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Clinical Research

Pericardial Window Operation in Oncology Patients: Analysis of Long-Term Survival and Prognostic Factors

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Background: Pericardial effusion (PE) is a serious condition in cancer patients, primarily arising from malignant dissemination. Pericardial window formation is a surgical intervention for refractory PE. However, the long-term outcomes and factors associated with postoperative survival remain unclear.
Methods: We retrospectively analyzed data from 166 oncology patients who underwent pericardial window formation at Samsung Medical Center between 2011 and 2023. We analyzed survival and PE recurrence regarding surgical approach, cancer type, and cytopathological findings. To identify factors associated with survival, we utilized Cox proportional-hazards regression.
Results: All patients had tumors documented in accordance with the American Joint Committee on Cancer staging manual, including lung (61.4%), breast (9.6%), gastrointestinal (9.0%), hematologic (3.6%), and other cancers (16.4%). Surgical approaches included mini-thoracotomy (67.5%) and thoracoscopy (32.5%). Postsurgical cytopathology confirmed malignancy in 94 cases (56.6%). Over a median follow-up duration of 50.0 months, 142 deaths and 16 PE recurrences occurred. The 1-year overall and PE recurrence-free survival rates were 31.4% and 28.6%, respectively. One-year survival rates were significantly higher for thoracoscopy recipients (43.7% vs. 25.6%, p=0.031) and patients with negative cytopathology results (45.1% vs. 20.6%, p<0.001). No significant survival difference was observed between lung cancer and other types (p=0.129). Multivariate analysis identified New York Heart Association class, cancer stage, and cytopathology as independent prognostic factors.
Conclusion: This series is the largest to date concerning window formation among cancer patients with PE. Patients' long-term survival after surgery was generally unfavorable. However, cases with negative cytopathology or earlier tumor stage demonstrated comparatively high survival rates.

Keywords: Pericardial effusion, Pericardial window techniques, Neoplasms

Introduction

While primary tumors of the pericardium are rare, approximately 20% of patients with advanced malignancies develop cardiac or pericardial metastasis [1]. Malignancies may contribute to the development of pericardial effusion (PE) or cardiac tamponade. Symptomatic malignant PE (MPE) predominantly occurs in patients with lung, breast, and hematologic cancers, while benign PE is often idiopathic, infection-related, or secondary to radiation or cancer treatment drug therapy [2,3]. MPE can lead to life-threatening cardiac tamponade. Traditionally, MPE is associated with a very short median survival time, often 3 months or less [4,5]. However, appropriate treatment can relieve symptoms and may allow patients to continue systemic therapy for the primary malignancy.

Nevertheless, assessing the long-term benefits of surgical intervention remains difficult for clinicians, given the generally limited life expectancy of patients with malignant diseases. Additionally, no consensus exists regarding the

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optimal management approach, which should prioritize minimal morbidity and maximize long-term survival without incurring procedure-related mortality. Among cancer patients, pericardiocentesis (PCC) alone has been associated with a recurrence rate of 90% within 3 months [6]. The surgical creation of a pericardial window is theoretically superior to percutaneous methods in reducing the risk of PE recurrence; however, this benefit was not clearly demonstrated in a previous large cohort study [7]. Moreover, survival outcomes may differ based on a variety of clinical factors, including cancer type [8]. The specific factors influencing survival after pericardial window surgery, particularly in patients with cancer, have not been extensively studied.

Identifying a subset of patients who are particularly likely to benefit from pericardial window creation is essential for informing future cancer treatment strategies. Consequently, this study was conducted to assess survival and recurrence outcomes following pericardial surgery for PE in patients with cancer, utilizing data from a large registry. Additionally, this study examined various prognostic factors that may be useful in clinical decision-making, including the type of cancer, the surgical technique employed, and the cytopathological confirmation of malignancy within the PE.

Methods

Study population

In this retrospective single-center observational study, we reviewed the medical records of all cases involving pericardial window formation. Between February 2011 and February 2023, we identified a total of 172 patients who had undergone an initial pericardial window operation. Patients under 18 years old (n=1), those who underwent concurrent thoracic procedures (n=1), and those with other etiologies of PE such as infection (n=4) were excluded (Fig. 1). Ultimately, 166 consecutive cancer patients with PE were included. The Institutional Review Board of Samsung Medical Center granted approval for this study (SMC 2023-05-016-001; approval date: May 18, 2023) and waived the requirement for informed consent from individual patients, given the minimal risk associated with this retrospective research.

Surgical procedures and pathologic analysis

The pericardial window formation was conducted via either open thoracotomy or video-assisted thoracoscopic surgery (VATS). Typically, mini-thoracotomy was the preferred method when the patient exhibited low oxygen saturation or unstable blood pressure, which made one-lung ventilation challenging. For mini-thoracotomy, a left-sided approach was used, entering through the fourth or fifth intercostal space (ICS) with a submammary incision of 5 to 7 cm. After identification of the phrenic nerve, an anterolateral pericardial window 3 to 4 cm in diameter was created over the left ventricle. When tamponade was found to be caused by fluid collection in the posterior region, a posterior pericardial window was created below the phrenic nerve. A chest tube was placed through a separate incision.

For VATS, all patients were intubated with a double-lumen endotracheal tube. A left-sided approach and semi-lateral positioning were preferred for VATS procedures. A 10-mm port was established in the second or third ICS along the anterior axillary line. A second port was placed in the sixth ICS along the mid-axillary line, and a third port was placed in the eighth ICS along the posterior axillary line. Through the anterior port, a camera was introduced to al-

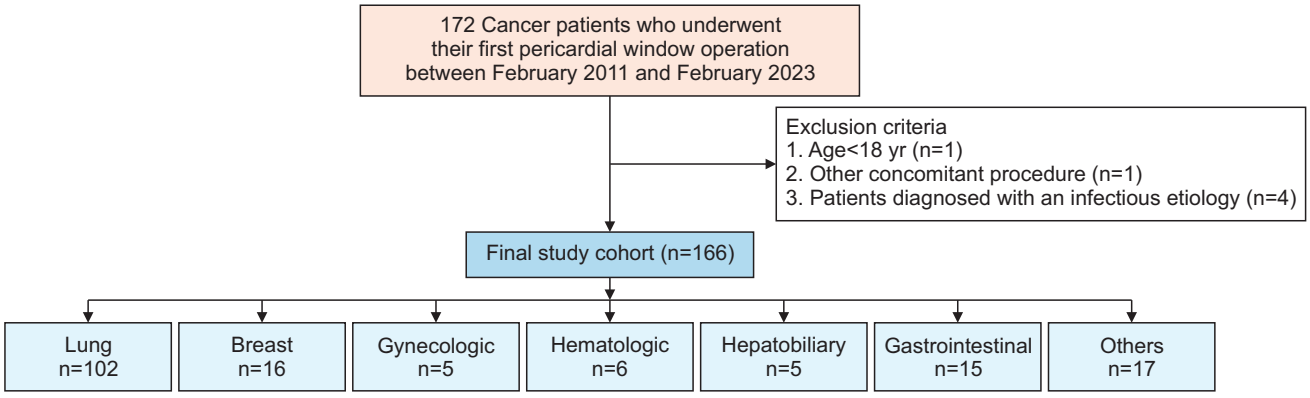

Fig. 1. Flow diagram of patients included in the study.

low for inspection of the pleural space and the pericardial surface. Using a surgical grasper introduced through the posterior port, the pericardium was secured and then incised with an electrocautery hook or thoracoscopic scissors inserted through one of the posterior ports. Following the initial incision into the pericardium, the heart was carefully examined to ensure a safe distance from the cautery and sharp instruments. A pericardial window approximately 3 cm in diameter was then created. Subsequently, a chest tube was inserted into the pericardial space through this window.

Following surgery, pathologists examined pericardial fluid and tissue biopsy samples for cytopathologic evaluation using light microscopy. The presence of malignant cells in the PE or tissue was categorized as either positive or negative, indicating the presence or absence of malignancy, respectively.

Study endpoints

The primary outcome of this study was overall survival (OS), which refers to the duration from the date of surgery to the date of death or the last follow-up for censored patients. Recurrence-free survival (RFS) was characterized as the period from the date of surgery to the date of PE recurrence or death. Recurrent PE was identified as a situation requiring further intervention, such as PCC or a repeat window operation following the initial surgical procedure.

Statistical analysis

For normally distributed continuous variables, values were reported as mean±standard deviation; these variables were compared using the 2-sample Student t-test. For non-normally distributed continuous variables, values were presented as median and interquartile range (IQR); these were compared using the Mann-Whitney U test. Survival analysis was performed using Kaplan-Meier survival curves and the log-rank test. To identify potential risk factors influencing long-term OS, the Cox proportional hazards model was employed for multivariate survival analysis. The multivariable model was adjusted for variables that had p-values of less than 0.2 in the univariable analyses and/or for variables with clinical importance. For all variables, p-values of less than 0.05 were considered to indicate statistical significance. Statistical analyses were conducted using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA) and R ver. 4.3.0 (The R Foundation, Vienna, Austria).

Results

Baseline characteristics

Among the 166 participants, 81 (48.8%) were male, with a median age of 60 years (IQR, 51–67 years). Echocardiography revealed a mean ejection fraction of 61.6%. Tamponade physiology was observed in 81 patients (48.8%). The median Sequential Organ Failure Assessment score was 1 (IQR, 0–2), with only 8 patients (4.8%) requiring inotropic and vasopressor medication. Based on the New York Heart Association (NYHA) classification system, 42.8% of the patients were categorized as class III and 5.4% as class IV. Elevated levels of N-terminal pro–B-type natriuretic peptide (>1,000 pg/mL) were detected in 21.7% of the patients. A mini-thoracotomy approach was employed in 112 patients (67.5%), while VATS was utilized in 54 patients (32.5%). Detailed patient characteristics are presented in Table 1.

Cancer type and stage

All patients had a cancer diagnosis in accordance with the eighth edition of the American Joint Committee on Cancer staging manual, with lymphoma cases categorized using the Ann Arbor staging system. Among cases with clinical suspicion of MPE, only 19.9% involved cytologic confirmation prior to surgery. The most common primary malignancy was lung cancer, accounting for 61.4% of cases, followed by breast cancer at 9.6%, gastrointestinal cancers at 9.0%, hematologic malignancies at 3.6%, gynecologic cancers at 3.0%, and hepatobiliary cancers also at 3.0%. Other types of malignancies accounted for 10.2% of study patients (Table 2). The distribution of clinical stages was as follows: stage IV (70.5%), stage III (15.7%), stage II (10.2%), and stage I (3.0%).

OS and recurrence

Over the follow-up period (median, 50.0 months; IQR, 38.6–81.0 months), 142 patients died, and 16 experienced PE recurrence necessitating re-intervention. No procedure-related deaths occurred. In the overall population, the 1-year OS rate was 31.4%, while the 1-year RFS rate was 28.6% (Fig. 2). Of the 51 patients who survived for 1 year after surgery, 45 (88.2%) remained free from PE recurrence, whereas only 6 (11.8%) required re-intervention.

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Table 1. Baseline characteristics (N=166)

Characteristic	Value
Male sex	81 (48.8)
Age (yr)	60 (51–67)
Height (cm)	162.4±8.2
Body weight (kg)	61.1±16.4
Body mass index (kg/m^2)	23.2±4.1
Physical performance	
ECOG 0–2	136 (81.9)
ECOG 3–4	30 (18.1)
Underlying medical disease	
Hypertension	59 (35.5)
Diabetes mellitus	25 (15.1)
Tuberculosis	16 (9.6)
Receiving dialysis	3 (1.8)
Atrial fibrillation	14 (8.4)
Previous PCI	5 (3.0)
Previous cardiac surgery	4 (2.4)
Echocardiography	
Left ventricular ejection fraction (%)	61.6±8.7
Tamponade physiology	81 (48.8)
Preoperative pericardiocentesis (≤60 day)	48 (28.9)
Shock category	
Systolic blood pressure <80 mm Hg	2 (1.2)
Heart rate >100 bpm	73 (44.0)
Use of inotropes or vasopressors	8 (4.8)
SOFA score	1 (0–2)
Dyspnea (NYHA class)	
I	14 (8.4)
II	72 (43.4)
III	71 (42.8)
IV	9 (5.4)
NT-pro BNP (pg/mL) >1,000	36 (21.7)
Surgical approach	
Mini-thoracotomy	112 (67.5)
Video-assisted thoracoscopic surgery	54 (32.5)

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
ECOG, Eastern Cooperative Oncology Group score; PCI, percutaneous coronary intervention; SOFA, sequential organ failure assessment; NYHA, New York Heart Association; NT-pro BNP, N-terminal pro–B-type natriuretic peptide.

Outcomes by surgical approach

The operative outcomes, stratified by the type of surgical approach, are presented in Supplementary Table 1. No significant differences were observed in the duration of the operation (mini-thoracotomy: 54.8±36.6 minutes versus VATS: 59.2±28.7 minutes; p=0.432), the intraoperative drainage volume (mini-thoracotomy: 443.3±245.2 mL versus VATS: 399.1±263.8 mL; p=0.290), or the length of hospital stay (mini-thoracotomy: 12.9±13.1 days versus VATS: 10.5±7.1 days; p=0.209).

Table 2. Cancer type, stage, and preoperative cancer treatment among study participants (N=166)

Variable	No. (%)
Preoperative confirmation of MPE	
Confirmed	33 (19.9)
Not confirmed	133 (80.1)
Primary cancer type	
Lung	102 (61.4)
Breast	16 (9.6)
Gynecologic	5 (3.0)
Hematologic	6 (3.6)
Hepatobiliary	5 (3.0)
Gastrointestinal	15 (9.0)
Others	17 (10.2)
Cancer stage[a)]	
I	5 (3.0)
II	17 (10.2)
III	26 (15.7)
IV	117 (70.5)
Metastasis site	
Pericardium	28 (16.9)
Other organs	116 (69.9)
Cancer treatment before window operation	
Cancer surgery	70 (42.2)
Chemotherapy	132 (79.5)
Radiotherapy (thoracic)	37 (22.2)

MPE, malignant pericardial effusion.
[a)]One patient with acute myeloid leukemia whose stage could not be numerically expressed was excluded.

The 1-year OS rate was significantly higher in the VATS group than in the mini-thoracotomy group (43.7% versus 25.6%, p=0.031) (Fig. 3A). However, the 1-year RFS rates did not differ significantly between the mini-thoracotomy and VATS groups (38.7% versus 23.7%, p=0.119) (Fig. 3B). Seven patients who underwent mini-thoracotomy and 5 patients treated with VATS required revision surgery due to recurrent PE.

Outcomes by cancer type, previous pericardiocentesis, and surgical cytopathology

Survival and recurrence outcomes, stratified by the type of primary malignancy, are presented in Supplementary Table 2. The 1-year survival rates for various cancer categories were as follows: lung cancer (29.4%), breast cancer (31.3%), gynecologic cancer (0%), hematologic cancer (60.0%), hepatobiliary cancer (60.0%), gastrointestinal cancer (24.0%), and other cancers (39.7%). When lung cancer (the most common type) was compared to other cancers, no significant difference in survival was observed (p=0.129) (Supplementary Fig. 1). OS curves for each cancer type are

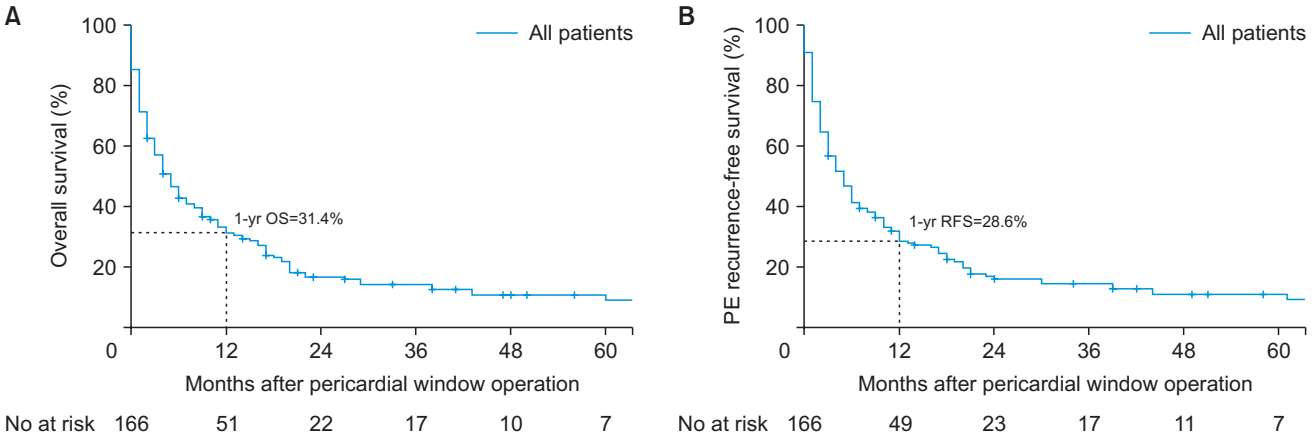

Fig. 2. (A, B) Overall survival (OS) and pericardial effusion (PE) recurrence-free survival (RFS) for all patients.

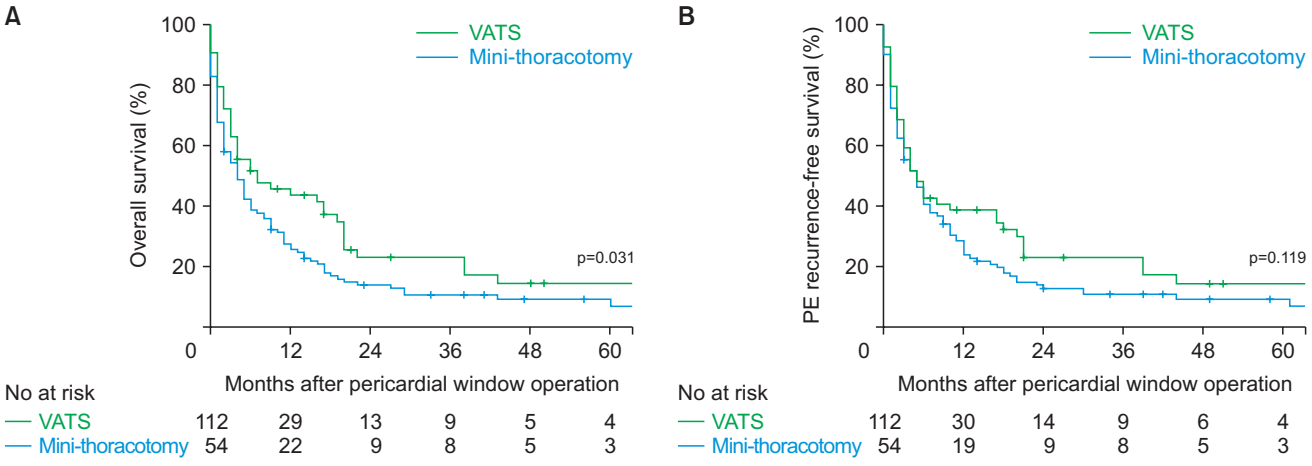

Fig. 3. (A) Overall survival according to surgical approach (mini-thoracotomy vs. video-assisted thoracoscopic surgery [VATS]). (B) Pericardial effusion (PE) recurrence-free survival according to surgical approach (mini-thoracotomy vs. VATS).

presented in Supplementary Fig. 2, while adjusted hazard ratios (aHRs) comparing lung cancer to each of the other cancer types are provided in Supplementary Table 3. When comparing RFS between the 48 patients who received PCC prior to the window operation and those who did not, no statistically significant difference was found (p=0.118) (Supplementary Fig. 3).

Additional analysis focused on the influence of cytopathologic outcomes on patient survival. Positive MPE findings were established in 94 patients (56.6%). The 1-year OS rate was significantly better among patients with negative surgical cytopathology compared to those with positive findings (45.1% versus 20.6%, p<0.001) (Fig. 4A). Similarly, the 1-year RFS rate was significantly higher in the group with negative cytopathology than among those with positive results (45.3% versus 15.7%, p<0.001) (Fig. 4B). Among the 16 patients who experienced recurrent PE, 12 (75%) displayed positive cytopathology for cancer cells, whereas 4 (25%) had negative cytopathology.

Multivariate Cox model of prognostic factors for overall survival

In the multivariate model, age, sex, and previous PCC did not significantly impact OS (Fig. 5). However, certain baseline characteristics, such as an NYHA categorization of class IV, were associated with reduced OS (versus class I: aHR, 3.24; 95% confidence interval [CI], 1.13–9.26; p=0.028). Regarding surgical approach, the use of VATS was associated with superior OS (versus mini-thoracotomy: aHR, 0.66; 95% CI, 0.44–0.97; p=0.033). As anticipated, earlier cancer stage (non-stage IV) was independently associated with more favorable OS (versus stage IV: aHR, 0.54; 95% CI, 0.35–0.84; p=0.006). Even after adjusting for

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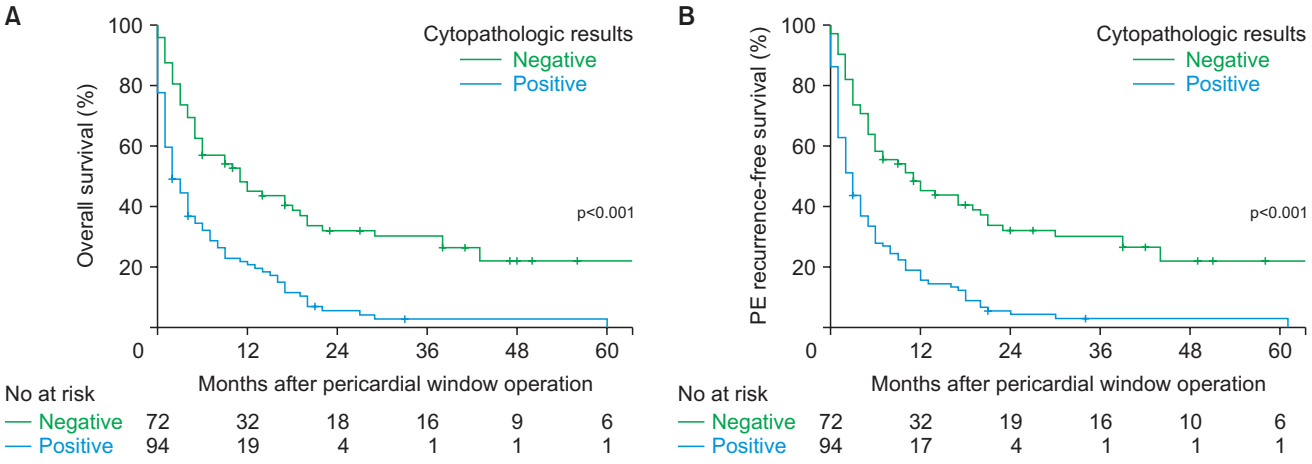

Fig. 4. (A) Overall survival according to cytopathologic results. (B) Pericardial effusion (PE) recurrence-free survival according to cytopathologic results.

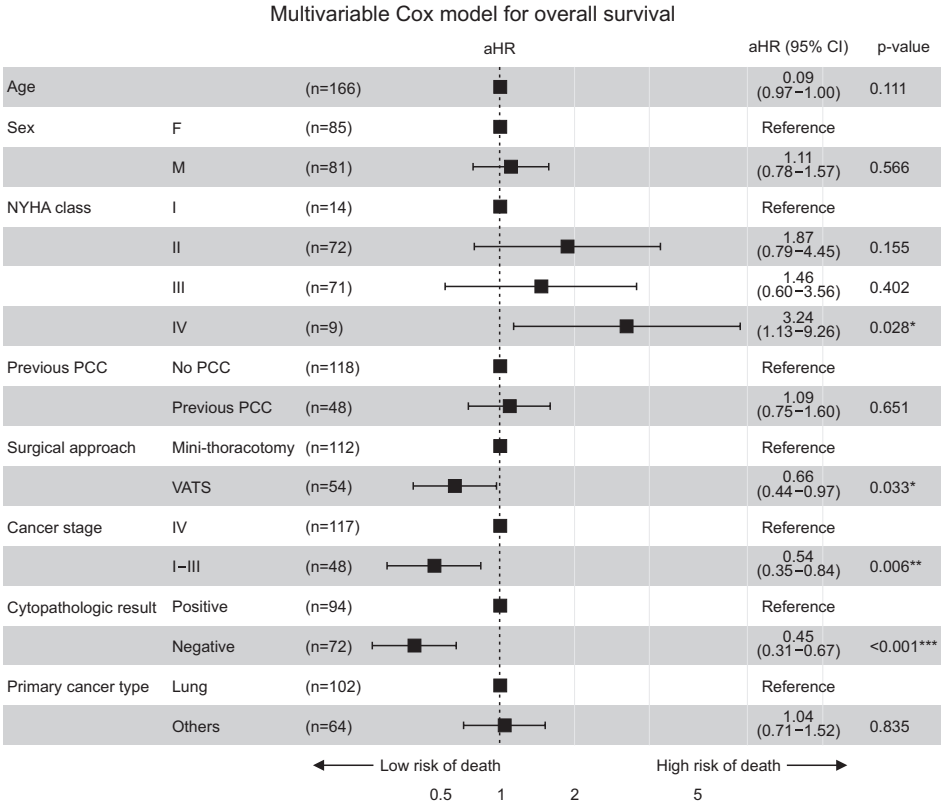

Fig. 5. Forest plot presenting the results of multivariate survival analysis. aHR, adjusted hazard ratio; CI, confidence interval; F, female; M, male; NYHA, New York Heart Association; PCC, pericardiocentesis; VATS, video-assisted thoracoscopic surgery. *p<0.05. **p<0.01. ***p<0.001.

these variables, negative surgical cytopathology findings remained significantly associated with superior OS (aHR, 0.45; 95% CI, 0.31–0.67; p<0.001). The type of cancer did not emerge as a significant prognostic factor following window formation in cancer patients with PE (lung cancer versus other types: aHR, 1.04; 95% CI, 0.71–1.52; p=0.835).

Discussion

In this study, we comprehensively examined clinical characteristics, surgical outcomes, and prognostic factors among cancer patients who underwent pericardial window formation for PE. To our knowledge, this research represents the largest sample to date for an investigation of pericardial window formation in cancer patients, including

a total of 166 patients with various underlying primary cancers. Our study offers valuable insights into the impact of surgical approach on survival, the influence of primary cancer type on outcomes, and the importance of negative cytopathological results as an indicator of prognosis.

An intriguing finding of this study was the low recurrence rate observed following window operation among cancer patients with PE. The analysis revealed that OS and RFS rates were remarkably similar in the overall population, indicating that recurrence of PE necessitating drainage is uncommon among survivors. Only 9.6% of patients required re-intervention due to PE recurrence. This finding aligns with previous studies that have documented the long-term effectiveness of window formation [4,9,10]. Our research contributes to the growing body of evidence supporting the durability of this procedure as a therapeutic option for PE, potentially lessening the burden of recurrent effusion.

Notably, while VATS was associated with better survival than mini-thoracotomy, no significant difference was observed in recurrence rates between these surgical approaches. The favorable survival observed in the VATS group could be due to potential selection bias, wherein patients with medical conditions associated with poor prognosis (for example, tamponade physiology) are more frequently treated with thoracotomy, as previously reported [1,11]. Nevertheless, it is important to recognize that both techniques are comparable in preventing PE recurrence. This finding implies that the choice of surgical approach should be tailored based on the medical condition of the patient, irrespective of concerns about recurrence.

A unique feature of our study is the discovery of negative surgical cytopathology as a robust and independent favorable prognostic factor among cancer patients with PE who underwent window formation. Patients with negative cytopathologic findings exhibited significantly better 1-year OS and RFS rates. Prior research in this field has yielded inconsistent findings; some studies have reported no association, while others have noted poor clinical outcomes in patients with MPE compared to those with benign PE [12-15]. As the most extensive study to date on the pericardial window procedure in cancer patients, our findings not only contribute to resolving the debate over the clinical relevance of cytopathology in advanced cancer stages but also suggest that cytopathology results should be considered in future treatment planning. Despite the poor prognosis typically associated with MPE, appropriate management enables patients to continue essential systemic treatments [16,17]. Therefore, it is imperative that cardiothoracic surgeons recognize the importance of cytopathologic examination and communicate the results with referring physicians. By doing so, aggressive cancer treatment strategies can be implemented following pericardial window formation in carefully selected patients.

We also examined the survival outcomes of the study population following window operation based on primary cancer type [4,8,9,18]. While lung cancer was the most common primary malignancy, our analysis did not reveal a significant difference in survival rates across cancer types. Consequently, we might infer that the beneficial influence of window formation on survival appears to be consistent across primary cancers. Nevertheless, we noted that certain cancer types, such as hematological malignancies, exhibited encouraging survival outcomes following window formation, whereas others, including gynecological cancers, demonstrated extremely poor OS. Similar positive results after window formation in patients with hematologic malignancies were reported by Celik et al. [9] and Wagner et al. [19]. However, these observations stem from a very limited number of patients within each cancer category, which complicates the task of drawing conclusions about the specific impact of window formation on individual cancer types. Future studies with larger cohorts will be essential to yield more definitive insights.

Our study had several limitations that warrant acknowledgment. First, the retrospective design may have introduced biases and confounders, potentially influencing the outcomes. Notably, differences in baseline characteristics were present between the patients who underwent VATS and those who received thoracotomy. The fact that thoracotomy was chosen when one-lung ventilation was not available was intended to provide context for the choice of procedure. However, we did not directly investigate the availability of one-lung ventilation as a contributing factor, nor did we evaluate its potential role as a confounding variable. Second, our study population initially consisted of patients with clinically suspected MPE. This selection criterion may raise questions about the authenticity of the cases as definitive MPE. The literature suggests that the sensitivities of pericardial fluid analysis and biopsy for detecting malignant cells are approximately 75% and 65%, respectively. This indicates that negative results do not conclusively exclude malignancy in patients with cancer [15]. Furthermore, the varied mechanisms by which PE can develop in cancer patients further complicate the diagnostic process [20]. Consequently, the decision to define our study cohort based on clinical suspicion of MPE may be justifiable, as it allows for a more comprehensive evaluation

of the outcomes of window operation in oncology patients.

In conclusion, our study represents the largest series to date on pericardial window formation for cancer patients with PE. Although the low recurrence rate highlights the clinical efficacy of this procedure, the long-term survival of cancer patients who underwent window formation was not favorable. However, comparatively good OS was observed in cases where malignant cells were absent from the pericardium or pericardial fluid, as well as for relatively early-stage cancers. Additional research is needed to define appropriate indications for pericardial window formation. Further research on the effect of window formation in advanced cancer patients is needed and could potentially provide valuable insights for clinical decision-making regarding this procedure.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary materials

Supplementary materials can be found via https://doi.org/10.5090/jcs.23.113. **Supplementary Table 1**. Operative outcomes by surgical approach. **Supplementary Table 2**. Recurrence and survival rate by cancer type. **Supplementary Table 3**. Hazard ratio by cancer type. **Supplementary Fig. 1**. Overall survival according to primary cancer type (lung cancer vs. others). **Supplementary Fig. 2**. Overall survival of patients undergoing pericardial window operation across 7 cancer type categories. **Supplementary Fig. 3**. Recurrence-free survival (RFS) according to previous pericardiocentesis (PCC).

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