Prognostic Factors in the Surgical Management of Pericardial Effusion in the Patient With Concurrent Malignancy*

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Background: **Pericardial effusion in the patient with cancer presents a unique management problem. Although multiple methods of operative and nonoperative drainage of pericardial effusions have been described, surgical pericardial window remains the standard approach to long-term drainage. Selecting the patient who may benefit from an operative approach presents a difficult challenge. In the present study, we retrospectively analyzed the clinical outcome of 63 consecutive patients with malignancy who underwent surgical pericardial window for symptomatic pericardial effusion between January 1, 1990, and July 1, 2001, at City of Hope National Medical Center in order to try to determine whether the type of cancer, the presence of malignant cells in pericardial fluid, or tissue specimens or the method of surgery influenced the incidence of recurrent pericardial effusion or duration of survival.**

Methods: **The cohort was comprised of 15 patients with non-small cell lung cancer (NSCLC), 22 patients with breast cancer, 17 patients with hematologic malignancy, and 9 patients with other solid tumors. Pertinent clinical, laboratory, hospital stay, and outcome data including long-term follow-up were recorded. Patients were followed up until the time of last clinical follow-up or death. Univariate survival analyses were performed to determine significant clinical factors contributing to outcome.**

Results: **Median follow-up was 6.6 months for the group and 8.3 months for those alive at last follow-up. Median survival rates for patients with lung, breast, hematologic, and other solid-tumor malignancies were 3.2 months, 8.8 months, 17 months, and 16.4 months, respectively. Preoperative factors that negatively correlated with survival included a diagnosis of NSCLC ($p = 0.0014$), the presence of a pleural effusion ($p = 0.003$), or positive pathologic ($p = 0.02$) or cytologic findings ($p = 0.02$).**

Conclusions: **A surgical approach to pericardial drainage is effective (< 5% failure rate) and provides an opportunity for continued therapy with the potential for relief of dyspnea and improvement in quality of life and survival in selected patients.** ***(CHEST 2004; 125:1328–1334)***

Key words: cardiac tamponade; malignancy; palliative surgery; pericardial effusion; pericardial window

Abbreviations: CI = confidence interval; LOS = length of stay; NSCLC = non-small cell lung cancer

Pericardial effusions, particularly those that occur in patients with malignant disease, present a complex management problem. Although pericardial effusions occur with less frequency than pleural effusions in the cancer patient, autopsy series reveal an incidence between 2% and 20% in patients with malignancy.[1,2] The pathologic cause of the effusive process often involves metastasis to the parietal pericardium, although direct invasion of the epicardial surface or myocardium can also be present. Alternatively, the presence of mediastinal lymph node metastases or a history of radiotherapy to the chest or mediastinum may lead to disruption of homeostatic mechanisms of lymphatic drainage resulting in pericardial effusion.[3]

Clinical presentation is variable, with the vast majority of patients demonstrating gradual onset of symptoms rather than acute tamponade. Because of

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this, the diagnosis of pericardial effusion may be delayed or missed due to vague symptoms of fatigue, shortness of breath, or chest heaviness attributed to a gradual deterioration in cardiopulmonary function or ascribed to an advanced disease state. Identification and prompt treatment may dramatically relieve patients of symptoms, allowing for continued systemic therapy and preventing early death in an otherwise controllable disease.[4]

The benefit to long-term control in the setting of a limited life expectancy presents a challenge for the clinician to select the patient who might most benefit from an operative approach. Patients with malignant pericardial effusion are usually symptomatic with dyspnea, often markedly so, and are at immediate risk of death. Although prompt treatment may decrease short-term risk of death from the effusion, many of these patients have major comorbidity associated with widespread metastatic disease limiting both quality of life and survival, even with optimal management of the pericardial effusion. Despite the generally bleak outlook, in some cases the pericardial effusion is unrelated to the underlying malignancy and long-term survival might be attainable. Although pericardiocentesis alone will reliably relieve tamponade, rapid recurrence is typical. To complicate matters further, there are a number of different interventions, ranging from catheter drainage to subtotal pericardiectomy, available to clinicians seeking to offer palliation.

This report describes the City of Hope National Medical Center experience with 63 consecutive patients with malignant disease who underwent surgical pericardial window. Our objective was to examine clinical and pathologic predictors of morbidity and outcome in cancer patients undergoing an operative pericardial window, in order to try to determine whether the type of cancer, the presence of malignant cells in fluid or tissue specimens, or the method of surgery influences the incidence of recurrent pericardial effusion or duration of survival.

Materials and Methods

This study was approved by the Institutional Review Board at the City of Hope National Medical Center. We retrospectively reviewed all records of patients with malignant disease who underwent surgical pericardial window for symptomatic pericardial effusion between January 1990 and July 2001. All patients had a diagnosis of malignancy and were undergoing treatment. The clinical status of each patient was determined from medical records. Cardiac tamponade was defined either clinically (by the presence of pulsus paradoxus, elevated jugular pressure, tachycardia, and hypotension) or with echocardiographic findings of tamponade (including right atrial compression, right ventricular diastolic collapse, left atrial compression, left ventricular diastolic compression, or a swinging heart).[5] Patients undergoing primary and secondary surgical procedures for the treatment of disease associated with pericardial effusion were included in the study group. Thoracoscopic and open-thoracic procedures were carried out by a single thoracic surgeon (F.W.G.). Most of the subxiphoid procedures were performed by general oncologic surgeons by individual preference, but in some instances a subxiphoid approach was chosen because prior thoracotomy or pleurodesis made a thoracic approach difficult or impossible.

In subxiphoid cases, a short upper midline incision was created and deepened through the midline fascia between the rectus abdominis muscles, but not through peritoneum. The xiphoid process was excised and the lower pericardium exposed by anterior retraction of the sternum. A 3- to 4-cm pericardial window was created. Although local anesthesia has been described for this operation, our preference was for light general anesthesia.

Our current technique of choice is thoracoscopic partial pericardiectomy. Preliminary bronchoscopy is performed to rule out endobronchial tumor obstruction preliminary to placement of a double-lumen tube or endobronchial blocker catheter. The patient is placed in a lateral decubitus position and, after institution of single-lung ventilation, thoracoscopy is performed, preferably on the left side, through a 2-cm anterior axillary line incision in the seventh intercostal space. The pericardium is punctured percutaneously with a 16-gauge, 5-inch-long needle, under direct vision, and fluid is aspirated through the plastic outer cannula after removal of the sharp inner needle (BD Angiocath 16 gauge, 5.25 inch, 1.7 × 133 mm; Becton Dickinson Infusion Therapy Systems; Sandy, UT). When the parietal pericardium becomes flaccid, it is picked up with an endoscopic curved forceps introduced through a second intercostal incision. The phrenic nerve is identified before one or more round incisions approximately 3 to 4 cm in diameter are created using an endoscopic scissor and electrocautery. Larger windows might allow cardiac herniation. A 32F chest tube is left in place for a day or two after surgery.

In some cases, a 6- to 8-cm anterior thoracotomy was necessary because of hemodynamic instability, inability to safely use single-lung ventilation because of contralateral endobronchial tumor, or when extensive pleural adhesions were found at thoracoscopy. In cachectic patients, or in patients with prior ipsilateral mastectomy, a pericardial window could sometimes be created through a single anterior intercostal incision approximately 2 cm in length without the need for thoracoscopic techniques.

Operative procedures and times, complications, clinical outcomes, and hospital stay data were recorded. Recurrence of a pericardial effusion was defined as reaccumulation of pericardial fluid demonstrated by echocardiography and requiring intervention. Patients were followed up until time of last clinical follow-up or death.

Overall survival was calculated from date of operation (median follow-up, 8.3 months). Kaplan-Meier survival estimates were tested using the Mantel-Haenszel (log-rank) test. We calculated 95% confidence intervals (CIs) on the Kaplan-Meier estimates using a logit transformation of the Greenwood estimate of the variance. Continuous factors possibly associated with overall survival were examined by univariate Cox regression analysis. Analysis of the following clinical variables for prognostic importance was performed: age, cancer diagnosis, stage, left ventricular ejection fraction prior to surgery, positive cytologic or histologic findings, and surgical procedure.

Results

The clinical characteristics of the 63 patients are summarized in Table 1. The group was comprised of

Table 1—*Patient Characteristics*

Characteristics	No. (%)
Gender	
Male	22 (35)
Female	41 (65)
Disease	
NSCLC	15 (24)
Breast cancer	22 (35)
Hematologic	17 (27)
Other	9 (14)
Previous chemotherapy	
Yes	41 (65)
No	22 (35)
Previous chest wall radiation	
Yes	28 (44)
No	35 (56)
Pleural effusion	
Yes	37 (59)
No	26 (41)
Tamponade (n = 53)	
Yes	24 (45)
No	29 (55)
Method of surgery	
Subxiphoid	14 (22)
Thoracoscopic	30 (48)
Thoracotomy	13 (21)
Limited anterior incision	6 (10)

Table 2—*Characteristics of Pericardial Effusion*

Characteristics	No. (%)
Gross	
Bloody	32 (50)
Serosanguinous	14 (23)
Serous	15 (24)
Purulent	2 (3)
Cytologic findings	
Positive	28 (44)
Negative	27 (43)
Atypical cells	3 (5)
Not sent	5 (8)
Pathologic findings	
Positive	15 (24)
Negative	32 (51)
Pericarditis	9 (14)
Not sent	7 (11)
Volume of effusion, mL	
Not recorded	21 (33)
< 300	7 (11)
300–600	22 (35)
601–900	6 (10)
901–1,200	6 (10)
≥ 1,200	1 (2)

41 women and 22 men (mean age, 50 years; range, 20 to 82 years). Previously diagnosed malignancies included 15 patients with non-small cell lung cancer (NSCLC), 22 patients with breast cancer, and 17 patients with hematologic malignancy. Seven patients had other solid tumor malignancies including colon cancer, cervical cancer, melanoma, or esophageal cancer. Two patients had an unknown primary tumor. Forty-one patients had been previously treated with chemotherapy. Twenty-eight patients had received previous thoracic or chest wall radiation therapy (mean dose, 4,280 cGy).

The most common presenting symptoms were dyspnea and fatigue. Thirty-seven patients had a concurrent pleural effusion at the time of surgery. The method of pericardial drainage was performed at the discretion of the operative surgeon and consisted of a limited anterior intercostal incision in 6 patients, a subxiphoid approach in 14 patients, an anterior thoracotomy in 13 patients, and a thoracoscopic pericardiopleural window in 30 patients.

The characteristics of the pericardial effusions are demonstrated in Table 2. Mean pericardial effusion volume was 565 mL. The effusion was grossly bloody in 32 patients, serosanguinous in 14 patients, straw colored in 15 patients, and purulent in 2 patients. Cytology was available for 58 patients, and pathology was available for 56 patients. Effusions were diagnosed as malignant based on the histologic findings of the excised pericardium and/or the cytologic evaluation of the aspirated fluid. In 15 cases, cytology and histopathologic analysis revealed the presence of malignant cells. In 13 cases, cytology alone was positive for the presence of malignancy. No patient had histopathologic evidence of malignancy in the absence of positive cytology findings. The relationship of cytologic and histologic findings to survival is demonstrated in Figure 1. One-year and 2-year survival was poor, 17.8% (95% CI, 0 to 38.8%) and 8.9% (95% CI, 0 to 25%), respectively, in those patients with both positive cytology findings and pathologic evidence of disease.

Forty-one patients had an additional procedure performed at the time of pericardial window. There were no intraoperative deaths. All patients who were hemodynamically compromised responded immediately to surgical decompression; however, six patients became hypotensive again in the immediate postoperative period and required pressor support. One patient died of cardiogenic shock on postoperative day 2. Postoperative cardiac arrhythmias developed in 4 patients, and pulmonary complications following drainage developed in 14 patients. Postoperative morbidity was not dependent on procedure ($p = 0.56$) but was more likely to occur in patients with hematologic disease than in those with breast, lung, or other solid-tumor diagnoses ($p = 0.03$). Mean ICU days and length of stay (LOS) were 2.5 days and 11 days, respectively. Mean ICU days and LOS for patients by individual diagnoses are displayed in Figure 2. Eight patients (13%), three with

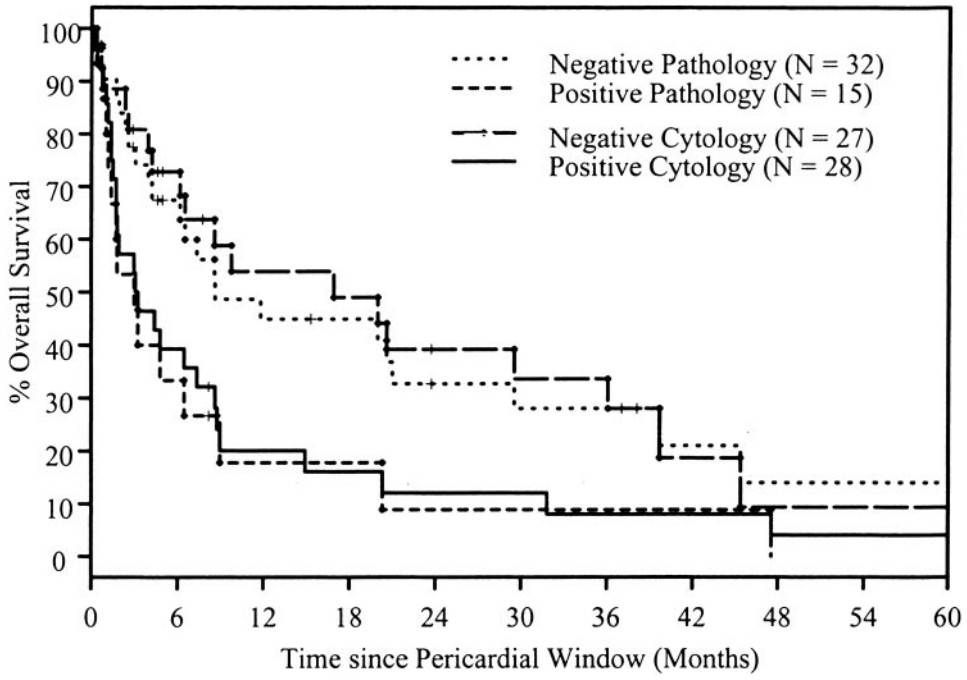

FIGURE 1. Relationship of cytologic or histologic findings to overall survival.

a diagnosis of breast cancer and five with hematologic disease, died during the same hospital admission.

Median follow-up of all patients was 6.6 months; for those still alive at last follow-up, it was 8.3 months. All patients were followed up either clinically, with monthly chest radiographs, or more recently with monthly echocardiography. Thirty-six patients have been followed up with at least one echocardiogram performed at monthly intervals after surgery demonstrating adequate drainage with no evidence of recurrent pericardial effusion.

Overall, a diagnosis of lung cancer carried a worse prognosis than breast cancer ($p = 0.02$), hematologic malignancy ($p = 0.05$), or other solid-tumor malignancy ($p = 0.02$). Other preoperative factors that correlated with a poor outcome included the presence of a pleural effusion ($p = 0.003$), positive cytologic evidence of malignancy ($p = 0.02$), or positive histopathologic evidence of malignancy ($p = 0.02$).

Over the follow-up period, a reaccumulation of pericardial fluid requiring repeat surgical drainage developed in three patients (4.8%). One patient, a 49-year-old man with lymphoma, was initially treated via a subxiphoid approach, recurred 15 weeks later, and was treated thoracoscopically. Two patients re-

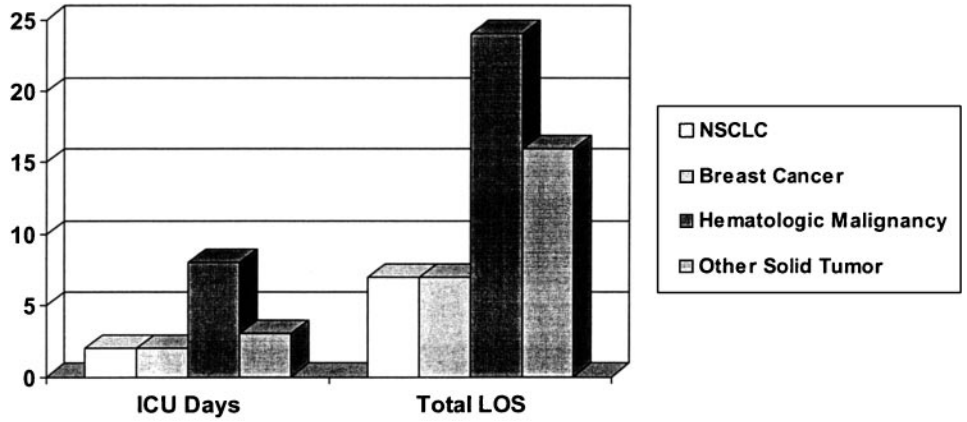

FIGURE 2. Median ICU days and LOS by individual diagnoses.

quired repeat operative drainage on two separate occasions. The first was a 40-year-old patient with breast cancer who initially underwent a subxiphoid approach, recurred approximately 14 weeks later, was treated via a thoracoscopic approach, and 7 weeks later again recurred—ultimately undergoing another subxiphoid procedure for control of her symptomatic pericardial effusion. The second was a 41-year-old patient with lung cancer who initially underwent a pericardial window via a thoracotomy. The patient recurred 5 weeks later and was treated via a limited anterior approach. He again recurred 4 weeks later and was treated via a contralateral thoracotomy.

Discussion

The development of a pericardial effusion is a relatively common complication in the patient with malignancy.[6] Well documented in patients with solid tumors, pericardial effusion has also been described in patients with hematologic malignancy undergoing bone marrow transplantation.[3,7,8] Comparison of the value and efficacy of operative vs nonoperative treatment is difficult due to heterogeneity of patient populations as well as the multiplicity of factors that may ultimately determine patient outcome and survival (Fig 3).

There is little published information on thoracoscopic pericardial window. Few previous published articles offer prolonged follow-up using chest radiography and echocardiography to provide evidence of prevention of recurrent effusion.

Small published series of patients provide data that allow us to make limited comparisons. Noninvasive modalities including mediastinal irradiation and systemic chemotherapy may be considered in the patient population that presents with mild or slowly progressing symptoms. Mediastinal irradiation for malignant effusions caused by a variety of malignancies has an overall 50 to 60% response rate, with best success seen in radiosensitive tumors such as lymphoma or leukemia.[9] The dose required is often close to that which may cause myocarditis, and use is generally restricted to those patients who have not had previous mediastinal radiation.[10] Improvement is usually limited and recurrence of effusion not infrequent.[11] The use of intrapericardial chemotherapeutic agents, instillation of intrapericardial radionucleotides, and sclerotherapy have also been attempted.[12–14] These methods have also, however, demonstrated significant recurrence rates with an overall failure rate of 20% at 30 days.[9] Pericardiocentesis is associated with significant complication rates and is seldom adequate for long-term palliation, with reported recurrence rates as high as 90% at 3 months.[9,15] There is a small experience with control of pericardial window using percutaneous balloon dilation techniques.[16]

Surgical creation of a pericardial window is usually

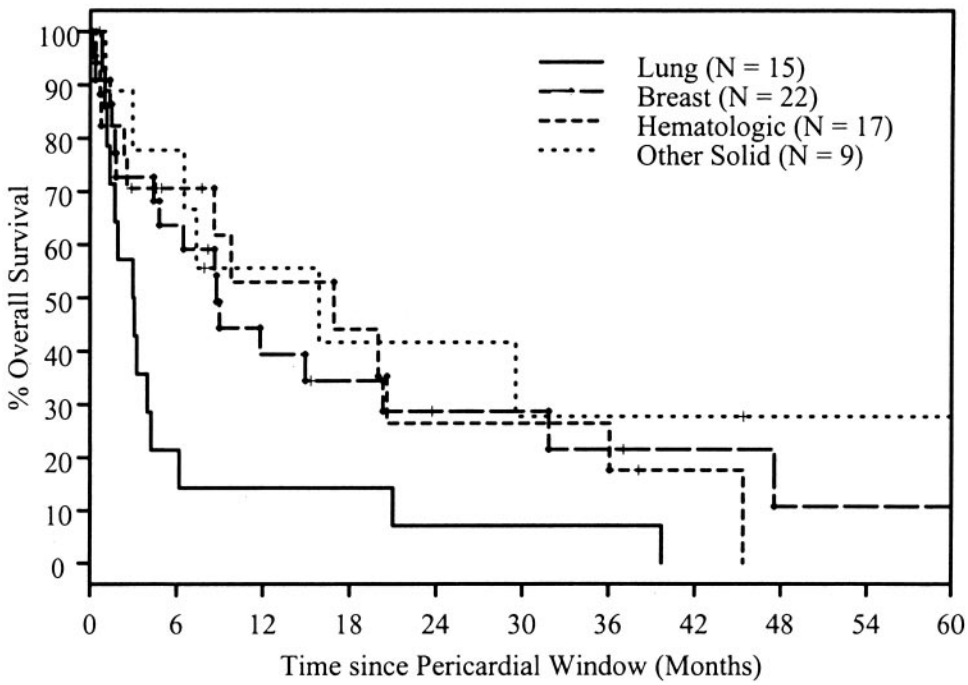

Figure 3. Survival with respect to underlying disease process.

successful in the permanent control of the pericardial effusive process. In those who were discharged from the hospital in this study, 95% remained free of recurrence and were successfully palliated by the creation of a surgical pericardial window. Controversy exists among surgeons as to the best surgical method. Subtotal pericardial resection has proven to have an excellent clinical efficacy but has prolonged recovery time, and today is seldom performed in patients with limited anticipated time of survival. Thoracoscopic or open-thoracic approaches provide wide communication between the pericardial and pleural space allowing the treatment of coexistent pericardial and pleural effusions as well as better addressing loculated pericardial collections.[17] Both, however, require the administration of general anesthesia risking further hemodynamic compromise. Some investigators create subxiphoid windows under local anesthesia and thus might be better tolerated by the high-risk patient.[18,19] The type of surgical procedure did not demonstrate an association with postoperative morbidity or mortality in this study. The evaluation of outcome by method of surgical drainage in this and other series is difficult, due to significant patient heterogeneity.

The survival associated with drainage of a pericardial effusion in patients with lung cancer in this and other studies is dismal. In a review of 20 patients with lung cancer and pericardial effusions, Edoute et al[20] noted that all patients died within 9 months from the time of diagnosis of pericardial effusion. There are limited data suggesting improved survival for patients with breast or lung cancer who receive systemic chemotherapy following drainage.[4,21] It is likely that underlying performance status and lack of effective therapy for advanced disease had a negative impact on survival in this group of patients.

In the presence of malignancy, optimal treatment of the pericardial effusive process should balance treatment efficacy with life expectancy. There are no randomized controlled trials comparing the relative merits of various treatment modalities for control of pericardial effusion, and thus it is difficult to draw conclusions about the superiority of one modality over another. Sample size and statistical assumptions of a random, equal distribution of disease processes prevent us from comparing the efficacy and outcome of patients by surgical method in our series. In addition, morbidity and mortality were high, especially in patients with hematologic malignancy, compared to those with breast, lung, or other solid tumors. The fact that the majority of patients with hematologic disease were in the process of bone marrow transplantation with significant morbidity associated with the underlying disease process, the immunocompromised state, graft-vs-host disease, anemia, leukopenia, and thrombocytopenia may explain this difference in outcome.

The number of patients who were able to leave the hospital and remain free of pericardial effusion demonstrates the beneficial effect of operative drainage. Surgical pericardial drainage is effective, with an overall failure rate of $< 5\%$. Therapy aimed at treating the cancer patient with pericardial effusion must be individualized, taking into consideration the hemodynamic status of the patient and the underlying disease process. The benefit of an operative approach to pericardial drainage may be in the ability to provide a long-term symptom-free interval allowing further aggressive treatment of disease.

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