"Salvage" Surgery for Primary Mediastinal Malignancies

Is it Worthwhile?

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Introduction: Indications and results of salvage surgery in mediastinal tumors are still unclear. This study analyzes a single-center experience to assess its mortality, morbidity, and long-term results.

Methods: Mediastinal salvage surgery (MSS) was defined as surgical resection of persistent or recurrent primary mediastinal tumors after previous local treatments with curative intent or exclusive chemotherapy in case of bulky tumors. Clinical data of patients undergoing MSS between 1998 and 2005 were analyzed. Overall and disease-specific long-term survival was calculated.

Results: Twenty-one patients (15 men and 6 women, mean age 41 years) underwent MSS. Eleven patients suffered from thymic tumors (eight thymomas, three thymic carcinoma) whereas 10 patients suffered from nonthymic tumors (one lung adenocarcinoma + thymoma, two mediastinal monophasic sinovial sarcoma, one mediastinal neuroendocrine tumor, one mediastinal teratoblastoma, one mediastinal disgerminoma, one Hodgkin's lymphoma, one mediastinal atypic carcinoid, two medullary thyroid carcinoma). MSS required extended vascular resection in 10 cases and cardiopulmonary bypass in one case. Median operation time was 215 minutes (range 140–720). One postoperative death and four major complications were recorded (overall mortality 4.7%, morbidity 19.0%). With a median follow-up of 30.6 months, overall 1-, 3-, and 5-year Kaplan-Meier survival was 89.7, 71.2, and 56.6%, respectively. Thymic neoplasms had a better prognosis (1-, 3-, and 5-year survival was 100, 87.5, 87.5%, respectively) when compared with others (1-, 3-, and 5-year survival was 77.8, 53.3, 26.7%, respectively—logrank $p = 0.0128$).

Conclusions: MSS can offer a chance of curative treatment in selected patients with an acceptable morbidity and mortality. Thymic tumors obtain the best results in term of long-term survival.

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Mediastinal malignancies are a heterogeneous group of diseases most of which are suitable for curative surgical resection, such as thymic tumors, nonseminomatous germ cell tumors (nonresponders after chemotherapy), and mesenchymal malignancies. In the case of extensive disease infiltrating contiguous vascular, cardiac or pulmonary structures, or in the case of recurrent mediastinal tumors after previous surgical resection, patients are often considered inoperable. Afterward, patients usually receive nonsurgical treatments with curative intent and some of them with persistent disease and without any other potential treatment are referred to thoracic surgeons.

In some instances, the indication for an extended "salvage" procedure can be discussed in young and fit patients. This salvage surgery often requires long operating time, extended vascular or pulmonary resections, and it results in higher postoperative morbidity. This increased risk is not well defined because the impact of mediastinal salvage surgery (MSS) is masked by the presence of standard resections in reported surgical series of thymic tumors, mesenchymal and germ cell malignancies.[1]

The aim of this study was to review our experience in the subset of mediastinal malignancies requiring salvage extended mediastinal resection to assess postoperative morbidity and mortality, with the secondary aim of searching of long-term survival predictors after radical resection.

PATIENTS AND METHODS

MSS was defined as surgical resection of persistent or recurrent primary mediastinal tumors after previous local treatments with curative intent or exclusive chemotherapy in case of bulky tumors. Patients affected by mediastinal metastases from nonthoracic primary tumors were not included in the present study.

In all cases, surgery was planned to obtain complete tumor removal by radical mediastinectomy (removal of all mediastinal tissues from the upper thymic lobes to diaphrag-

TABLE 1. Clinicopathologic and Surgical Features of Patients

Case No.	Age/Sex	Diagnosis	Previous Treatment	Surgery	CPB	Approach
1	38/M	Lung adenocarcinoma + SVC infiltration + thymoma	CT	Right upper lobectomy + resection of thymoma + SVC reconstruction	No	Sternotomy + TMA + cervicotomy
2	21/F	Mediastinal monophasic sinovial sarcoma	Nonradical surgery + CT	Right pneumonectomy	No	Right hemiclamshell
3	32/F	Malignant thymoma	RT	Left pleuropneumonectomy + resection of thymoma	No	Left hemiclamshell
4	29/M	Malignant thymoma	CT	Resection of thymoma (+pericardiectomy + left phrenic nerve resection + left upper lobe wedge resection)	No	Sternotomy
5	24/M	Malignant thymoma	Nonradical surgery + CT	Completion resection of thymoma + right pleurectomy + right lung bimetastasectomy	No	Right hemiclamshell
6	29/F	Mediastinal monophasic sinovial sarcoma	Nonradical surgery + CT	Tumor resection + left upper lobectomy + phrenic and recurrent nerves resection + left brachiocepahlic vein reconstruction	No	Left hemiclamshell
7	61/F	Thymic carcinoma	RT	Thymectomy + left common carotid resection/reconstruction + left hemithyroidectomy + left giugular vein resection	No	TMA
8	13/F	Mediastinal mesenchymal neuroendocrine tumor	CT	Explorative Thoracotomy (complete cardiac infiltration)	No	Left hemiclamshell
9	44/M	Thymic carcinoid	CT	Thymectomy + pericardiectomy + phrenic nerve resection	No	Sternotomy
10	30/M	Mediastinal teratoblastoma	CT	Tumour resection + right upper lobe wedge resection + pericardiectomy + left and right brachiocephalic veins resection/reconstruction	No	Clamshell
11	55/M	Malignant thymoma	CT	Thymectomy + SVC resection/reconstruction	No	Sternotomy
12	41/M	Disgerminoma	CT	Tumour resection + middle lobe and left upper lobe wedge resection, pericardial and right phrenic nerve resection	No	Sternotomy
13	45/M	Malignant thymoma	CT	Resection of thymoma + SVC resection and reconstruction	No	Sternotomy
14	38/M	Malignant thymoma	RT	Resection of thymoma	No	Left hemiclamshell
15	47/M	Hodgkin's lymphoma	CT	Tumor resection	No	Sternotomy
16	73/M	Mediastinal atypical carcinoid	CT	Tumor resection	No	TMA + sternotomy
17	47/M	Thymic carcinoma	CT	Tumor resection + left upper lobe resection + left brachiocephalic vein resection/reconstruction	No	Left hemiclamshell
18	54/M	Medullary thyroid carcinoma	CT + radio metabolic therapy	Explorative cervico sternotomy	No	Cervicosternotomy + manubriotomy
19	27/M	Malignant thymoma	CT	Resection of thymoma + left pleuropneumonectomy + left brachiocephalic vein resection/reconstruction	No	Left hemiclamshell
20	54/M	Medullary thyroid carcinoma	Radiometabolic therapy + nonradical surgery	Thymectomy + brachiocephalic artery reconstruction + omentoplasty	No	Cervicosternotomy
21	50/F	Malignant thymoma	CT	Resection of thymoma + SVC resection and reconstruction + right atrium resection	Yes	TMA + sternotomy

CT, chemotherapy; RT, radiotherapy; TMA, transmanubrial approach.

matic pericardial fat pad and from the left to the right phrenic nerves) and resection of all the involved contiguous anatomic structures.

We retrospectively reviewed data base information on patients who had undergone MSS to evaluate postoperative mortality (defined as any death occurring during hospital stay or within 30 days after surgery), morbidity (pulmonary, cardiac, surgical, and others), and long-term survival.

We analyzed the impact of eight variables (age, sex, preoperative forced expiratory volume in 1 second, previous treatments, associated lung or vascular resections, operating time, use of cardiopulmonary bypass [CPB]) on postoperative morbidity and mortality. Comparisons were made using the Student *t* test for continuous variables and the χ^2 test for categorical variables; *p* values were considered significant when <0.05.

Follow-up was obtained by telephonic contact in January 2006. Overall 5-year survival was calculated by the Kaplan-Meier method; comparisons between groups (thymic tumors versus others) were performed by logrank test.

RESULTS

From January 1, 1998 to January 1, 2005, we performed 21 mediastinal salvage procedures. Patient characteristics are shown in Table 1. Eleven patients suffered from thymic tumors (eight thymomas, three thymic carcinoma) whereas 10 patients suffered from nonthymic tumors (one lung adenocarcinoma + thymoma, two mediastinal monophasic sinovial sarcoma, one mediastinal neuroendocrine tumor, one mediastinal teratoblastoma, one mediastinal disgerminoma, one Hodgkin's lymphoma, one mediastinal atypic carcinoid, two medullary thyroid carcinoma).

Surgical approaches were median sternotomy in six cases; sternotomy and transmanubrial approach (TMA) in two cases, right hemiclamshell in two cases, left hemiclamshell in six cases, TMA alone in one case, clamshell in one case, combined approaches in three cases.

Median operation time was 215 minutes (range 140–720). We performed eight extended venous vascular resections (four superior vena cava resections and four brachiocephalic veins resections), two arterial resections (one carotid artery resection and one brachiocephalic artery resection), one operation (4.7%) required CPB for cardiac infiltration. Together with mediastinectomy, we performed anatomic pulmonary resections in five cases (two were lobectomies, one pneumonectomy, and two pleuropneumonectomies).

No intraoperative deaths were recorded, one postoperative death after right upper lobectomy + thymomectomy + superior vena cava reconstruction was recorded (overall 30 days mortality: 4.7%,), 4 major complications were recorded (overall morbidity 19.0%): two vascular prosthesis thrombosis (9.5%), one cardiac acute myocardial infarction (4.7%), and one bleeding requiring redo thoracotomy 4.7%. We had two explorative thoracotomies (9.5%). Mean postoperative intensive care unit stay was 11 days (range, 0–77days).

TABLE 2. Proportional Hazard Model (Cox Regression) Overall Survival Risk Factors—Reduced Model

	Hazard Ratio (95% CI)	Significance Level (*p*)
Others vs. thymus	10.61 (2.09–53.88)	0.0044
Lung resection	3.73 (0.79–17.61)	0.0962
Vascular resection	2.63 (0.51–13.69)	0.2482

Univariate analyses showed no significant association between morbidity or mortality with age, sex, forced expiratory volume in 1 second, and previous treatments; only

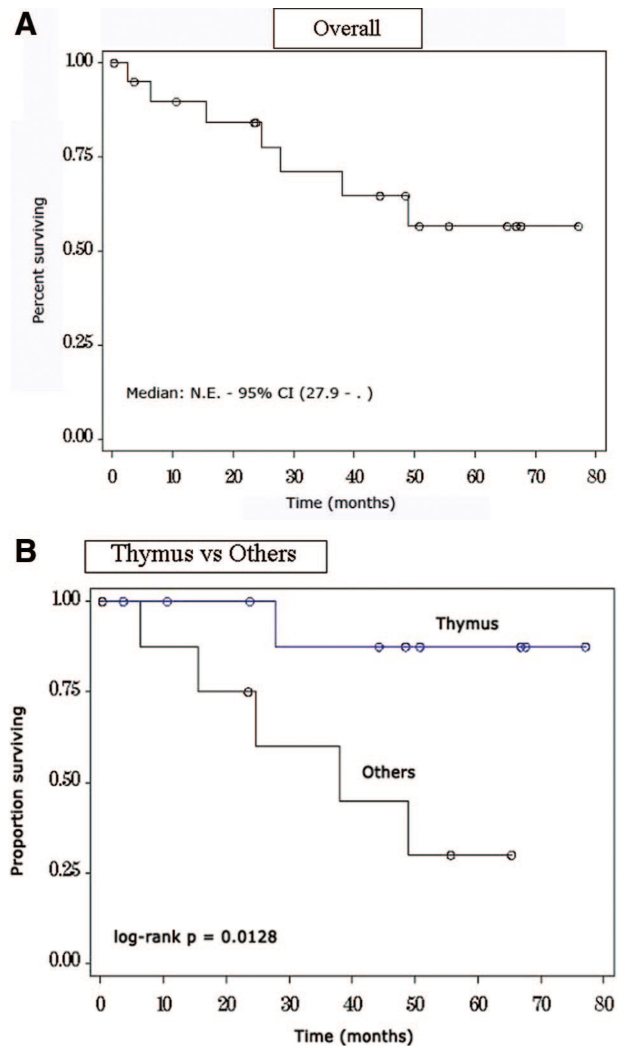

FIGURE 1. *A*, Overall 5 years Kaplan-Meier survival curve (NE: not evaluable); upper limit of confidence interval not assessable. *B*, Comparison between 5 years Kaplan-Meier survival curve of thymic and nonthymic groups.

TABLE 3. Survival by Group at 1, 3, and 5 Years (Kaplan-Meier Estimates)

Time (yr)	Group	Survival ± SE	Patients at Risk
1	Thymus	100%	9
	Others	77.8% ± 13.9%	7
	Overall	89.7% ± 6.9%	16
3	Thymus	87.5% ± 11.7%	7
	Others	53.3% ± 17.3%	4
	Overall	71.2% ± 11.0%	11
5	Thymus	87.5% ± 11.7%	5
	Others	26.7% ± 15.9%	1
	Overall	56.6% ± 12.8%	5

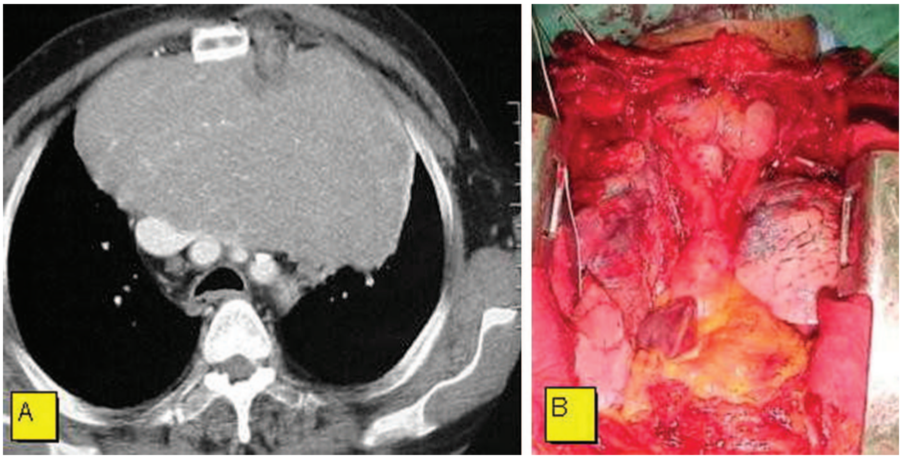

FIGURE 2. Intraoperative views of "second-line" mediastinal resections: single surgeon personal series. *A*, CT scan disclosing huge thymic carcinoma after chemotherapy. *B*, Intraoperative view of the huge thymic carcinoma resection.

associated vascular and pulmonary resections showed a slightly increased risk; however, not statistically significant (Table 2).

Overall 1-, 3-, and 5-year Kaplan-Meier survival was 89.7, 71.2, and 56.6%, respectively. Thymic neoplasms had a better prognosis (1-, 3-, and 5-year actuarial survival was 100, 87.5, 87.5%, respectively) when compared with others (1-, 3-, and 5-year actuarial survival was 77.8, 53.3, 26.7%, respectively—log rank $p = 0.0128$) (Figures 1*A*, *B* and Table 3). None of the considered variables affected long-term survival.

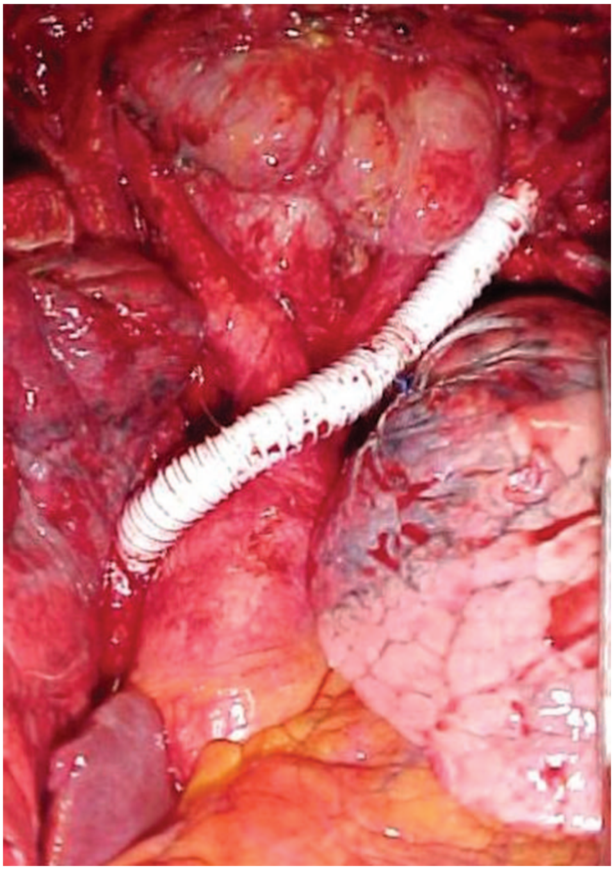

FIGURE 3. Vascular reconstruction after thymic resection (left innominate vein reconstructed by polytetrafluoroethylene (PTFE) prosthesis).

DISCUSSION

In surgical oncology, complete resection is necessary to prolong survival, offering the patients the most effective therapeutic option.[1,2] Successful complete resection in extremely large mediastinal malignancies, which have been previously treated with curative intent, is an oncological and technical challenge.

Results from our series confirmed that the judgment of inoperability can be reevaluated in selected cases given that they may benefit from extensive surgery, with an acceptable surgical mortality and postoperative morbidity rate. This

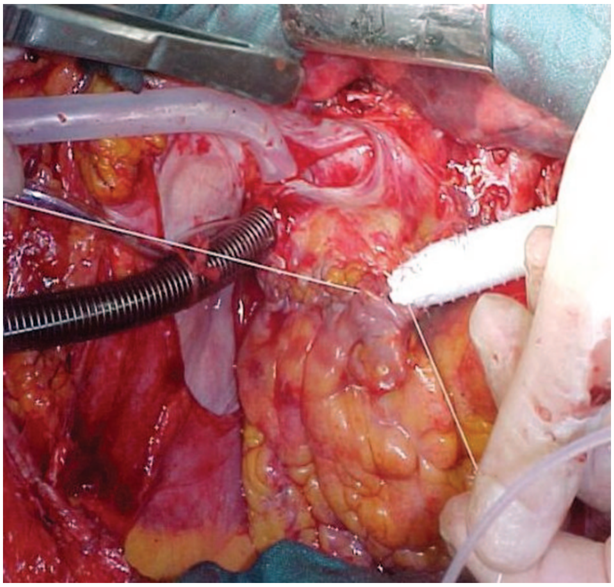

FIGURE 4. Atrial resection and reconstruction by polytetrafluoroethylene (PTFE) prosthesis after invasive thymoma resection.

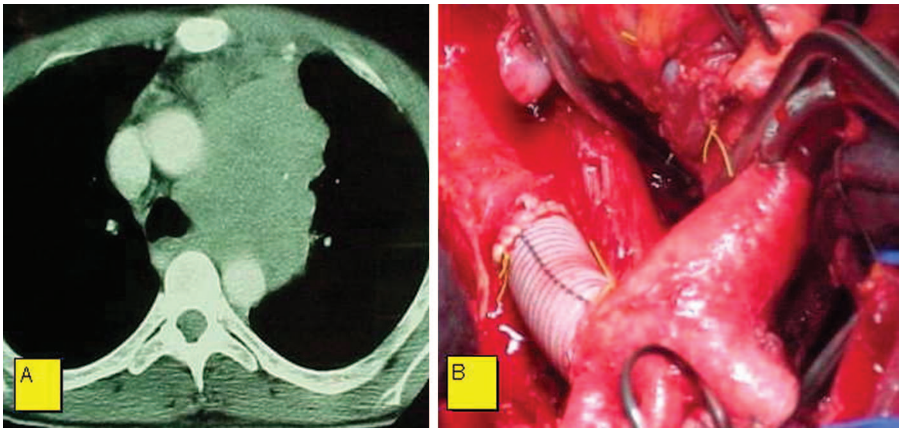

FIGURE 5. *A*, CT scan disclosing left thymic carcinoma after chemotherapy. *B*, Intraoperative view of thymic carcinoma resection with aortic resection and prosthetic reconstruction and pulmonary artery resection and direct reconstruction.

information was already available for thymic tumors[3,4] (Figures 2–4); as far as we know, our study is the first to also consider salvage surgery for nonthymic malignant neoplasms. On the one hand, the decision to analyze all the types of mediastinal malignancies together creates a heterogeneous population, which represents a limitation in this study. On the other hand, it permits a comparison of thymic and nonthymic diseases surgically treated homogeneously at the same institution. Results demonstrate that in the case of radical resection, nonthymic tumors have an acceptable long-term survival rate suggesting that they should not be excluded from salvage surgery when feasible. Our results confirmed that thymic neoplasms have the best long-term survival rate after radical resection (87.5% at 5 years), representing the ideal condition for successful salvage surgery. None of the selected variables statistically influenced postoperative morbidity rate; probably the small number of patients reported in the present series conditioned statistical evaluation of the results.

MSS very often requires an alternative approach other than sternotomy because complete exposure is crucial for the efficacy of extensive surgery. We have already described the combination of the TMA and sternotomy to access the mediastinum in the case of huge mass.[5] Marta et al. recently described inverse T incision for the upper mediastinum.[6]

Even with the best exposure, the risk involved in nonradical resection must be considered, for functional and oncological reasons. From the functional point of view, the limit is represented by diseases involving both phrenic nerves, which cannot be resected without causing bilateral diaphragmatic palsy and consequent respiratory failure; it can lead to a nonradical resection, as it once occurred in our series (case no.18). From the oncological point of view, unexpected or underestimated infiltration of mediastinal structures can represent another cause of explorative procedure. Cardiac infiltration is not per se an absolute contraindication to resection, as myocardial resection is feasible by the use of CPB.[4,9,10] CPB use in oncology is still controversial because of the risk of systemic tumor dissemination caused by suction of blood, which is then returned to the circuit system, resulting in a generalization of a thus far localized disease.[7,8,12] The use of a passive shunt or of a femorofemoral heparinized extracorporeal membrane oxygenator has been proposed to reduce the risk of neoplastic cell dissemination occurring mainly during great vessels resection.[2,11] During the study period, we used only conventional extracorporeal circulation in 1 patient in the present series because the above-mentioned risk still remains theoretical and in our experience with CPB in thoracic oncology, we did not record a higher risk of distant metastases (Figure 5).

In conclusion, according to our present results, second-line MSS may represent the sole effective therapy for nonresponders to other curative treatments when patients were considered ineligible to surgery at any time of the history of their disease. In this situation, salvage surgery offers a satisfactory long-term survival with an acceptable surgical mortality and postoperative morbidity. Thymic neoplasms represent mediastinal malignancies with the best results after radical salvage resection. In nonthymic tumors, indication to salvage surgery should be discussed case by case, considering that long-term survival in completely resected patients is not negligible (26.7% at 5 years).

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