Original Article

Comparison of outcomes of surgical and other invasive treatment modalities for malignant pleural effusion in patients with pleural carcinomatosis

Joshua Schramm[1], Elina Eslauer[2], Sameer Hammoudeh[3], Sebastian Stange[3], Zsolt Sziklavari[3]

[1]Department of General and Visceral Surgery, REGIOMED Klinikum Lichtenfels, Lichtenfels, Germany; [2]Department of Anaesthesiology, University Medical Center Augsburg, Augsburg, Germany; [3]Department of Thoracic Surgery, REGIOMED Klinikum Coburg, Coburg, Germany

Contributions: (I) Conception and design: J Schramm, Z Sziklavari; (II) Administrative support: E Eslauer, S Hammoudeh; (III) Provision of study materials or patients: Z Sziklavari; (IV) Collection and assembly of data: E Eslauer; (V) Data analysis and interpretation: J Schramm, S Stange; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Zsolt Sziklavari, MD, PhD. Department of Thoracic Surgery, REGIOMED Klinikum Coburg, Ketschendorfer Straße 33, 96450 Coburg, Germany. Email: sziklavari_zsolt@yahoo.com.

Background: Treatment modalities for malignant pleural effusion (MPE) are diverse. The objectives were to analyze actual clinical data from patients with MPE and pleural carcinomatosis and to compare the outcomes of different treatment modalities with regard to effectiveness, survival, morbidity, and mortality as well as the duration of hospitalization.

Methods: Patients with pathologically proven pleural carcinomatosis or MPE from 2018 to 2020 were included in this retrospective-observational study with additional questionnaires. We identified four treatment modalities: (I) video-assisted thoracic surgery with pleurodesis (VATS, mechanical/chemical); (II) VATS with pleurodesis combined with indwelling pleural catheter (IPC) placement; (III) VATS (without pleurodesis) combined with IPC placement; and (IV) management with IPC placement alone.

Results: We enrolled 91 patients aged 38–90 years who were treated by either VATS-pleurodesis (N=22), VATS-IPC placement (N=21), a combination of VATS with pleurodesis and IPC placement (N=22), or IPC placement alone (N=26). The mean survival time was 138.3 days. No significant differences were detected among treatment groups regarding the outcome of pleurodesis failure, either initially or later. Patients in the VATS-pleurodesis with IPC group experienced significantly more complications than those in the other treatment modality groups [odds ratio (OR): 3.288, P=0.026]. However, no statistically significant differences were observed regarding the type of adverse event and survival. Hypoalbuminemia, systemic therapy, and successful pleurodesis (P=0.008; P=0.011; P=0.044, respectively) were significantly correlated with survival. In multiple linear regression, hypoalbuminemia persisted as an independent predictor of survival (P=0.031). The type of intervention showed significant differences regarding the duration of hospitalization (P=0.017). IPC placement alone shortened the mean total hospitalization time by 7.9, 5.9, and 7.0 days compared to VATS-pleurodesis (P≤0.001), VATS-IPC placement (P=0.004), and VATS-pleurodesis with IPC placement (P≤0.001), respectively.

Conclusions: The survival time was very short, and each treatment group had pros and cons. Therefore, decisions should be made on a case-by-case basis. The use of an IPC, even if the lung is not trapped, can significantly reduce the length of hospital stay. VATS is needed when histology is needed. The ideal method for treating recurrent MPE should be simple, effective, and inexpensive, with minimal disturbance to the patient.

Keywords: Malignant pleural effusion (MPE); thoracic; surgery; pleurodesis; indwelling catheter

Submitted Aug 14, 2023. Accepted for publication Nov 24, 2023. Published online Feb 23 2024.
doi: 10.21037/jtd-23-1247
View this article at: https://dx.doi.org/10.21037/jtd-23-1247

Introduction

Background

In addition to cardiovascular diseases, malignant neoplasia is the most common cause of death in Germany. Almost all advanced-stage malignant tumors can affect the pleural cavity, resulting in malignant pleural effusion (MPE). As cancer incidence rises and overall survival improves, the prevalence of MPE is expected to increase (1). The annual incidence of MPE approaches 150,000 cases in the United States and 100,000 cases in Europe (2,3). Effusions usually signify an advanced stage of malignancy, with an overall survival of approximately three to twelve months after initial diagnosis (4). Frequent symptoms in most patients with MPE include dyspnea, cough, and chest pain. The symptoms can be treated in different ways: conservative, interventional or surgical methods. The surgical procedures are diverse.

Rationale and knowledge gap

The best therapy for MPE is still controversial and is often discussed. Here, we report our latest experiences.

Highlight box

Key findings
- Our patients were treated by either video-assisted thoracic surgery (VATS)-pleurodesis, VATS-indwelling catheter, a combination of VATS-pleurodesis and indwelling catheter, or catheter placement alone. The techniques achieved the same pleurodesis success, but VATS-pleurodesis with a catheter experienced more complications than other techniques. No differences were observed regarding the type of adverse event and survival. Systemic therapy and successful pleurodesis were significantly correlated with survival. Hypoalbuminemia persisted as an independent predictor of survival. Catheter placement alone shortened the hospitalization compared to other procedures.

What is known and what is new?
- Effusions signify an advanced stage of malignancy with a poor prognosis. The symptoms can be treated in different ways: conservative-interventional or surgical methods.
- The surgical procedures are controversial and discussed.

What is the implication, and what should change now?
- Each treatment group had pros and cons. Decisions should be made on a case-by-case basis. The use of catheters can significantly reduce hospitalization. The ideal method for treating recurrent malignant pleural effusion should be simple, effective, and with minimal disturbance to the patient.

Objective

The present study aimed to analyze the clinical data of patients with MPE and pleural carcinomatosis hospitalized at the REGIOMED Clinics and to evaluate and compare outcomes of different treatment modalities concerning effectiveness, survival, morbidity, and mortality as well as the duration of hospital stay. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1247/rc).

Methods

Adult patients with symptomatic MPE due to pleural carcinomatosis hospitalized at any of the REGIOMED Clinics facilities in Germany (Southern Thuringia and Northern Bavaria) from January 2018 to December 2020 were included in this retrospective observational chart-based study. Follow-up was completed in December 2020. Additionally, questionnaires were sent to the respective oncologists or primary care physicians if important information was missing. We also conducted an additional follow-up at 54 months (range, 39–69 months) concerning long-term survival. All of our patients underwent surgical treatment. Each specialist/surgeon (n=4) was allowed to decide how the operation would occur. Nonetheless, in the case of an entirely trapped lung, no pleurodesis was performed. Patients who did not meet these criteria, patients with nonmalignant effusions or patients who received interventions other than those of interest were excluded from the analysis.

The four treatment options were as follows:

(I) Video-assisted thoracic surgery (VATS) with pleurodesis (mechanically by pleurectomy or chemically by talc);
(II) VATS with pleurodesis combined with indwelling pleural catheter (IPC) placement [PleurX™ catheter system] (Becton, Dickinson and Company, Franklin Lakes, United States);
(III) VATS without pleurodesis and IPC placement;
(IV) Management with IPC placement alone.

The intervention types were compared regarding survival and length of hospital stay (LOS) as the primary outcomes. Additionally, secondary endpoints assessed the effectiveness of treatment and associated morbidity and adverse events (AEs).

The effectiveness of the different treatment modalities was evaluated based on clinical, sonographic, and radiological investigations. Treatment was deemed successful if the patient had symptom relief, an acceptable X-ray and if no further intervention was performed. Intervention failure was defined as recurrent or persistent symptoms related to pleural effusion or fluid shown on chest imaging (approximately ≥500 mL) with/without thoracocentesis. Survival times were calculated and assessed from the time of intervention until death or, for patients who were still alive at the end of data entry. Morbidity included all complications and AEs occurring after and related to the intervention. Any hospital admission involving a stay of one or more days was included; one day referred to a hospital stay past midnight. Patients with day-case procedures (e.g., chemotherapy) were excluded. Hospitalization times were calculated and assessed from admission until discharge or in-hospital death.

Initial successful therapy was defined as no symptoms related to MPE or no fluid shown on radiological images of the chest at admission. Late pleurodesis failure was defined as either recurrence of symptoms related to MPE or fluid detected on chest imaging.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the International Ethics Board of the Medical School REGIOMED Coburg which approved this type of research based on §2 of the statutes (sign STWA/MICA, March 18, 2022, approval ID: 2022-14), and individual consent for this retrospective analysis was waived.

Data collection

Data on all hospital admissions were collected from electronic databases and case records. Sociodemographic and medical information, including age and sex, baseline patient characteristics, date of death or the most recent date on which the patient was confirmed to be alive, tumor entity, comorbid conditions, duration of hospital stay, readmissions, need for further interventions, clinical findings, complications, diagnostic approach, date and intervention modalities, was extracted from case records. In addition, data on physical examination findings at admission, serum albumin levels, receipt of systemic therapy, and histopathological results were obtained. Initially, a list of record numbers of patients diagnosed with MPE or pleural carcinomatosis was generated. Subsequently, all patients were confirmed to meet the inclusion criteria, and data were collected and analyzed. Medical records with important missing information were excluded from the analysis.

Statistical analysis

Statistical analysis and evaluation were performed in a completely anonymous fashion. The data were explored and analyzed using IBM SPSS Statistics for Macintosh, Version 28.0.1.1 (IBM Corp., Armonk, NY, USA). Normality testing was performed analytically by the Shapiro-Wilk test and graphically by histograms and Q-Q plots. Baseline characteristics of patients from the dataset are presented as frequencies (N) and percentages (%) for categorical variables and as means and standard deviations or medians and interquartile ranges for continuous variables according to the distribution of data. Descriptive and frequency statistics were obtained for the variables of interest. The chi-square (χ^2) test was used to determine differences between groups regarding categorical variables. To determine differences between groups for continuous variables with a normal distribution, one-way ANOVA or independent samples *t*-test was used. In contrast, the Kruskal-Wallis or Mann-Whitney *U* tests were used for continuous variables with a non-normal distribution.

Overall survival was calculated from the date of surgery to the date of death. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test for dichotomous variables. In contrast, Cox regression analysis was performed for continuous or ordinal variables. The Pearson correlation coefficient (r) was used to identify the correlations of variables of interest with survival time. Subsequently, multiple linear regression was used to determine significant independent predictors of survival from the final model including the significant variables. The level of statistical significance was set at a P value <0.05 for all comparisons.

Results

The study included 91 patients who completed follow-up. The average follow-up time was 18.5 months. The sample had an almost equal sex distribution; 48 patients were male (52.7%), and 43 were female (47.3%). The mean age of the total group of patients at the time of intervention was 66.83 years, ranging from 38 to 90 years. The lung was the most common organ of tumor origin (45.1%), followed by malignancies of the breast (23.1%), genitourinary tract (13.2%), and gastrointestinal tract (7.7%). Two patients (2.2%) had cancer of unknown primary origin, and only one patient had mesothelioma. All parameters describing the main characteristics of the study population are presented

Table 1 Patient characteristics of treatment groups

Variables	Value (N=91)
Age at intervention (years)	65.83±12.33 [38–90]
Gender	
Male	48 (52.7)
Female	43 (47.3)
Comorbidities	
Cardiovascular	65 (71.4)
Renal	21 (23.1)
Primary malignancy	
Lung	41 (45.1)
Breast	21 (23.1)
Genitourinary	12 (13.2)
Upper gastrointestinal	5 (5.5)
Lower gastrointestinal	2 (2.2)
Hematological	1 (1.1)
Liver	1 (1.1)
Mesothelioma	1 (1.1)
Other	5 (5.5)
Unknown (CUP)	2 (2.2)
Treatment group	
VATS + pleurodesis	22 (24.2)
VATS + IPC	21 (23.1)
VATS + pleurodesis + IPC	22 (24.2)
IPC	26 (28.6)
Systemic therapy	74 (81.3)
Hypoalbuminemia	43 (47.2)

Data are presented as mean ± standard deviation with [range] or n (%). Hypoalbuminemia was defined as serum albumin value below 35 g/L. CUP, cancer of unknown primary; VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

in *Table 1*. Since this was a retrospective study, whether the treatment groups were comparable regarding essential patient characteristics was investigated. The tests showed homogeneity among the parameters (P>0.05). The VATS with pleurodesis group comprised 22 patients (12 men). The VATS-IPC group consisted of 21 patients (13 men). Another 22 patients (12 men) were treated by combining VATS with pleurodesis and IPC placement. The last group was managed by IPC placement alone and comprised 26 patients, including 15 females (57.7%). The demographics and patient characteristics of the treatment groups are shown in *Table 2*.

Treatment outcomes

Eighty-three patients (91.2%) had initial success after the intervention (*Table 3*). Treatment was initially successful in 19 patients (86.4%) in the VATS with pleurodesis group. The same applied to the VATS-IPC group, with 18 (85.7%) patients with initial treatment success. Furthermore, similar initial success rates were observed in the VATS pleurodesis-IPC group and IPC placement alone group, with 21 patients (95.5%) and 25 patients (96.2%), respectively. Conversely, eight patients (8.8%) did not initially respond to the treatment they received. There was, however, no statistically significant difference among the treatment groups regarding initial pleurodesis failure (P=0.436). Also included in *Table 3* are the late treatment outcome success rates for all 69 patients (75.8%), the late failure rates for all 22 patients (24.2%), and the late success and failure rates for the respective treatment groups. Similarly, no statistically significant difference was observed between treatment groups regarding late pleurodesis failure (P=0.068).

Morbidity and AEs

An overview of the number and rate of AEs within treatment groups is provided in *Table 4*. Twenty-one AEs (23.1%) were recorded among all 91 patients. Four patients (18.2%) experienced an AE in the VATS with pleurodesis group. Five patients treated with VATS and IPC placement had complications (23.8%). The VATS with pleurodesis and IPC placement group had nine AEs (40.9%). Three patients who underwent IPC placement experienced complications (11.5%). Details of AEs are shown in *Table 5*. The most common complications after intervention were IPC dysfunction (N=5, 23.8%; one case in the VATS-IPC group, two cases in the VATS with pleurodesis and IPC placement group, and two cases in the IPC placement alone group), followed by pneumonia (N=3, 14.3%; all occurring in the VATS with pleurodesis and IPC placement group) and respiratory insufficiency (N=3, 14.3%; two cases in the VATS with pleurodesis group and one case in the VATS with pleurodesis and IPC placement group). There was a statistically significant difference among the groups

Table 2 Demographics and patient characteristics within treatment groups

Variables	Total (N=91)	Intervention				P†
		VATS + pleurodesis (N=22)	VATS + IPC (N=21)	VATS + pleurodesis + IPC (N=22)	IPC (N=26)	
Gender						0.593
Male	48	12 (54.5)	13 (61.9)	12 (54.5)	11 (42.3)	
Female	43	10 (45.5)	8 (38.1)	10 (45.5)	15 (57.7)	
Age at intervention (years)		66.94±12.08 [38–84]	68.88±10.23 [52–85]	62.20±13.46 [38–87]	65.48±12.95 [47–90]	0.427
Primary malignancy						0.820
Lung	41	11 (50.0)	12 (57.1)	8 (36.4)	10 (38.5)	
Breast	21	4 (18.2)	4 (19.0)	6 (27.3)	7 (26.9)	
Genitourinary	12	2 (9.1)	1 (4.8)	4 (18.2)	5 (19.2)	
Upper gastrointestinal	5	1 (4.5)	2 (9.5)	2 (9.1)	0	
Lower gastrointestinal	2	1 (4.5)	0	1 (4.5)	0	
Hematological	1	0	1 (4.8)	0	0	
Liver	1	1 (4.5)	0	0	0	
Mesothelioma	1	1 (4.5)	0	0	0	
Other	5	0	0	1 (4.5)	4 (15.4)	
Unknown	2	1 (4.5)	1 (4.8)	0	0	

Data are presented as n (%) or mean ± standard deviation with [range]. †, chi-square test. VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

Table 3 Pleurodesis outcomes among different therapeutic interventions

Outcomes	Total (N=91)	Intervention				P
		VATS + pleurodesis (N=22)	VATS + IPC (N=21)	VATS + pleurodesis + IPC (N=22)	IPC (N=26)	
Initial pleurodesis failure	8 (8.8)	3 (13.6)	3 (14.3)	1 (4.5)	1 (3.8)	0.436
Initial pleurodesis success	83 (91.2)	19 (86.4)	18 (85.7)	21 (95.5)	25 (96.2)	
Late pleurodesis failure	22 (24.2)	8 (36.4)	2 (9.5)	8 (36.4)	4 (15.4)	0.068
Late pleurodesis success	69 (75.8)	14 (63.6)	19 (90.5)	14 (63.6)	22 (84.6)	

Data are presented as number (%) of patients. Pleurodesis success is defined as no further intervention needed. Pleurodesis failure is defined as symptoms related to pleural effusion and/or fluid ≥500 mL on X-ray. Initial is defined as before discharge from hospital. Late is defined as after discharge from initial hospitalization. VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

regarding the occurrence of AEs, with patients treated by VATS with pleurodesis and IPC placement experiencing complications more frequently [P=0.026, odds ratio (OR): 3.288, 95% confidence interval (CI): 1.147–9.430]. No statistically significant differences were observed among the treatment groups regarding the type of AE (P=0.103).

Survival analysis

Table 6 and *Figure 1* give an overview of the mortality and survival times of the study population. Out of 91 patients, 67 died (73.6%), and 24 were still alive (26.4%) at the end of 2020. The mean survival time after the surgical intervention

Table 4 Adverse events according to treatment groups

Treatment groups	Adverse events (N=21)	OR (95% CI)	P†
VATS + pleurodesis (N=22)	4 (18.2)	0.679 (0.202–2.29)	0.533
VATS + IPC (N=21)	5 (23.8)	1.055 (0.334–3.327)	0.927
VATS + pleurodesis + IPC (N=22)	9 (40.9)	3.288 (1.147–9.430)	0.026
IPC (N=26)	3 (11.5)	0.341 (0.091–1.275)	0.109

Data are presented as number (%) of patients. †, Chi-square test. OR, odds ratio; 95% CI, 95% confidence interval; VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

Table 5 Type of adverse event according to treatment group

Type of adverse event (N=21)	Treatment groups			
	VATS + pleurodesis (N=22)	VATS + IPC (N=21)	VATS + pleurodesis + IPC (N=22)	IPC (N=26)
IPC dysfunction (N=5)	0	1	2	2
Pneumonia (N=3)	0	0	3	0
Respiratory insufficiency (N=3)	2	0	1	0
Empyema (N=2)	0	1	0	1
Wound healing disorder (N=2)	0	0	2	0
Cardiovascular instability (N=2)	1	1	0	0
Subcutaneous emphysema (N=1)	0	0	1	0
Pulmonary edema (N=1)	0	1	0	0
Hemorrhagic shock (N=1)	0	1	0	0
Acute dyspnea (N=1)	1	0	0	0

Data are presented as numbers. VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

Table 6 Survival overview

Treatment groups	Survival					
	Days, mean ± SD	<30 days, n (%)	30–90 days, n (%)	91–180 days, n (%)	>180 days, n (%)	Alive, n (%)
VATS + pleurodesis (N=22)	74.95±97.46	6 (27.3)	5 (22.7)	3 (13.6)	4 (18.2)	4 (18.2)
VATS + IPC (N=21)	129.76±218.69	6 (28.6)	2 (9.5)	2 (9.5)	5 (23.8)	6 (28.6)
VATS + pleurodesis + IPC (N=22)	125.05±176.80	3 (13.6)	3 (13.6)	1 (4.5)	7 (31.8)	8 (36.4)
IPC (N=26)	81.46±85.48	3 (11.5)	8 (30.8)	4 (15.4)	5 (19.2)	6 (23.1)
Total (N=91)	138.31±160.82	18 (19.8)	18 (19.8)	10 (11.0)	21 (23.1)	24 (26.4)

VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter; SD, standard deviation.

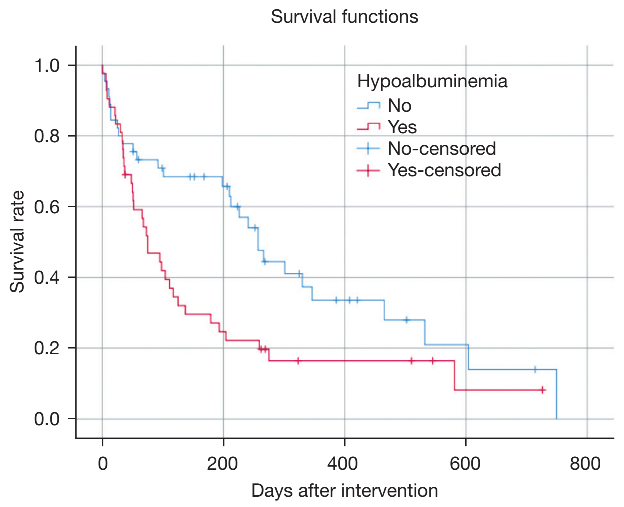

Figure 1 Kaplan-Meier survival curves for hypoalbuminemia.

Table 7 Bivariate correlation between different parameters and survival

Parameters	Survival	
	Pearson correlation coefficient (r)	P value (2-tailed)
Type of intervention	0.030	0.811
Tumor entity	0.082	0.508
Age	0.116	0.350
Gender	−0.062	0.616
Hypoalbuminemia	−0.322	0.008**
Systemic therapy	0.310	0.011*
Pleurodesis failure	−0.015	0.907
Pleurodesis success	0.247	0.044*
Adverse events	−0.099	0.426

*, correlation is significant at the 0.05 level (2-tailed). **, correlation is significant at the 0.01 level (2-tailed). Hypoalbuminemia was defined as serum albumin value below 35 g/L. Pleurodesis failure is defined as symptoms related to pleural effusion and/or fluid ≥500 mL on X-ray. Pleurodesis success is defined as no further intervention needed.

was 138.3 days (4.6 months). Eighteen patients (19.8%) died within 30 days. Another 18 patients (19.8%) survived for 30 to 90 days. Ten patients (11.0%) had survival times ranging from 90 days to 180 days. Twenty-one patients (23.1%) survived more than six months. No statistically significant difference was observed in the median survival times analyzed by age group [log rank (Mantel-Cox), chi-square, P=0.587]. No statistically significant difference was observed in the median survival times analyzed by tumor type [log rank (Mantel-Cox), chi-square, P=0.429]. The mean survival time in the VATS with pleurodesis group was the shortest, at 75 days, followed by a mean survival of 81 days in the group managed by IPC placement alone. The mean survival time in the VATS with pleurodesis and IPC placement group was 125 days. The longest mean survival time of 130 days was observed in the VATS-IPC group. However, no statistically significant differences in survival were observed between groups (P=0.554). Univariate analysis and a multiple linear regression model were used to identify prognostic factors for survival. Univariate analyses revealed that hypoalbuminemia (serum albumin level below 35 g/L) was significantly correlated negatively with survival (r=−0.322, P=0.008), whereas the receipt of systemic therapy and successful pleurodesis were associated with significantly longer survival times (r=0.310, P=0.011; r=0.247, P=0.044, respectively) (*Table 7*). These variables were also examined by multivariate analysis, and hypoalbuminemia (b=−83.333, P=0.031) persisted as an independent and significant unfavorable predictor of survival in patients with MPE due to pleural carcinomatosis (*Table 8*). Survival curves for hypoalbuminemia using the Kaplan-Meier method are shown in *Figure 1*. The comparison was made using a log-rank test (P=0.008). There were no significant differences in median survival times based on sex, multimorbidity, cardiovascular disease, or renal system disease (P=0.040, P=0.462, P=0.787 and P=0.438, respectively). The median survival time was higher in patients who received systemic therapies (P<0.001). The median survival time was 241 days (95% CI: 176.5–305.5) in the subgroup of patients with Eastern Cooperative Oncology Group (ECOG) status 2. The median survival time was 98 days (95% CI: 60.8–135.2) in the subgroup of patients with ECOG status 3. The median survival time was statistically significantly higher in the subgroup of patients with ECOG status 2 [log rank (Mantel-Cox), chi-square, P=0.033]. The combined effect of ECOG status, age and primary malignancy on survival was analyzed using Cox regression. Only ECOG status showed a statistically significant association with survival time. This suggests that a lower ECOG status indicates better survival (hazard ratio: 0.481, 95% CI: 0.279–0.831; P=0.009). At the late follow-up at 54 months, only five patients (5/91, 5.5%) were still alive, and four had received checkpoint inhibitor therapy.

Table 8 Multiple linear regression analysis (dependent variable: survival in days)

Predictors	Unstandardized beta coefficients	Standard error	Standardized beta coefficients	*t*	P
Constant	46.060	64.251	–	0.717	0.476
Hypoalbuminemia	−83.333	37.783	−0.260	−2.206	0.031
Systemic therapy	74.797	46.408	0.195	1.612	0.112
Pleurodesis success	91.100	57.566	0.185	1.583	0.119

R^2=0.190; adjR^2=0.151; F(3;63)=4.918; P=0.004. Hypoalbuminemia was defined as serum albumin value below 35 g/L. Pleurodesis success is defined as no further intervention needed.

Table 9 Duration of hospital stay

Treatment groups	LOS in days	LOS readmission in days	LOS total in days
VATS + pleurodesis (N=22)	12.50±5.88	2.09±3.28	14.59±6.19
VATS + IPC (N=21)	11.71±6.26	0.81±2.60	12.52±6.68
VATS + pleurodesis + IPC (N=22)	11.32±4.56	2.32±3.88	14.50±5.18
IPC (N=26)	5.69±4.09	1.53±3.31	6.65±4.91
Total	10.09±5.86	1.53±3.31	11.62±6.50

Data are presented as mean ± standard deviation. LOS, length of hospital stay; VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

Duration of hospital stay

The mean duration of hospitalization from the day of admission was 10.09±5.86 days (*Table 9*) for all treatment groups. For the VATS with pleurodesis group, the mean length of stay was 12.50±5.88 days; for the VATS with pleurodesis and IPC placement group, the mean length of stay was 11.32±4.56 days; and for the VATS-IPC group, the mean length of stay was 11.71±6.26 days. The shortest duration of the entire stay was observed for the IPC group, with a mean of 5.69±4.09 days. The differences between treatment groups regarding the LOS showed statistical significance (P=0.017). ANOVA with a post hoc Tukey Honest Significant Difference (HSD) test demonstrated statistically significant results for IPC placement, which shortened the initial and total LOS compared to the other treatment modalities (*Table 10*).

Discussion

In men, lung cancer is the most common tumor metastatic to the pleura, and in women, breast cancer is the most common tumor, accounting for 60–65% of all malignant effusions, which significantly reduce patients' quality of life (QoL) (5). Unfortunately, the prognosis for patients with MPE is usually poor, ranging between 3 and 12 months (6). Treatment options vary, but in any case, palliative management of MPE involves the treatment of the major symptoms, especially dyspnea (7). Particular emphasis on the treatment of MPE due to pleural carcinomatosis in the present study was placed on four surgical treatment modalities.

High-quality evidence on various therapeutic approaches is unfortunately lacking; therefore, it is not surprising to find variability in the management of this condition.

Due to the development of a broader range of therapeutic options, diversity in daily practice has increased, becoming particularly evident when comparing the results of surveys completed by pulmonologists and thoracic surgeons, which underlines this trend (8). While pulmonary specialists prefer placement of IPCs or offer pleurodesis as a talc slurry to patients requiring treatment, only referring 20% for VATS, their surgical counterparts regard pleurodesis via VATS as the first-line and preferred therapeutic option (9). As we have shown, there was no dominant surgical method in our hospitals, which means there is no standard approach, and the four methods had similar success rates.

It should be noted that an IPC is a foreign body that

Table 10 Multiple comparisons of hospitalization times between interventions

Length of hospitalization	(I) Intervention	(J) Intervention	Mean difference (I–J)	Standard error	Sig.	95% confidence interval	
						Lower bound	Upper bound
LOS initial	IPC	VATS + pleurodesis	–6.808*	1.511	<0.001	–10.76	–2.85
		VATS + IPC	–6.022*	1.530	0.001	–10.03	–2.01
		VATS + pleurodesis + IPC	–5.626*	1.511	0.002	–9.58	–1.67
LOS readmission	IPC	VATS + pleurodesis	–1.129	0.955	0.639	–3.63	1.37
		VATS + IPC	0.152	0.967	0.999	–2.38	2.68
		VATS + pleurodesis + IPC	–1.357	0.955	0.490	–3.86	1.14
LOS total	IPC	VATS + pleurodesis	–7.937*	1.662	<0.001	–12.29	–3.58
		VATS + IPC	–5.870*	1.683	0.004	–10.28	–1.46
		VATS + pleurodesis + IPC	–6.983*	1.662	<0.001	–11.34	–2.63

*, ANOVA with post hoc Tukey Honest Significant Difference (HSD) test, the mean difference is significant at the 0.05 level. LOS, length of hospital stay; VATS, video-assisted thoracic surgery; IPC, indwelling pleural catheter.

can cause infection and discomfort for patients. On the one hand, VATS is generally regarded as more invasive and resource-consuming than the other interventions commonly used in the diagnosis and treatment of MPE; on the other hand, VATS has potential advantages, including high-quality histopathology, the possibility of mechanical abrasion of the pleural surfaces and, if necessary, even pleurectomy and decortication (10). VATS also offers the ability to perform adhesiolysis and even disperse inflammatory substances in the pleural space, even though this carries a higher risk of complications (11). Most studies report a success rate of over 90%, although this highly depends on patient selection and the proposed definition of treatment success as an outcome measure (12). Similar success rates were observed in our study using VATS with pleurodesis, with an initial treatment success rate of 86.4% and even 95.5% when combined with IPC placement. Additionally, regarding long-term effectiveness, VATS with pleurodesis has shown promising results in other studies, with a one-year recurrence-free survival rate of 67% (13,14). Our study also underlines this finding, with long-term success rates of almost 65%. This study demonstrated an effective approach to managing MPE by combining thoracoscopic pleurodesis and IPC placement into a single procedure. Our initial pleurodesis success rates of 95% compare well with other studies, such as that of the TAPPS randomized clinical trial (15), even though the long-term success rates of 64% did not exactly reach the reported rates of 71.1% and 78.8% at 3 and 6 months, respectively. For patients for whom pleurodesis was unsuccessful, IPC placement was a safety net that improved dyspnea despite the need for continued placement.

Finally, it is noteworthy that performing thoracoscopy without using any sclerosing agent or mechanical abrasion has a 50% chance of autopleurodesis in patients with MPE (10). This finding might explain this study's high late-treatment success rates, especially in patients treated with a combination of VATS and IPC placement (16,17).

In a study by Pollak *et al.* (18), the effectiveness of IPCs was assessed in 28 patients with MPE. Dyspnea was improved in 94% of patients at 48 hours and 91% of patients on Day 30 postprocedure. MPE control was achieved in 90% of patients at the end of the study. They concluded that IPCs require a shorter duration of hospitalization and placement, and management could be achieved in the outpatient setting. Regarding potential complications of pleural catheters, dislodgement and infections were observed most often. However, serious complications were uncommon (2). Reflecting the findings of several other studies, including those by Markowiak *et al.* (19) and Dilkaute *et al.* (20), IPC placement drastically reduced the LOS for patients compared to the other more invasive treatment options. The mean duration of hospital stay in our IPC group at initial admission was six days. This reduced the mean period of initial hospitalization by seven days compared to VATS with pleurodesis, by six days compared to VATS with IPC placement, and five days compared to VATS with pleurodesis and IPC placement.

Furthermore, this means that 91.2% of patients could be safely discharged within 3 to 6 days, reducing reliance on hospital bed capacity, which may be severely limited in situations such as the coronavirus pandemic. A short LOS is also likely important to patients, given the limited survival time for individuals with MPE.

The high initial success rates of the combined approach of VATS with pleurodesis and IPC placement were also accompanied by a significantly higher rate of complications compared to the other treatment groups, with nine patients (40.9%) experiencing AEs. This might be explained by mounting the respective advantages of the individual treatments and their complications. In our report, 85.7% of patients undergoing VATS and IPC placement responded well to therapy and 23.8% experienced complications. Patients managed with IPC placement alone had an excellent initial treatment success rate of 91.2%, with 11.5% experiencing an AE, following a large meta-analysis by Van Meter *et al.* (21).

One major difference from other studies was the longer length of stay in the hospital in our study. This study started from the day of initial admission and hospitalization, in contrast to the time of intervention, which is often used as a starting point in other research articles. This is one reason for the longer total time spans, as opposed to generally shorter time intervals, as seen in the similar articles mentioned above (19). The longer LOS, apart from IPC placement, was also due to our surgical procedure because we routinely apply a level of suction of 20 cmH_2O for at least 72 hours after talc pleurodesis.

In our three VATS with pleurodesis groups, late treatment failure was defined as the recurrence of effusion or symptoms related to effusion after initially successful pleurodesis, whereas in the pleural catheter groups, late failure was defined as the recurrence of effusion or effusion-associated symptoms after initial successful control. One possible criticism of the current study is how the efficacy of the two procedures was compared. However, we maintain that treatment is successful if there is no pleural fluid reaccumulation occurs or if no pleural effusion-related symptoms occur, regardless of whether a catheter is present. This partly explains the difference in outcomes regarding late treatment success.

The overall mean survival time in this study of 138.3 days (4.6 months) was at the lower end of reported survival times, which might partly be explained by the high proportion of advanced-stage lung cancer patients. The survival rate of our patients was analyzed, as well as predictive factors correlating with survival. Reported survival times differ widely across studies. A study conducted by Stefani *et al.* (22) found an overall median survival time of 7.7 months. On the other hand, Antevil *et al.* (23) reported an overall median survival time of 3.48 months. These observations also translate more into what we found in our study concerning the patient characteristics and primary tumor site. The type of surgical treatment modality used did not significantly affect survival. Studies that evaluated the prior site as an overall survival prognostic factor have reported controversial results, with our research displaying no correlation. However, in other series, the histology of the primary tumor was an independent prognostic factor, with breast cancer being the histological type with a better prognosis and lung cancer, together with gastrointestinal cancer, being the histological types with a worse prognosis (24). The majority of our patients had lung carcinoma with a poor prognosis.

The late follow-up at 54 months showed that only five patients (5/91, 5.5%) were still alive, and four had received checkpoint inhibitor therapy, which shows a positive trend in modern oncology. The impact of preoperative immunotherapy or targeted therapy on surgical benefits or complications has yet to be clarified and investigated. We noted 21 AEs. In this group, six patients had an infection, five of these patients received systematic therapy, and only one had an additional checkpoint inhibitor. Although the patient population was small, in our opinion, modern oncologic therapy did not have a negative impact on the surgical complication rate.

In other studies, a lower concentration of pleural fluid protein has also been associated with lower survival. Bielsa *et al.* (25) showed a mean survival time of 2.2 months when the pleural fluid total protein value was less than 3.85 g/dL, which proved statistically significant in multivariate analysis. Our study included patients with low protein levels who had received previous oncological treatment in which MPE was a sign of disease progression. On the other hand, Anevlavis *et al.* (26) studied 90 patients with a good performance status who had received no systemic treatment for cancer at the time of the primary cancer diagnosis by thoracoscopy. In this sample, the total protein concentration in the pleural fluid was unrelated to patient survival. The explanation may be the advanced stage of cancer, which is strongly associated with hypoproteinemia and hypoalbuminemia (25).

Our study's univariate analysis showed a significant positive correlation between successful pleurodesis and systemic therapy and survival outcomes. Hypoalbuminemia also showed a significant, but negative, correlation with survival. This result also remained significant in multivariate analysis, showing that hypoalbuminemia was an independent negative predictor of survival for patients in our study. In this regard, the effect of regular loss of pleural effusion on a patient's nutritional status after IPC placement may also warrant further investigation.

Similar to our result, the report of a recently published systematic review by Hassan *et al.* (27) demonstrated a survival difference according to pleurodesis outcomes in patients with MPE. Additionally, the type of malignancy and respective oncological treatment have been shown to be associated with survival and even pleurodesis outcomes. In patients with MPE, several factors affect pleurodesis outcomes, survival, or both. If there is an accurate correlation between pleurodesis outcomes and survival, it is crucial to control for possible confounders.

In our study, primary and late treatment failures were clearly defined as recurrence of the effusion or symptoms related to effusion after surgical intervention. On the other hand, the international evaluation of outcome measures in MPE treatment is seen as a necessity since effectiveness is often judged as the only determinant of success and pleurodesis occurrence based on the radiological assessment (28,29).

Fortunately, patient-centered outcomes, including duration of hospitalization or avoidance of readmission to the hospital, QoL, and relief of symptoms, have recently gained more attention as primary outcome measures and are increasingly used as a measure of success instead of reaccumulation of pleural fluid as the only measure of the effectiveness of an intervention (30). An internationally agreed definition of pleurodesis success and the timing at which it should be assessed would be largely beneficial, along with a consensus about handling the inevitable patient attrition due to death (28).

One of the strengths of this research was the inclusion of patients with evidence of a trapped lung, which is most commonly included as an exclusion criterion in other studies, including the TAPPS randomized clinical trial by Bhatnagar *et al.* (15). Beyond that, this study did not exclude patients with an expected survival time of less than three months, frequently encountered in other published papers, which potentially portrays the general condition and outcomes of patients in a broader and more applicable context.

According to the German guidelines, we use talc for pleurodesis. Nevertheless, other substances and extracts exist to achieve pleurodesis. Lobaplatin or minocycline are currently being tested to improve pleura adherence and reduce LOS and costs. Other authors achieved an excellent overall response rate with the intrathoracic use of turmeric or mistletoe extract. Idopovidone has also been reported to be safe and efficient. Using intracavitary recombinant human endostatin or combined nanoparticle albumin-bound paclitaxel plus carboplatin allows for better effusion control (29). Oncological surgery in patients with pleural carcinomatosis is controversially discussed, so pleurectomy with or without the application of hyperthermic intrathoracic chemotherapy (HITOC) is not part of the German guidelines, apart from treatment of mesothelioma and thymic malignancies with pleural dissemination (30). However, the role of surgery and HITOC in selected cases was discussed in the international literature so that resection associated with HITOC may be considered in patients with stage IV disease but without extrathoracic metastasis (29).

For future research, novel sclerosing agents and drug-coated IPCs will be under investigation during the following years, as well as the optimal manner of combining pleurodesis and IPCs concerning correct timing and other practical considerations. Complementary therapeutic interventions tackling topics such as diet and exercise may also be beneficial adjuncts to standard pleural interventions in the holistic approach for patients with MPE (31,32).

Study limitations

There are, however, potential limitations to our study. First, the retrospective chart-based approach of the examination must be noted; therefore, causal relationships between variables cannot be established. Second, there was no randomization. This design also led to high rates of undocumented outcomes. This study tried to solve this issue by only including patients with complete medical case records. However, this also impacted the number of patients who could be accounted for in this study, resulting in a lesser degree of generalizability. LOS was described from the day of admission and not from the day of treatment. This is a limitation of the work because it can affect its efficacy.

Conclusions

Treatment should be individualized and led by an assessment of a patient's prognosis and driven by a balance of the expected benefit and morbidity of the proposed procedure and the individual desires of the patient. The ideal method for treating recurrent MPE should be simple, effective, and inexpensive, with minimal disturbance to the patient. The objective is to relieve distressing symptoms due to effusion, to prevent fluid reaccumulation and to return the individual to a functioning state of health. The survival time is short and expressed in months for patients with MPE. The goal of the treatment is to decrease the severity of symptoms, disease burden, and duration of time spent in the hospital and to improve patients' QoL. Freedom from hospital admissions is an important goal for patients and their families. With continued efforts to improve patient-centered endpoints, the combination of therapies offers promising alternatives over individual therapy alone. To summarize, each treatment modality (with or without VATS) has pros and cons; therefore, decisions should be made on a case-by-case basis. The use of an IPC, even if the lung is not trapped, can significantly reduce the LOS. VATS is needed when histology is needed.

Acknowledgments

This work was a dissertation of Joshua Schramm (first author) at the Medical School Coburg.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1247/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1247/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1247/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1247/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the International Ethics Board of the Medical School REGIOMED Coburg (ID: 2022-14). This type of research was based on §2 of the statutes (sign STWA/MICA, Marc 18, 2022), and individual consent for this retrospective analysis was waived.

References

1. Mishra EK, Muruganandan S, Clark A, et al. Breathlessness Predicts Survival in Patients With Malignant Pleural Effusions: Meta-analysis of Individual Patient Data From Five Randomized Controlled Trials. Chest 2021;160:351-7.
2. Esme H, Çalık M. Management of malignant pleural effusion. In: Firstenberg MS, editor. Principles and practice of cardiothoracic surgery. London: Intech Open; 2018:85-108.
3. Jany B, Welte T. Pleural Effusion in Adults-Etiology, Diagnosis, and Treatment. Dtsch Arztebl Int 2019;116:377-86.
4. Feller-Kopman DJ, Reddy CB, DeCamp MM, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med 2018;198:839-49.
5. Lumachi F, Mazza F, Ermani M, et al. Talc pleurodesis as surgical palliation of patients with malignant pleural effusion. Analysis of factors affecting survival. Anticancer Res 2012;32:5071-4.
6. Skok K, Hladnik G, Grm A, et al. Malignant Pleural Effusion and Its Current Management: A Review. Medicina (Kaunas) 2019;55:490.
7. Arora RD, Boster J. Malignant Pleural Effusion. 2023 February 26th. Treasure Island (FL): StatPearls Publishing; 2023.
8. Gayen S. Malignant Pleural Effusion: Presentation, Diagnosis, and Management. Am J Med 2022;135:1188-92.
9. Scarci M, Caruana E, Bertolaccini L, et al. Current practices in the management of malignant pleural

effusions: a survey among members of the European Society of Thoracic Surgeons. Interact Cardiovasc Thorac Surg 2017;24:414-7.
10. Shojaee S, Lee HJ. Thoracoscopy: medical versus surgical-in the management of pleural diseases. J Thorac Dis 2015;7:S339-51.
11. Trotter D, Aly A, Siu L, et al. Video-assisted thoracoscopic (VATS) pleurodesis for malignant effusion: an Australian teaching hospital's experience. Heart Lung Circ 2005;14:93-7.
12. Koegelenberg CFN, Shaw JA, Irusen EM, et al. Contemporary best practice in the management of malignant pleural effusion. Ther Adv Respir Dis 2018;12:1753466618785098.
13. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Cochrane Database Syst Rev 2004;(1):CD002916.
14. Steger V, Mika U, Toomes H, et al. Who gains most? A 10-year experience with 611 thoracoscopic talc pleurodeses. Ann Thorac Surg 2007;83:1940-5.
15. Bhatnagar R, Luengo-Fernandez R, Kahan BC, et al. Thoracoscopy and talc poudrage compared with intercostal drainage and talc slurry infusion to manage malignant pleural effusion: the TAPPS RCT. Health Technol Assess 2020;24:1-90.
16. Kaifi JT, Toth JW, Gusani NJ, et al. Multidisciplinary management of malignant pleural effusion. J Surg Oncol 2012;105:731-8.
17. Sabur NF, Chee A, Stather DR, et al. The impact of tunneled pleural catheters on the quality of life of patients with malignant pleural effusions. Respiration 2013;85:36-42.
18. Pollak JS. Malignant pleural effusions: treatment with tunneled long-term drainage catheters. Curr Opin Pulm Med 2002;8:302-7.
19. Markowiak T, Ried M, Großer C, et al. Postoperative outcome after palliative treatment of malignant pleural effusion. Thorac Cancer 2022;13:2158-63.
20. Dilkaute M, Klapdor B, Scherff A, et al. PleurX drainage catheter for palliative treatment of malignant pleural effusion. Pneumologie 2012;66:637-44.
21. Van Meter ME, McKee KY, Kohlwes RJ. Efficacy and safety of tunneled pleural catheters in adults with malignant pleural effusions: a systematic review. J Gen Intern Med 2011;26:70-6.
22. Stefani A, Natali P, Casali C, et al. Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study. Eur J Cardiothorac Surg 2006;30:827-32.
23. Antevil JL, Putnam JB Jr. Talc pleurodesis for malignant effusions is preferred over the pleurx catheter (pro position). Ann Surg Oncol 2007;14:2698-9.
24. Abrao FC, de Abreu IR, Fogarolli M, et al. Prognostic Factors of 30-Day Mortality After Palliative Procedures in Patients with Malignant Pleural Effusion. Ann Surg Oncol 2015;22:4083-8.
25. Bielsa S, Salud A, Martínez M, et al. Prognostic significance of pleural fluid data in patients with malignant effusion. Eur J Intern Med 2008;19:334-9.
26. Anevlavis S, Kouliatsis G, Sotiriou I, et al. Prognostic factors in patients presenting with pleural effusion revealing malignancy. Respiration 2014;87:311-6.
27. Hassan M, Harriss E, Mercer RM, et al. Survival and pleurodesis outcome in patients with malignant pleural effusion - a systematic review. Pleura Peritoneum 2021;6:1-5.
28. Antony VB, Loddenkemper R, Astoul P, et al. Management of malignant pleural effusions. Eur Respir J 2001;18:402-19.
29. Divisi D, Zaccagna G, De Vico A, et al. Malignant pleural effusion in lung cancer: focus on treatment—through a review of literature. J Xiangya Med 2020;5:28.
30. Ried M, Eichhorn M, Winter H, et al. Expert Recommendation for the Implementation of Hyperthermic Intrathoracic Chemotherapy (HITOC) in Germany. Zentralbl Chir 2020;145:89-98.
31. Fitzgerald DB, Koegelenberg CFN, Yasufuku K, et al. Surgical and non-surgical management of malignant pleural effusions. Expert Rev Respir Med 2018;12:15-26.
32. Clive AO, Jones HE, Bhatnagar R, et al. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev 2016;2016:CD010529.

Cite this article as: Schramm J, Eslauer E, Hammoudeh S, Stange S, Sziklavari Z. Comparison of outcomes of surgical and other invasive treatment modalities for malignant pleural effusion in patients with pleural carcinomatosis. J Thorac Dis 2024;16(2):960-972. doi: 10.21037/jtd-23-1247