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Current Management of Symptomatic Pericardial Effusions in Cancer Patients

Neoplasia and hematologic malignant diseases are common causes of acute pericardial effusion. The presence of malignant pericardial effusion (MPE) is associated with poor prognosis in these patients, with a shortened survival median time. The best management for symptomatic MPE (surgical drainage vs. percutaneous pericardiocentesis [PCC]) is controversial and is based on local experience. PCC could represent a less invasive, equally efficient, valuable option, although the lack of standardization of procedures could remain a confounding factor (1,2). The aim of our work was to evaluate the features and clinical outcomes (survival, effusion recurrence) of patients with symptomatic MPE that was managed by either PCC or surgical drainage.
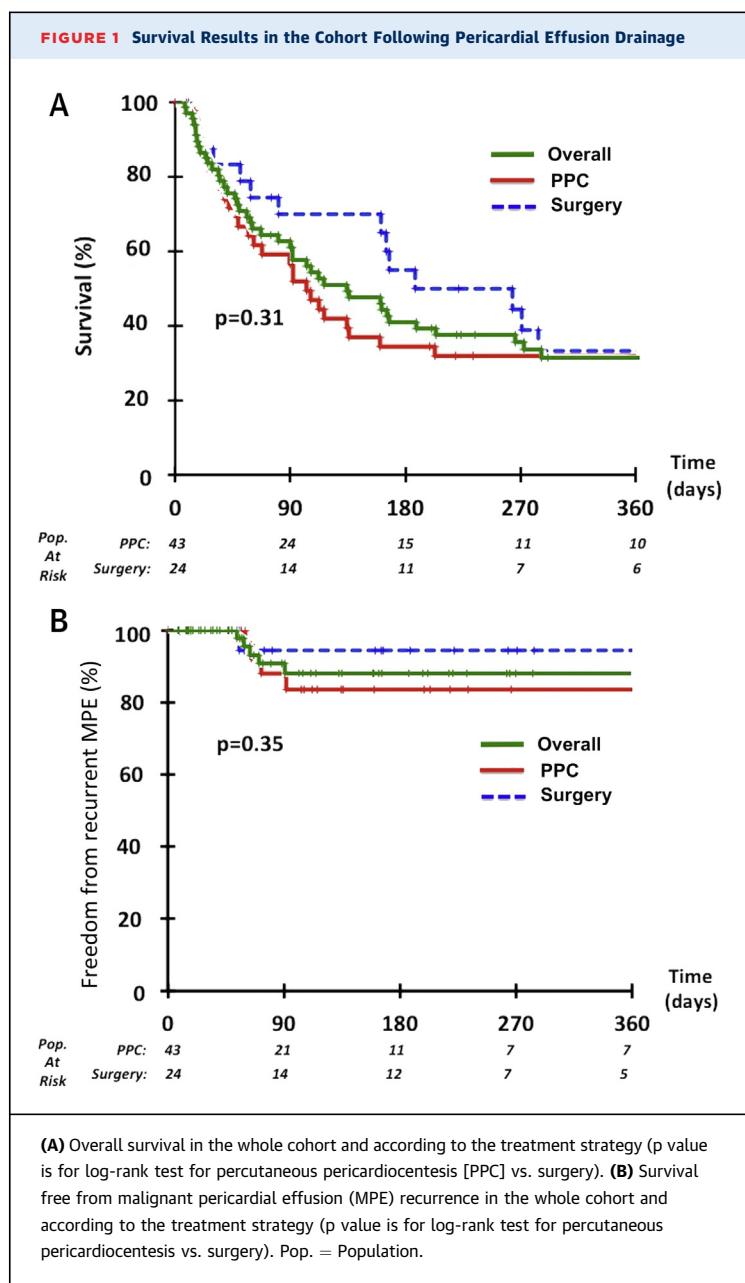
We prospectively included as MPE all patients referred to our institution, the Institut Mutualiste Montsouris in Paris, France, who had a first episode of pericardial effusion requiring PCC or surgical drainage in the context of an ongoing or previous recent (<1 year) solid tumor or blood disorder between January 1, 2014, and December 31, 2017. Patients were excluded if they had pericardial effusion related to cardiac surgery, interventional procedures, or inflammatory disease.

Pericardial effusion drainage was considered in case of clinical symptoms and/or clinical tamponade. The procedure was chosen on the basis of a heart team decision according to the echocardiographic data, anatomic considerations, and surgical risk evaluation.

PCC was performed in a cardiac catheterization laboratory using fluoroscopic and echocardiographic guidance from the infrasternal angle, and a catheter was then inserted within the pericardial. A sample of pericardial liquid was analyzed (chemistry, cytology including fluid preparation evaluation and cell block evaluation with immunohistochemistry, and bacterial testing). Patients were all monitored in an intensive care unit, with echocardiographic evaluation once a day, and the pericardial catheter was removed when fluid drainage was <20 ml/day, without residual pericardial effusion. No sclerosing agent was used during the procedure. Echocardiography was performed a week later in our center to assess the disappearance of the effusion.

Surgical drainage was mostly performed by sub-xiphoid pericardiostomy, with a Redon drain positioned along the diaphragmatic surface of the heart. A pericardial window was performed only in case of recurrent MPE. Pericardial biopsy was sent for pathology analysis.

Recurrent pericardial effusion was documented by echocardiography and was defined as reaccumulation of pericardial fluid within 3 months after surgical drainage or pericardiocentesis. Management included repeated PCC, surgical drainage, and eventually placement of a surgical pericardial window.

FIGURE 1 Survival Results in the Cohort Following Pericardial Effusion Drainage

(A) Overall survival in the whole cohort and according to the treatment strategy (p value is for log-rank test for percutaneous pericardiocentesis [PPC] vs. surgery). **(B)** Survival free from malignant pericardial effusion (MPE) recurrence in the whole cohort and according to the treatment strategy (p value is for log-rank test for percutaneous pericardiocentesis vs. surgery). Pop. = Population.

The primary endpoint was the occurrence of any death. Secondary endpoints included recurrent MPE requiring intervention, minor or major bleeding, and peri-intervention complications.

All statistical analyses were performed using SPSS software version 21.0 for Mac (IBM Corp., Armonk, New York). Quantitative variables were described as median (interquartile range), and categorical variables were described in terms of counts and percentages. Patient characteristics were analyzed using the chi-square test and Mann-Whitney test,

respectively, for qualitative and quantitative data. Survival curves were constructed for time-to-event variables by using Kaplan-Meier estimates and were compared by log-rank test. Patients who were lost to follow-up were censored at the time of the last contact. Multivariable Cox models were used to assess the relationship of clinical and procedural covariates with the incidence of the primary endpoint within 1 year following the procedure. Univariable Cox proportional hazards regression analyses were performed first. Then all covariates with a p value of <0.15 were included in the multivariable regression model, and backward stepwise elimination was performed to identify independent predictors of the primary endpoint.

Between January 1, 2014, and December 31, 2017, a total of 310 subjects underwent pericardial effusion drainage in our institution, including 68 patients with MPE (22%). Among these subjects, 44 patients (65%) underwent PCC, and 24 patients (35%) benefited from surgical pericardiocentesis (that included an associated pleuropericardial window in 3 cases).

The most frequent tumors associated with MPE were lung (49%), breast (18%), and digestive tract (15%) cancers. MPE occurred in patients with previously identified metastasis in 68% of the cases. Interestingly, malignant cells were identified by pericardial fluid pathology analysis in only 40% of cases. There was no significant difference between the 2 groups regarding cancer types, clinical characteristics, performance status, or pericardial fluid volume and regarding baseline coagulation profile, occurrence of bleeding events, or pre-defined peri-intervention complications. No major event related to surgery or PCC or to failure of the drainage was recorded. Subsequent chemotherapy was provided within 6 weeks following drainage in 36% of the patients (39% in PCC group vs. 29% in surgery group; p = 0.43).

The outcome of MPE patients was poor: the overall 1-year global survival was 32.1 ± 6.1%, and the median survival time was 106 days (range 36 to 284 days) (**Figure 1A**). We did not observe any significant difference in survival between the PCC and surgical management groups (31.9 ± 7.1% vs. 33.3 ± 10.1%; p = 0.31 log-rank test) (**Figure 1A**).

Multivariable Cox regression analysis revealed that presence of malignant cells within the pericardial fluid (hazard ratio: 2.1; 95% confidence interval: 1.13 to 3.93; p = 0.02) and previously identified metastasis (hazard ratio: 2.6; 95% confidence interval: 1.24 to 5.47; p = 0.01) were the only independent predictors of death in this cohort, whereas cardiac tamponade as clinical presentation, sex, age, history of previous mediastinal radiation therapy, PPC treatment, and

World Health Organization performance status were not associated with outcome.

MPE recurrence was observed in 5 cases during the follow-up period. Surgical redo pericardiocentesis was provided to all of these patients. The 1-year survival free from recurrent MPE was 87.9 ± 5.1% and did not differ between the PCC and surgical management groups (83.6 ± 7.5% vs. 94.4 ± 5.4%, respectively; p = 0.35 log-rank test) (Figure 1B).

The current data show that the presence of MPE as associated with high mortality in cancer patients. The presence of a symptomatic pericardial effusion thus reflects a more advanced carcinomatous disease (at least in the case of solid tumors) with direct invasion of the heart or severe mediastinal infiltration (see later text). Interestingly, we observed that MPE was diagnosed in the absence of any previously identified metastasis in one-third of our patients. Furthermore, multivariable analysis revealed that MPE was a stronger predictive factor of outcomes than metastasis. These results are in line with previously published results, including for the similar distribution of the primary malignant disease (1) (almost two-thirds of patients with lung or breast cancers). In this series, we observed the presence of malignant cells in only 40% of the cases. This finding reflects the diversity of mechanisms leading to pericardial effusion in the context of neoplasia. Malignant cells can be identified within pericardial fluid in cases of direct cancer involvement of the pericardium (metastasis spread through blood or lymphatics), which probably accounts for the poorer prognosis associated with this finding. When no malignant cells can be identified by cytology analysis, other mechanisms have to be hypothesized. Pericardial effusion could be related to obstruction of the mediastinal lymphatic system by tumor infiltration or radiotherapy-induced fibrosis. Other potential causes include opportunistic infections (cytomegalovirus, tuberculosis pericarditis, and fungal pericarditis from Candida and Aspergillus), systemic therapies such as alkylating agents, local inflammation, chest radiation pericarditis, or fluid retention triggered by certain chemotherapies.

There was no significant difference in outcomes and risk of recurrent effusion between PCC and surgical treatment, a finding suggesting that both strategies are valuable options to manage MPE. Several studies evaluated the rate of pericardial effusion recurrence following percutaneous pericardiocentesis and surgical drainage for MPE, but these series reported variable techniques and duration of catheter drainage. PPC with a short drainage time led to a recurrence rate (approximately 10%) comparable to that observed with surgical treatment in the study by El Haddad et al. (2) and in the present series, as well as comparable outcomes and fewer complications. According to the 2015 European Society of Cardiology guidelines, the treatment of cardiac tamponade related to MPE is a Class I indication for pericardiocentesis (3). In patients with a large pericardial effusion without tamponade, systemic antineoplastic treatment is recommended as baseline therapy, pericardiocentesis is then used to relieve symptoms and establish a diagnosis (Class I, Level of Evidence: B), and finally, intrapericardial instillation of sclerosing agents is used to prevent recurrences (3). Surgical pericardiotomy is indicated when pericardiocentesis cannot be performed (Class IIa, Level of Evidence: B), but it is associated with a higher rate of complications and does not improve outcomes over pericardiocentesis (3). In our daily practice, a multidisciplinary team including an interventional cardiologist, a cardiothoracic surgeon, and an intensivist discusses the most appropriate option for each patient. PCC is the first option for MPE management, but the patient could be managed surgically if the anatomy is unsuitable for PCC (i.e., long distance between the xyphoid appendix and the pericardial cavity, enlarged liver blocking access to pericardium, solid tumor adhering to the pericardium) or the estimated fluid volume is limited as shown by echocardiographic analysis.

These data confirm that MPEs are mostly related to solid tumors and are associated with poor prognosis, particularly when malignant cells are identified in the pericardial fluid. There is no significant difference in outcomes and risk of recurrent effusion between PCC and surgical treatment. Patients' quality of life and the prognosis of neoplastic disease have to be taken into account in the management of MPE.

PCC could represent a less invasive, equally efficient, valuable option for the treatment of MPE, with no significant difference in outcome when compared with surgical treatment. Given that we observed very limited cases of recurrence with PCC in the present series, further research is needed to confirm that this strategy is a valuable option for MPE management.

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