
No.	Gender	Age (years)	Description	Treatment	EN BLOC	Recurrence (M)	Metastasis (M)	Followed up (M)
1	M	52	Giant invasive solitary fibrous tumor	Middle mediastinal tumor resection and superior vena cava repair	Yes	No	No	79
2	M	57	Giant thymoma	Resection of anterior mediastinal tumor (intubation via femoral artery)	Yes	No	No	74
3	M	61	Giant thymic squamous cell carcinoma with local invasion of left upper lung	Resection of anterior mediastinal tumor and partial resection of left upper lung	Yes	No	No	63
4	M	38	Giant thymic squamous cell carcinoma with pericardium and main pulmonary artery invasion	Middle mediastinal tumor resection and partial pericardiectomy (intubation via femoral artery)	Yes	No	No	58
5	F	45	Giant mediastinal primary T cell lymphoma with pericardial, aortic and pulmonary artery involvement	Mediastinal tumor resection and partial pericardiectomy and innominate vein repair (intubation via femoral artery) and postoperative chemotherapy	No	-	-	Loss
6	M	61	Squamous cell carcinoma of left lung hilus	Left pneumonectomy	No	-	-	Loss
7	M	64	Invasive fibrous tumor of right middle and lower lung with mediastinum and diaphragm involvement	Middle and lower lobectomy and mediastinal tumor resection and partial hepatectomy and diaphragmatic reconstruction	Yes	No	No	34
8	M	52	Giant extraosseous osteosarcoma in left lung hilus	Left pneumonectomy	No	4	4	13
9	F	60	Giant thymoma	Resection of anterior mediastinal tumor	Yes	No	No	42
10	M	41	Thymic squamous cell carcinoma with main pulmonary artery and superior vena cava involvement	Resection of anterior mediastinal tumor (intubation via femoral artery)	No	31	48	63
11	F	55	Giant leiomyosarcoma of left hilar lung	Left lower lobectomy	Yes	15	No	27
12	M	49	Giant thymoma	Resection of anterior mediastinal tumor	Yes	No	No	28
13	F	60	Giant fibrosarcoma of pericardium	Pericardial tumor resection and pericardiectomy	Yes	13	13	15
14	F	58	Giant leiomyosarcoma in right atrium and right lower lung	Right atrium tumor resection and right lower lung resection	Yes	No	No	127

during surgery is the key point of treatment for refractory thoracic tumors.<sup>9,10</sup>

However, most giant refractory thoracic tumors seriously invade important mediastinal tissues and organs.<sup>11,12</sup> The postoperative recurrence rate is extremely high and the prognosis is poor when surgeons cannot completely remove the tumors using conventional thoracic surgery.<sup>13</sup> As expected, the two patients with major resection in the present study both suffered from local recurrence. In addition, reoperation is also recommended to completely remove the

recurrent tumor if the patient's condition permits.<sup>14,15</sup> Thus, surgeons are constantly exploring strategies to completely remove refractory tumors safely and reliably during surgery to improve the prognosis.

The main risks during surgery are damage to the surrounding important tissues and organs and instability of the respiratory and circulation systems.<sup>16–19</sup> These risks limit the implementation of conventional thoracic surgery. Preoperative multidisciplinary consultation, detailed assessment of the positional relationship between the tumor and the



**FIGURE 1** Kaplan–Meier analysis of overall survival of patients who have been regularly followed up after surgery with cardiopulmonary bypass (red line), and who have experienced postoperative distant metastasis (green line) and local recurrence (blue line). No difference was found between distant metastasis survival and local recurrence survival. ( $p = 0.99$ )

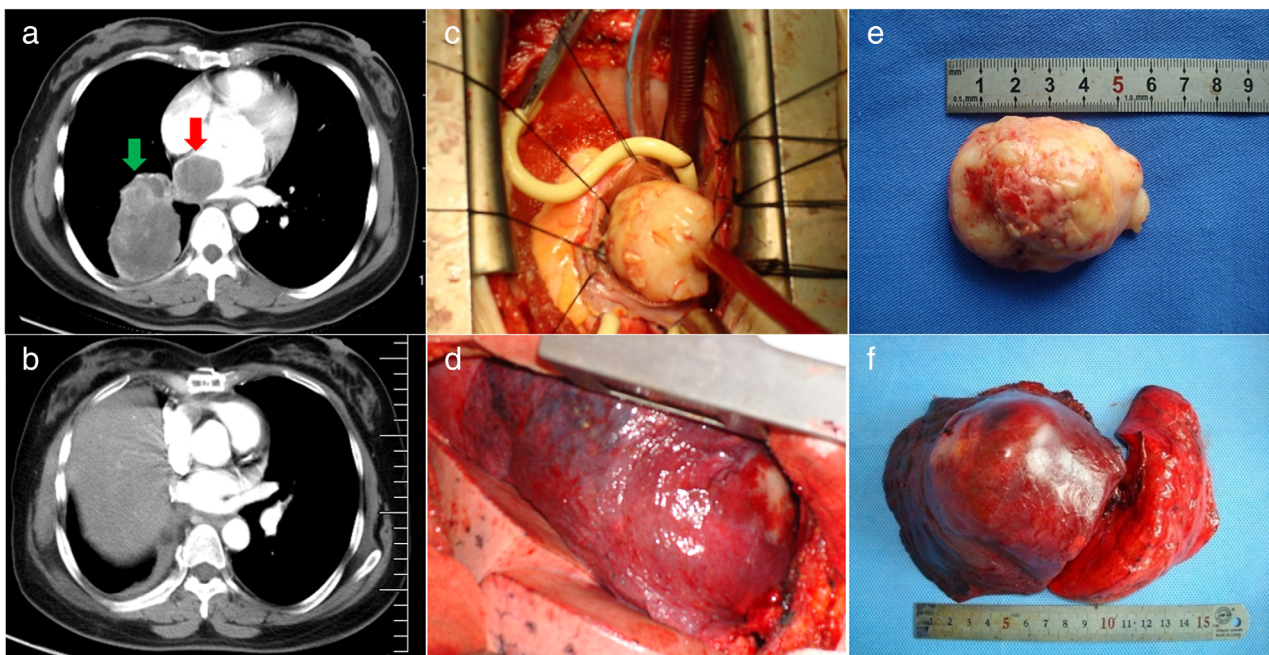
surrounding tissues and organs,<sup>11,20</sup> careful management of the anesthetic process,<sup>19</sup> and active use of CPB or extracorporeal membrane oxygenation (ECMO) can all help thoracic surgeons to effectively overcome surgical difficulties in order to reduce the risk of the operation<sup>5,21</sup> and achieve a complete removal of tumor tissues with better prognosis.<sup>5,22</sup>

However, CPB or ECMO may increase the chance of some complications.<sup>16–18</sup> For example: (1) due to the abundant tumor tissue blood supply, anticoagulant therapy during and after surgery may cause serious bleeding in the tumor invasion wound, (2) CPB and ECMO processes may destroy blood components, and (3) the chance of a systemic

inflammatory stress response may be increased. Serious complications may prolong hospital stay, increase economic burden, and even cause death. Fortunately, the probability of serious complications is extremely low with a favorable prognosis, as long as standardized medical care management is implemented during the perioperative period.<sup>5</sup> Prior studies have shown that patients who undergo a careful preoperative multidisciplinary evaluation and are treated with CPB according to the preoperative plan during surgery have a significantly better prognosis than patients who undergo emergency CPB during surgery.<sup>23</sup>

There are only a few scattered case reports investigating whether CPB increases the risk of postoperative distant metastasis,<sup>24</sup> which remains to be confirmed by more follow-up studies.

In the past 11 years, 14 patients have been treated under CPB in our department, and most of them were followed up for a long time. Three patients (25%) suffered from distant metastasis during the long-term follow-up. Only one patient (1/10) experienced distant metastasis with complete resection, while two patients with incomplete resection both had distant metastasis. Noticeably, the patient with leiomyosarcoma in the right atrium and right lower lung who had undergone right atrium tumor resection and right lower lung resection under CPB, has been regularly followed up for 127 months without noting distant metastasis and local recurrence (Figure 2). Therefore, the rate of postoperative distant metastasis is not high for patients undergoing refractory thoracic tumor surgery under CPB, especially when complete resection is performed.



**FIGURE 2** Patient with leiomyosarcoma in the right atrium and right lower lung underwent right atrial tumor resection and right lower lung resection with the use of cardiopulmonary bypass. (a) Preoperative chest computed tomography (CT). The red arrow indicates the tumor in the right atrium and the green arrow indicates the tumor in the right lower lung. (b) Chest CT 10 years after operation. (c, e) Tumor in the right atrium. (d, f) Tumor in the right lower lung

However, distant metastasis may be related to both pathological characteristics and incomplete resection. The two patients with invasive fibrous tumors with complete resection did not suffer from distant metastasis. Among the three patients with thymic squamous cell carcinoma, only one patient without a complete resection suffered from distant metastasis in the right upper lobe 4 years after surgery. Among the four sarcoma patients (one case of extrasosseous osteosarcoma without complete resection, one case of fibrosarcoma, and two cases of leiomyosarcoma with complete resection), two patients (one case of fibrosarcoma and one case of extrasosseous osteosarcoma) suffered from extensive distant metastasis. Out of 19 reported mediastinal leiomyosarcoma cases in Japan, nine had synchronous or metachronous metastases to various organs within an average follow-up of 25.5 months.<sup>25</sup> A patient with surgically resected fibrosarcoma in the left atrium died 5 months later.<sup>26</sup> In terms of extrasosseous osteosarcoma outcomes, distal metastasis or local recurrence occurred even if the surgical procedure included a complete tumor resection. Out of five patients who had undergone surgery for extrasosseous osteosarcoma, three patients died less than 1 year after surgery due to distal metastasis and local recurrence.<sup>4</sup> The extrasosseous osteosarcoma patient in the present study had survived for more than 1 year after surgery. Thus, it is possible that distant metastasis may be related to both pathological characteristics and incomplete resection, rather than CPB. Unfortunately, the small sample size limits the classification analysis and requires further verification.

The first basic principles and quality control standards for surgical treatment of giant thoracic tumors have recently been published in China.<sup>27</sup> They provide reliable practical guidance for thoracic surgeons. They emphasize that the surgical treatment of giant thoracic tumors must include a multidisciplinary consultation combined with cardiovascular surgical techniques, when necessary. Under the guidance of this standard, more patients will receive surgical treatment under CPB, and more cases will be accumulated to evaluate the influence of CPB on postoperative distant metastasis.

The present study has some limitations. Since retrospective studies with long-term follow-up are rare, the number of cases in the present study was small and included a variety of pathologies. This study also utilized single-center data.

In conclusion, CPB is an effective strategy for complete resection of the giant refractory thoracic tumors with an acceptable risk of postoperative distant metastasis for some patients.

#### ACKNOWLEDGMENTS

This study was supported by the Jiangsu Key Research and Development Plan (Social Development) Project (BE2020653), Suzhou Key Laboratory of Thoracic Oncology (SZS201907), Suzhou Key Discipline for Medicine (SZXK201803), Municipal Program of People's Livelihood Science and Technology in Suzhou (SS2019061), and

Discipline Construction Project of the Second Affiliated Hospital of Soochow University (XKTJ-XK202004).

#### CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

#### ORCID

Yongbing Chen  <https://orcid.org/0000-0002-7595-092X>

#### REFERENCES

- Byrne JG, Leacche M, Agnihotri AK, Paul S, Bueno R, Mathisen DJ, et al. The use of cardiopulmonary bypass during resection of locally advanced thoracic malignancies: a 10-year two-center experience. *Chest*. 2004;125(4):1581–6.
- Reames DL, Mohila CA, Sheehan JP. Treatment of intracranial solitary fibrous tumors with gamma knife radiosurgery: report of two cases and review of literature. *Neurosurgery*. 2011;69(4):1023.
- Zhou Y, Zheng J, Zhu Q, Xia W, Bhagat SK. Solitary fibrous tumor of the salivary gland: a case report. *Oncol Lett*. 2016;11(1):901–3.
- Tsunezuka Y, Oda M, Takahashi M, Minato H, Watanabe G. Primary chondromatous osteosarcoma of the pulmonary artery. *Ann Thorac Surg*. 2004;77:331–4.
- Langer NB, Mercier O, Fabre D, et al. Outcomes after resection of T4 non-small cell lung cancer using cardiopulmonary bypass. *Ann Thorac Surg*. 2016;102:902–10.
- Darwazah AK, Shehata S. Detrimental effect of cardiopulmonary bypass (CPB) on malignant disease. *J Cardiothorac Surg*. 2011;6:13.
- Mei J, Qiang P, Zhu Y, et al. Reconstruction of the pulmonary trunk via cardiopulmonary bypass in extended resection of locally advanced lung malignancies. *J Surg Oncol*. 2012;106(3):311–5.
- Qedra N, Kadry M, Ivanitskaia-Kühn E, et al. Solitary fibrous mediastinal tumor with coronary vascular supply: an unusual case. *J Thorac Cardiovasc Surg*. 2010;139(2):23–5.
- Kohler M, Clarenbach CF, Kestenholz P, Kurrer M, Steinert HC, Russi EW, et al. Diagnosis, treatment and long-term outcome of solitary fibrous tumours of the pleura. *Eur J Cardiothorac Surg*. 2007;32(3):403–8.
- Chen L, Sang YH, Zhang ZW, Yang W, Chen Y. Strategy for initial en bloc resection of a giant mediastinal solitary fibrous tumor: judicious usage of cardiopulmonary bypass. *Thorac Cancer*. 2020;11:2048–50.
- Feng Z, Li M, Liu F, Peng Y, Ren W, Xie H, et al. Analysis of giant thoracic neoplasms: correlations between imaging, pathology and surgical management. *Thorac Cancer*. 2017;8(5):402–9.
- Suzuki S, Takahashi Y. Huge mediastinal germ cell tumor with “white-out” chest X-ray imaging of the left lung. *Thorac Cancer*. 2019;10(2):386–7.
- Misthos P, Papagiannakis G, Kokotsakis J, Lazopoulos G, Skouteli E, Lioulia A. Surgical management of lung cancer invading the aorta or the superior vena cava. *Lung Cancer*. 2007;56(2):223–7.
- De Raet J, Sacré R, Hoorens A, Fletcher C, Lamote J. Malignant giant solitary fibrous tumor of the mediastinum. *J Thorac Oncol*. 2008;3(9):1068–70.
- Van der Mieren G, Willems S, Sciort R, et al. Pericardial synovial sarcoma: 14-year survival with multimodality therapy. *Ann Thorac Surg*. 2004;78(3):41–2.
- de Perrot M, Fadel E, Mussot S, de Palma A, Chapelier A, Dartevelle P. Resection of locally advanced (T4) non-small cell lung cancer with cardiopulmonary bypass. *Ann Thorac Surg*. 2005;79:1691–6. (discussion 97).
- Arif R, Eichhorn F, Kallenbach K, Seppelt P, Ruhparwar A, Dienemann H, et al. Resection of thoracic malignancies infiltrating cardiac structures with use of cardiopulmonary bypass. *J Cardiothorac Surg*. 2015;10:87.
- Spaggiari L, D'Aiuto M, Veronesi G, et al. Extended pneumonectomy with partial resection of the left atrium, without cardiopulmonary bypass, for lung cancer. *Ann Thorac Surg*. 2005;79:234–40.

19. Li WWL, Van Boven WJP, Annema JT, Eberl S, Klomp HM, de Mol BAJM. Management of large mediastinal masses: surgical and anesthesiological considerations. *J Thorac Dis*. 2016;8(3):175–84.
20. Song JY, Kim KH, Kuh JH, Kim TY, Kim JH. Two-stage surgical treatment of a giant solitary fibrous tumor occupying the thoracic cavity. *Korean J Thorac Cardiovasc Surg*. 2018;51(6):415–8.
21. Zhang SX, Tan DL, Wu W, He B, Jing T, Tang M, et al. Extracorporeal membrane oxygenation (ECMO) assisted mediastinal tumor resection and superior vena cava replacement are safe and feasible. *Thorac Cancer*. 2019;10:1846–51.
22. Wiebe K, Baraki H, Macchiarini P, Haverich A. Extended pulmonary resections of advanced thoracic malignancies with support of cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 2006;29:571–7. (discussion 77–8).
23. Yıldızeli B, Darteville PG, Fadel E, Mussot S, Chapelier A. Results of primary surgery with T4 non-small cell lung cancer during a 25-year period in a single center: the benefit is worth the risk. *Ann Thorac Surg*. 2008;86:1065–75. discussion 1074–5.
24. Akchurin RS, Davidov MI, Partigulov SA, Brand JB, Shiriaev AA, Lepilin MG, et al. Cardiopulmonary bypass and cell-saver technique in combined oncologic and cardiovascular surgery. *Artif Organs*. 1997;21:763–5.
25. Yoshihito I, Hirohiko A, Yuki N, Kinoshita H, Hirata T. A case of primary Mediastinal Leiomyosarcoma in which long-term survival was achieved. *Ann Thorac Cardiovasc Surg*. 2020;26:95–9.
26. Basso C, Valente M, Poletti A, Casarotto D, Thiene G. Surgical pathology of primary cardiac and pericardial tumors. *Eur J Cardiothorac Surg*. 1997;12:730–8.
27. Zhuang WT, Gao Z, Zeng WS, et al. Basic principles and quality control of surgical treatment for giant thoracic tumors. *Chin J Clin Thorac Cardiovasc Surg*. 2020;27(9):996–1000.

**How to cite this article:** Chen L, Zhu X, Zhu R, Jin X, Tan L, Chen Y. Cardiopulmonary bypass does not consequentially contribute to postoperative distant metastasis of giant refractory thoracic tumors: A retrospective study with long-term follow-up. *Thorac Cancer*. 2021;12:2990–5. <https://doi.org/10.1111/1759-7714.14162>