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Is extended resection for locally advanced thoracic cancer with cardiopulmonary bypass justified?

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Abstract

Background Resection of intrathoracic tumor with cardiopulmonary bypass (CPB) remains a relatively under-reported intervention in literature, and its role in managing locally advanced mediastinal and lung cancers is a topic of ongoing debate. Our aim was to review our experience and assess the role of CPB for treating locally advanced mediastinal and lung cancers.

Methods Between 2015 and 2020, this study initially included 10 patients with primary locally advanced thoracic malignancies with apparent adjacent cardiovascular invasion demonstrated by thoracic imaging scans. Operation was performed based on a multidisciplinary tumor board consensus. Eventually, 8 patients (3 primary lung cancers and 5 mediastinal cancers) received either salvage or elective resection with CPB; two completed surgery without requiring CPB.

Results Regarding the extent of adjacent structure involvement, 4 patients presented with involvement of the superior vena cava (SVC), 1 involved the right atrium (RA), 2 involved the SVC and RA, and 1 involved the SVC, the origin of main pulmonary artery, and the ascending aorta. Thirty-day mortality occurred in two of three patients receiving salvage surgery due to respiratory insufficiency. With the long-term follow-up, one patient died of recurrence 25 months postoperatively, one survived with recurrence 30 months postoperatively, and four were alive without recurrence for 35, 36, 49, and 107 months after operations.

Conclusion In certain patients, particularly for elective surgical candidates rather than salvage resection, CPB allows for extended resection of locally advanced thoracic cancers with acceptable perioperative safety and survival.

Keywords Cardiopulmonary bypass (CPB), Extended resection, Locally advanced thoracic cancer

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Background

Surgical resection plays a crucial role in the treatment of patients with advanced thoracic malignant tumors with invasion of adjacent thoracic structures and may offer a chance for cure. However, such surgeries remain challenging even for experienced surgeons. Though controversial, cardiopulmonary bypass (CPB) can be used to allow resection and reconstruction of the great vessels and/or cardiac structures and, subsequently, complete extended resection of the tumor [1–5]. Radical resection of tumors has been shown to significantly improve the survival in select patients [6–8]. Even as the potential advantage and efficacy of CPB has been recognized, the underuse of CPB reflects the concerns of significant complications; including excessive bleeding secondary to full heparinization, increased pulmonary complications, and fears of CPB-related tumor dissemination [9] .

Thus far, little is known about the true pros and cons of CPB use in locally advanced thoracic malignancies. Over the last decades, only a few case series describing the technical possibilities in extended radical resections, the associated morbidities and mortalities, as well as the postoperative long-term survival outcomes have been published [3, 5–8, 10, 11]. Hence, the underlying benefit of CPB in aiding complete extended resection merits further investigation. Consequently, the present study aims to review our surgical experience of treating such advanced intrathoracic tumors using CPB and the perioperative and survival outcomes. Further, the rationale of using CPB in complete extended resection among such complex surgical procedures will be discussed with a compendious review of current relevant literature.

Method

Study design

This study is a single institutional case series conducted between January 2015 and December 2020, focusing on patients with primary thoracic cancers. We assessed the role of CPB in facilitating complete resection of tumors with highly suspected neighboring cardiovascular invasion, as identified by preoperative thoracic computed tomographic (CT) scans. The study protocol adhered to ethical guidelines and was approved by the institutional review board (KMUHIRB-E(II)-20230169).

Patient selection

Patient inclusion algorithm is presented in Fig. 1. A total of 10 patients with primary thoracic cancers highly suspected neighboring cardiovascular invasion based on CT scans were initially included in the study. Surgical indication and resection was principally performed with a curative intent and based on consensus reached by a multidisciplinary team including thoracic surgeons, cardiovascular surgeons, oncologists, and radiologists. Preoperative assessment was used to exclude patients with distant metastasis and advanced mediastinal lymph node

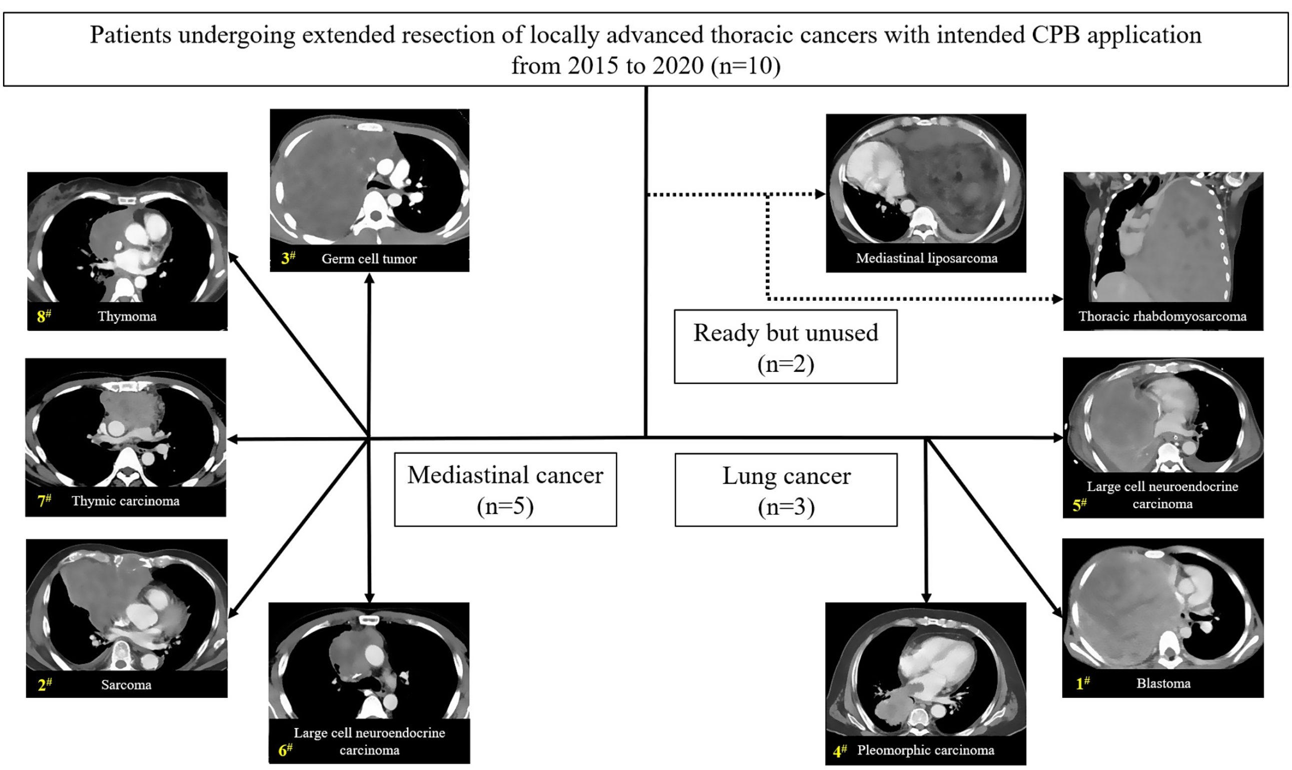

Fig. 1 Enrollment of patients with locally advanced thoracic cancers undergoing extended resection via CPB support. *CPB: cardiopulmonary bypass*

disease. Two patients (mediastinal liposarcoma and thoracic rhabdomyosarcoma) were excluded because surgery was able to be completed without the need for CPB (these patients' femoral artery and vein were catheterized in preparation for CPB). Regarding the intention of surgery, the remaining eight patients can be divided into elective and salvage surgeries. Patients undergoing elective surgery usually had good performance status with a well-organized perioperative therapeutic strategy, while patients receiving salvage surgery often exhibit inferior/marginal physical status and resection was determined when no alternative nonoperative therapy was available and based on the individual condition of each patient and approved after the multidisciplinary team discussion. In brief, these patients probably would have had a dismal chance of survival, without salvage resection and the associated challenges/risks.

Surgical techniques

All eight patients, comprising 3 with primary lung cancers and 5 with mediastinal cancers, underwent complete resection with the assistance of CPB. The operation was approached through median sternotomy with or without lateral thoracotomy extension (n=7) or postero-lateral thoracotomy (n=1). CPB was employed via ascending aorta and right atrial or bicaval cannulation, following full heparinization. Once CPB was initiated, the aorta was cross-clamped and the heart arrested with the aid of cold blood cardioplegia. Extended tumor resection and surgical reconstruction of the cardiovascular structure involved was then performed (Figs. 2D and 3C). Pulmonary extension of tumors required pneumonectomy in 4 patients, and bilobectomy, lobectomy, and wedge resection in the remaining 3 cases respectively. In the majority of patients, several cardiovascular and mediastinal structures were affected simultaneously. Therefore, resection involving superior vena cava (SVC) was performed in 4 patients, the right atrium (RA) in 1 patient, the SVC and

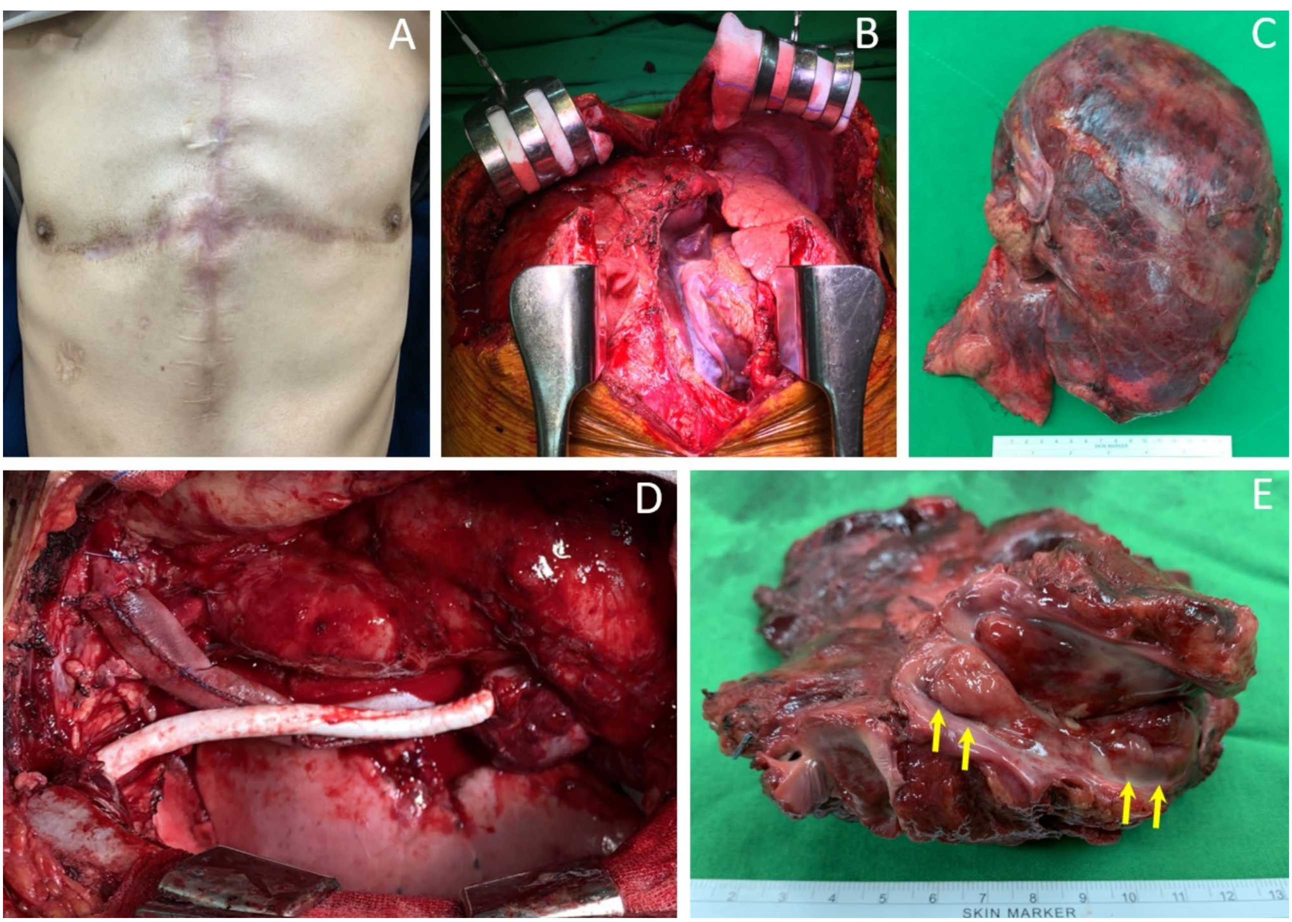

Fig. 2 Operative pictures of the representative patients 3# and 6#. (**A**) Delayed healing of postoperative wound in patient 3#. (**B**) Intraoperative view following salvage surgery using clamshell thoracotomy plus median sternotomy approach. (**C**) Resected specimen after the en bloc tumor resection plus right pneumonectomy. (**D**) Prosthetic reconstruction of the SVC and left innominate vein after radical resection in patient 6#. (**E**) Resected specimen showing intraluminal tumor invasion of SVC (arrow). *SVC: superior vena cava*

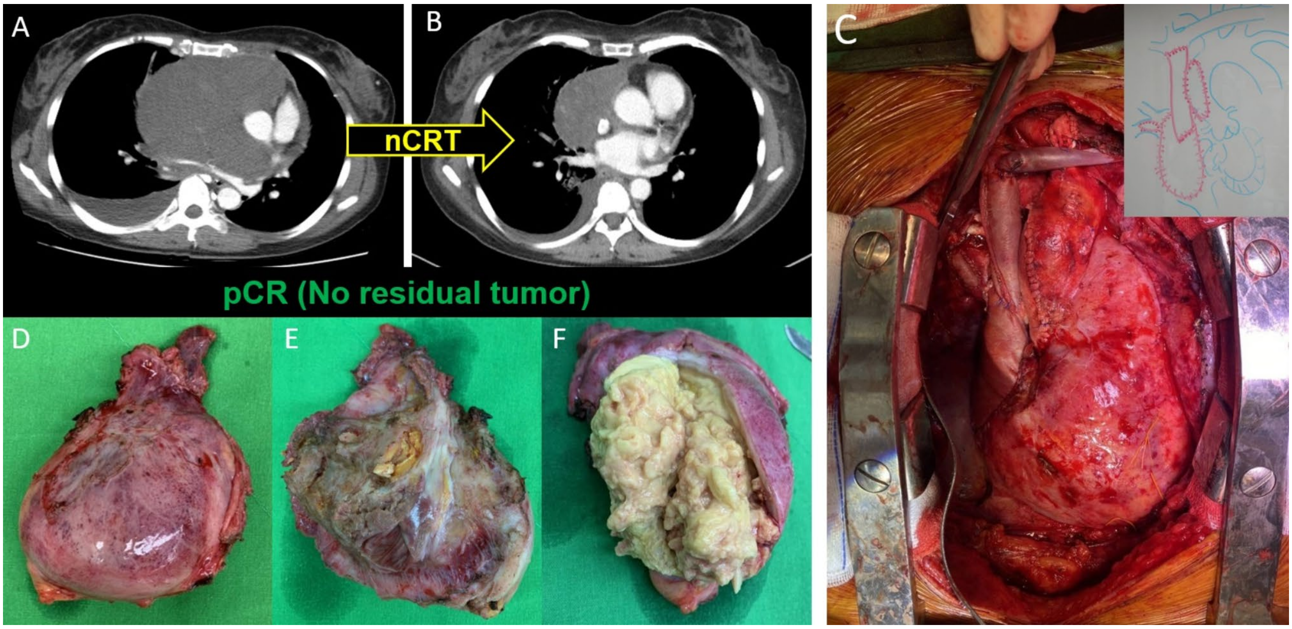

Fig. 3 Operative pictures of the representative patient 8#. (**A**) Pretreatment CT scan demonstrating bulky mediastinal thymoma invading the cardiovascular structure. (**B**) Preoperative CT scan showing marked shrinkage of tumor after induction chemoradiotherapy. (**C**) Prosthetic reconstruction of the SVC, right atrium, and proximal ascending aorta after radical resection. (**D**), (**E**) and (**F**) Resected specimen with gross appearance of necrotic content which confirmed pathological complete response. *nCRT: neoadjuvant chemoradiotherapy, pCR: pathological complete response, CT: computed tomography, SVC: superior vena cava*

the RA in 2 patients, and the SVC with the root of main pulmonary artery, and the ascending aorta in 1 patient.

Statistics

Descriptive statistics were used to summarize patient demographics, tumor characteristics, perioperative variables, and outcomes. Categorical variables were expressed as numbers with percentages and compared by the Chi-square test. Non-normally distributed data were described by medians with interquartile range (IQR) and were analyzed using Mann-Whitney U test. The latest follow-up endpoint for data collection was December 31, 2023. Recurrence-free survival (RFS) was defined as the time interval between surgery and the occurrence of tumor recurrence or the last follow-up date. Overall survival (OS) was defined as the time interval between surgery and death from any cause or the last follow-up date. Kaplan-Meier survival curves were generated to assess RFS and OS. A statistical significance was set at a p-value less than 0.05.

Results

Patient demographics

Clinical demographics of case details are listed in Table 1. In total, eight patients underwent extended resection of locally advanced thoracic cancers with CPB; including 3 salvage surgeries and 5 elective surgeries. Six patients were male with an age range of 7 to 73 years old with a mean of 52 years. Pathological diagnosis of the 5 mediastinal cancers were mediastinal sarcoma, mediastinal germ cell tumor, mediastinal large cell neuroendocrine cancer, thymic carcinoma, and thymoma; 3 lung cancers including pulmonary blastoma, pleomorphic lung cancer, large cell neuroendocrine lung cancer. The representative patient #3 underwent salvage surgery using clamshell thoracotomy plus median sternotomy for en-bloc resection of giant mediastinal germ cell tumor (Fig. 2A and B, and 2C), who required right pneumonectomy, partial SVC resection, pericardial resection and reconstruction [12]. Another representative patient #6 underwent elective surgery via median sternotomy for en-bloc resection of mediastinal large cell neuroendocrine carcinoma, who required bilobectomy, entire SVC resection, LBV resection and reconstruction (Fig. 2D and E).

Perioperative and postoperative outcomes

Perioperative and postoperative outcomes are summarized in Tables 1 and 2. Postoperative complications were graded using the Clavien-Dindo classification, 2 out of 5 patients with elective surgery had no postoperative complications. 4 patients had grade II-III complications, including arrhythmia, sternal wound dehiscence, vocal cord palsy, vascular graft thrombosis (subsequently treated with endovascular intervention+thrombolytic therapy). The aforementioned complications were all managed successfully and the patients returned to monitoring in the clinic setting. Two patients presented with

Table 1 Patient demographics and perioperative outcomes

Patient (intention of surgery)	Pathology	Age[a]	Sex	ECOG	ASA	Lung resection	CVS resection	OP Time[b] (min)	Blood loss[c] (mL)	ICU day[d]	Hospital day[e]
1# (elective)	Pulmonary blastoma	7	F	1	4	Pneumonectomy	SVC	360	200	3	9
2# (salvage)	Mediastinal sarcoma	73	M	3	4	Pneumonectomy	SVC	400	3400	24	24
3# (salvage)	Mediastinal teratoma	18	M	2	4	Pneumonectomy	SVC	600	1750	4	27
4# (elective)	Pleomorphic lung cancer	73	M	1	4	Lobectomy	LA	450	1000	10	16
5# (salvage)	Large cell neuroendocrine lung cancer	61	M	4	4	Pneumonectomy	SVC, LA	570	3000	12	12
6# (elective)	Mediastinal large cell neuroendocrine cancer	37	M	0	2	Bilobectomy	SVC, LBV	480	1850	3	12
7# (elective)	Thymic carcinoma	49	M	1	3	Wedge resection	LBV, MPA, Aorta	650	700	7	17
8# (elective)	Thymoma	53	F	1	3	Nil	SVC, RA, Aorta	660	650	18	34

ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists; CVS: cardiovascular structure; OP: operation; ICU: intensive care unit; min: minute; mL: milliliter; F: female; M: male; SVC: superior vena cava; LA: left atrium; LBV: left brachiocephalic vein; MPA: main pulmonary artery; RA: right atrium. Values are expressed as means ± standard deviations (SD)

[a] Mean ± SD, 46.4 ± 24.3 years

[b] Mean ± SD, 521 ± 114 min

[c] Mean ± SD, 1,568 ± 1,153 mL

[d] Mean ± SD, 10.1 ± 7.6 days

[e] Mean ± SD, 18.9 ± 8.7 days

Table 2 Pathological and postoperative outcomes

Patient	Pathological tumor stage	Complication (grade)	Resection margin	RFS[a] (months)	OS[b] (months)	Neoadjuvant Tx	Postoperative adjuvant Tx
1#	Lung blastoma, pT4NxM0, stage IIIA	No	R0	107	107 (alive)	No	Chemotherapy
2#	Mediastinal sarcoma, pT4N0M0, stage III	Mortality, grade 5	R1	0.8	0.8 (death)	No	No
3#	Mediastinal teratoma, ypT1aN0M0, stage I	Wound dehiscence, grade 3a	R0	6	25 (death)	Chemotherapy	Chemotherapy + radiotherapy
4#	Pleomorphic lung cancer, pT4N0M0, stage IIIA	No	R0	6	30 (lost follow-up)	No	chemotherapy
5#	Large cell neuroendocrine lung cancer, pT4N2M0, stage IIIB	Mortality, grade 5	R1	0.4	0.4 (death)	No	No
6#	Mediastinal large cell neuroendocrine cancer, pT3N0M0, stage III	Graft thrombosis, grade 3a	R0	49	49 (alive)	No	chemotherapy
7#	Thymic cancer, ypT3N0M0, stage III	Vocal cord palsy, Graft thrombosis, grade 3a	R0	36	36 (alive)	chemotherapy	No
8#	Thymoma, ypT0N0M0, pCR	Cardiac arrythmia required pacemaker implantation, grade 2	R0	35	35 (alive)	Chemotherapy + radiotherapy	No

RFS: resurrence-free survival; OS: overall survival; Tx: therapy. Values are expressed as means ± standard deviations (SD)

[a] Mean ± SD, 43 ± 17 months

[b] Mean ± SD, 58 ± 17 months

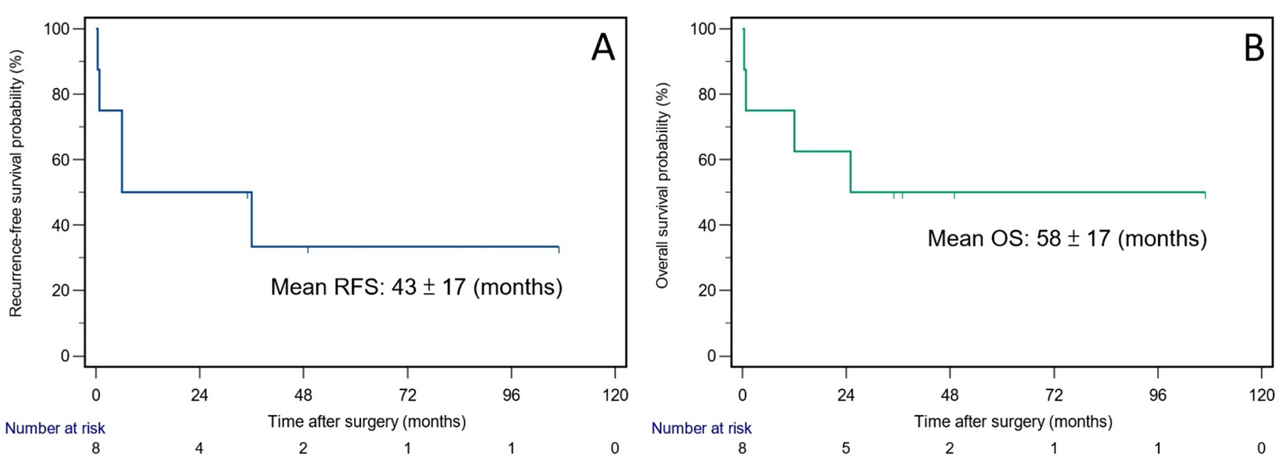

Fig. 4 Kaplan-Meier analysis of recurrence-free survival (RFS) and overall survival (OS) of included patients

grade V complications (in-hospital mortality) due to respiratory insufficiency; both patients received salvage surgeries. Notably, patient #8 underwent elective surgery following neoadjuvant chemoradiotherapy, which achieved pathological complete response (pCR) after resection (Fig. 3). In the long term, 4 patients presented with recurrence-free survival 35, 36, 49, and 107 months after operations, and one survived with recurrence 30 months postoperatively. One patient died with recurrence 25 months postoperatively. The mean recurrence free survival (RFS) was 43 ± 17 months and the mean overall survival (OS) was 58 ± 17 months. The Kaplan-Meier plot of RFS and OS are shown in Fig. 4.

Comparison between patients, who underwent salvage and elective surgery with CPB is summarized in Table 3. 5 patients received elective surgery and exhibited a

Table 3 Comparison between patients undergoing salvage and elective surgery

	Salvage surgery	**Elective surgery**	***p* value**
	***N*=3**	***N*=5**	
Age (year) [a]	61 [18–73]	49 [7–73]	0.54
Sex			0.46
Male	3	3	
Female	0	2	
ECOG scale			**0.01**
0–1	0	5	
2–4	3	0	
ASA grade			1.0
1–2	0	1	
3–4	3	4	
Operative time (mins)[a]	570 [400–600]	480 [360–660]	0.88
Blood loss (mL) [a]	3000 [1750–3400]	700 [200–1850]	**0.04**
Surgical margin			0.11
R0 resection	1	5	
R1 resection	2	0	
Extent of pulmonary resection			0.14
Pneumonectomy	3	1	
Lobectomy	0	2	
Wedge resection	0	1	
ICU stay (day)[a]	12 [4–24]	7 [3–18]	0.29
Postoperative hospital stay (day)[a]	24 [12–27]	16 [9–34]	0.54
Postoperative complication			0.07
No	0	2	
Grade 2	0	1	
Grade 3a	1	2	
Grade 5 (mortality)	2	0	

ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiology; ICU: intensive care unit; mins: minutes; mL: milliliter. [a] Values are expressed as median with [interquartile range]

significantly lower Eastern Cooperative Oncology Group (ECOG) scale ($p<0.01$) and blood loss ($p=0.04$). Though statistically insignificant, patients who received elective surgery versus salvage surgery presented with numerically shorter operative times (480 vs. 570 min, $p=0.88$), a higher number of R0 resections (5 vs. 1, $p=0.11$), shorter intensive care unit (ICU) stays (7 vs. 12 days, $p=0.29$), and shorter postoperative hospital stays (16 vs. 24 days, $p=0.54$).

Discussion

The surgical management of locally advanced thoracic cancer presents considerable challenges due to the proximity of vital structures such as the heart and major blood vessels. In the present series, we shared our experience and outcomes of extended resection procedures for both locally advanced lung and mediastinal cancer with the assistance of CPB. The present study demonstrates that patients with a better preoperative ECOG performance status undergoing elective surgery with CPB are more likely to have R0 resection, shorter operative times, lesser blood loss. In contrast, CPB use under salvage surgery was associated with higher morbimortality. Our findings emphasize the importance of discrete preoperative patient selection and surgical approaches with CPB.

Complete surgical resection remains the primary factor contributing to the survival in patients undergoing resection under CPB [13, 14]. For non-small cell lung cancer (NSCLC), stages up to pathology-proven T_4N_{0-1} may be acceptable for curative surgical resection [15, 16]. For thymic malignancies, radical resection is considered part of the multimodal treatment in patients of stage III and even stage IVa with pleural spread [17–19]. This treatment principles is also applicable to other rare types of locally advanced thoracic cancers, including mediastinal sarcoma [20], mediastinal teratoma [21], mediastinal large cell neuroendocrine cancer [22], pulmonary blastoma [23], pleomorphic lung cancer [24], and large cell neuroendocrine lung cancer [25], which were all also reported in our series. Regardless of the tumor histology, the extent of invasion of adjacent anatomical structures is the key determinant of surgical difficulty. CPB use to achieve en bloc resection has been successfully reported in tumors invading the SVC and RA with acceptable perioperative morbidity and mortality rates [4, 26–28]. CPB was utilized in our 8 patients with locally advanced thoracic tumors involving the SVC, atrium, main pulmonary artery, and ascending aorta. This highlighted the versatility of CPB in facilitating complete tumor resection in anatomically challenging cases. Additionally, surgical management of localized metachronous-NSCLC in pneumonectomized patients using extracorporeal life support has helped push the boundaries of patient operability thus extending survival for patients that could previously not be considered for surgery [29]. In brief, the adoption of CPB or extracorporeal life support may enable personalized treatment for a wide array of locally advanced chest malignancies [30]. Nevertheless, limited studies and the lack of consensus complicate the debate on the setting of obtaining extended resection for locally advanced lung and mediastinal cancers under CPB.

Proponents of CPB emphasize its role in enabling complete tumor resection and achieving negative surgical margins, which are crucial factors associated with improved long-term oncological outcomes. For example, a retrospective study by Ried et al. demonstrated that CPB-assisted extended resections for locally advanced thymic malignancies resulted in favorable survival outcomes, with a high rate of R0/R1 resection achieved [2]. Similarly, a systematic review by Muralidaran et al. concluded that CPB use was associated with improved overall survival and disease-free survival in patients undergoing extended resections for advanced lung cancer involving the mediastinum or great vessels [23]. Furthermore, Langer et al. [1] and Filippou et al. [5] supported that there is no inferiority in postoperative outcomes in CPB group compared with non-CPB group. However, CPB raise valid concerns regarding its associated risks and complications, including systemic inflammatory response, coagulopathy, end-organ dysfunction, and modest relationship with cancer progression [9]. In fact, controversy does exist in literature concerning the application of CPB for oncological interventions. No increase of distant metastases and tumor recurrence has been observed in systematic review by Muralidaran et al. [3]. In contrast, some authors hypothesize that increased intraoperative tumor cell dissemination promoted by the extracorporeal circulation could have been responsible for early relapse, as previously reported by other authors [31]. In a recent large case series, none of patients undergoing cardiac reconstruction with CPB support showed locoregional recurrence or distant metastasis within 6 months of the operation, thus, the authors concluded that evidence could not confirm the hypothesis of increased rate of early recurrence for tumors resected under CPB [8].

CPB itself is deemed to be a significant predictor of postoperative morbidity and mortality, particularly in cases involving extensive resections and prolonged CPB times [32, 33]. Considering the high-risk nature of such procedures, perioperative mortality ranging from 7 to 15% had been reported [6, 34]. The mortality rate in our series is relatively high (2/8, 25%), though both patients received salvage surgery. All the patients in the elective surgery group achieved at least 12 months of recurrence-free survival without lethal perioperative complications. These findings are consistent with the survival date found in literature [6–8, 10]. However, Byrne et al. [34] reported 43% of all CPB procedures to be performed for emergency situations. These data underlies the importance of CPB availability when surgery for advanced thoracic malignancies is being considered. Wiebe et al. also advised that pneumonectomy is associated with life-threatening complications [6].

Though patient selection criteria for CPB-assisted extended resections is crucial for favorable outcomes [11], the criteria remain unclear, leading to variability in practice patterns and institutional preferences. Current literature indicates decisions to operate are situational due to the variability of the disease entity, surgical capabilities, and high surgical risk. While CPB may be justified in cases where complete tumor resection cannot be achieved with conventional techniques, the decision to utilize CPB requires detailed multidisciplinary preoperative evaluation, including individual patient factors, tumor characteristics, and institutional expertise. This is echoed by our experience preferring that CPB application in elective surgery group in the present series exhibited a better prognosis.

It is important to acknowledge the limitations of our study, including its retrospective nature and relatively small sample size, which inherently limits firm statistical assessment. However, our data supports the feasibility of radical resection with CPB support for thoracic malignancies invading cardiovascular structures. Furthermore, the incidence of postoperative complications, including arrhythmias, pneumonia, and transient SVC syndrome, highlights the importance of close perioperative monitoring and management in optimizing patient outcomes.

Conclusions

In conclusion, while CPB can be considered a valuable surgical tool for locally advanced thoracic cancers, through patient selection, including lower ECOG scale and elective surgery, is necessary for CPB to confer its benefit. Future studies are warranted to validate our findings and to further elucidate the long-term survival benefits of CPB-assisted extended resection procedures in this patient population.

Abbreviations

CPB	Cardiopulmonary bypass
SVC	Superior vena cava
RA	Right atrium
CT	Computed tomographic

IQR	Interquartile range
RFS	Recurrence-free survival
OS	Overall survival
pCR	Pathological complete response
ECOG	Eastern Cooperative Oncology Group
ICU	Intensive care unit
NSCLC	Non-small cell lung cancer

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Author contributions
Conceptualization, Y-W Liu; methodology, validation, formal analysis, and investigation, J-W Huang, H-H Chiang, J-Y Lee, H-P Li, P-C Chang, and S-H Chou; writing—original draft preparation and writing—review and editing, J. Hsu, P-R Chou, and Y-W Liu; visualization, Y-W Liu; supervision, Y-W Liu. All authors have read and agreed to the published version of the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study complies with the standards of the Declaration of Helsinki and current ethical guidelines. The study protocol adhered to ethical guidelines and was approved by the institutional review board (KMUHIRB-E(II)-20230169). Informed consent was obtained from individual participant included in the study.

Consent for publication
Written informed consent for publication of their clinical details and clinical images were obtained from the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests
The authors declare no competing interests.

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