CASE REPORT

Malignant Pericardial Effusion: Case Report and Review Article

Karim O A Al-Naffi; CABM, FRCP (Glasgow)

College of medicine/karbala-Iraq

A sixty-five year old farmer presented with dry cough & mild exertional dyspnea for 10 days, he has no previous history of asthma or TB, he was not smoker, with no history of hypertension or diabetes, O/E he is well built not cyanosed, mild dyspoenic BP 130/80, PR96/min regular, respiratory rate 20/min.chest examination is clear, Heart examination is normal, abdominal examination also normal.

Chest X-Ray done for him shows normal lung field with enlarge cardiac globular shadow .He was sent for ECHO study which reveals normal cardiac chamber size& contractility with normal AV& semilunar valve. There is pericardial effusion of 21 mm depth posteriorly with early signs of tamponade. The patient was admitted to the hospital, initial hematological & biochemical investigations were normal. emergency pericardiocentesis done under ECHO & ECG monitoring where 300 CC of deep yellowish fluid aspirated and sent for laboratory study the results are protein =3.1gm/dl.sugar =43mg/dl/.microscopical examination reveals a hemorrhagic background with scattered sheets of atypical epithelial cells highly suggestive of malignant tumor most likely is squamous cell carcinoma of the lung.

CT scan of the chest showed 17x19 mm enhanced lung mass at left upper lobe near the aortic arch, no hilar LN with big pericardial effusion.

After three days the patient presented with severe dyspnea & the echo showed big pericardial effusion so surgery is planned. Percardiecctomy with segmental peumonectomy done, the surgery was smooth with normal convalescence. The histopathology of the pericardium did not recognize a malignant involvement and that of the lung revealed moderately differentiated adenocarcinoma, after the healing of the wound the patient reassessed with CX-Ray &ECHO which was normal &he started a course of chemotherapy. He did well for the last 7 months

Pericardium & Pericardial Effusion

In the human embryo, the pericardial cavity develops from the intraembryonic celom during the fourth week. The pericardial cavity initially communicates with the pleural and peritoneal cavities, but during normal development these are separated by the eighth week. Both the visceral and parietal pericardium are derived from the mesoderm, albeit from different parts of the embryo

Congenital absence of the pericardium can occur, and can be either partial or complete. It is often clinically silent, but can potentially lead to excessive cardiac motion (in the case of complete absence) causing vague chest pain or dyspnea, or, in case of partial absence with significant defects, strangulation of heart muscle and possible death.[1]

The pericardial space normally contains 15-50 mL of fluid, which serves as lubrication for the visceral and parietal layers of the pericardium. This fluid is thought to originate from the visceral pericardium and is essentially an ultrafiltrate of plasma. Total protein levels are generally low; however, the concentration of albumin

is increased in pericardial fluid owing to its low molecular weight

Pericardial effusion defines the presence of an abnormal amount and/or character of fluid in the pericardial space. It can be caused by a variety of local and systemic disorders, or it may be idiopathic. Pericardial effusions can be acute or chronic, and the time course of development has a great impact on the patient's symptoms

Malignant pericardial effusion.

The evidence and application to practice related to children may differ significantly from the information related to adults. In this summary, unless otherwise stated, evidence and practice issues as they relate to adults are discussed when specific information about the care of children is available, it is summarized under its own heading

Malignant pericardial effusions are one of the clinical manifestations of what is called cardiopulmonary syndrome which denote the following four items namely:

1-Dyspnea
2-Malignant pleural effusion
3-Malignantpericardial effusion
4-Superior vena cava syndrome

Malignant pericardial effusions occur in up to 21% of cancer patients (1-3) and are frequently not suspected until clinical signs or symptoms of pericardial tamponade develop. [4] Two thirds of patients have subclinical pericardial effusions with no overt cardiovascular signs or symptoms.[5,6] One half of cases of pericardial effusion initially present with symptoms of cardiac tamponade.[7] In one half of cases, pericardial effusion is the first sign of malignant disease.[8] Symptoms of pericardial effusion are often attributed to the underlying cancer. Dyspnea, fatigue, or asthenia may be the initial symptoms.[9] Symptomatic pericardial effusions are often a preterminal event; however, significant symptom palliation can be achieved by prompt diagnosis and management.

Of patients with malignant pericardial effusions, 50% will have concomitant pleural effusions, and one third will have pulmonary parenchymal disease. [4]

One third of patients with pericardial metastases will eventually die from pericardial tamponade. [4] Pericardial involvement contributed to the cause of death in 85% of patients in a series reported in 1962 but in only 46% of patients in a recent study.[10] Improvements in diagnostic and therapeutic options account for the decrease in mortality over the past 40 years.

Incidence and Prevalence

Malignant pericardial effusion occurs in up to 21% of autopsy series in patients with common malignancies.[4,7] Of patients with lung cancer, 33% have pericardial metastases at autopsy, and one third of cases of pericardial metastases are caused by lung cancer.

Breast cancer causes 25% of pericardial effusions, and about 25% of patients with breast cancer have pericardial effusion. Hematological malignancies (leukemia, Hodgkin disease, non-Hodgkin lymphoma) cause 15% of cases of malignant pericardial effusions. [11]

A retrospective review of 23,592 effusions over a 24-year period revealed 65 malignant effusions (17%) out of 375 pericardial effusions. Lung cancer was the most common cancer found among the malignant pericardial effusions in males, and breast cancer was the most common in females. In 43% of cases, pericardial effusion was the first detected sign of cancer. Of

patients diagnosed with malignant pericardial effusions, 86% died within 1 year of diagnosis, with nearly one third dying within the first month.[8]

In a study of 31 patients with both cancer and pericardial effusions, malignant pericardial effusion accounted for 58% of the effusions, 32% were caused by benign idiopathic pericarditis, and radiation pericarditis caused 10% of cases. [11,12]

Pathophysiology

Malignant involvement of the pericardium is the most common reason for development of pericardial effusions, which result from blockage of venous and lymphatic circulation of pericardial fluid. Such blockage may be caused by primary malignancy of the pericardium, as with pericardial mesothelioma, or by tumors arising in the myocardium, including angiosarcoma, rhabdomyosarcoma, and malignant fibrous histiocytosis. Malignancies can also involve the pericardium through direct extension from carcinomas of the lung or esophagus, thymoma, or lymphoma. [9] Lymphatic or hematogenous metastasis to the pericardium occurs most commonly with carcinomas of the breast and lung, leukemia, lymphoma, and melanoma. Primary tumors of the pleura or pericardium have recently been termed primary intrathoracic malignant effusions. [13]

Nonmalignant causes of pericardial effusion include pericarditis, myocardial infarction, uremia, hypothyroiddism, systemic lupus erythematosus, trauma, postsurgical pericardotomy syndrome, and intrapericardial hematomas.[14-16] AIDS may also cause pericardial effusion with pericarditis.[17] Radiation therapy or chemotherapy drugs can cause pericarditis without metastatic involvement of the pericardium. Radiation pericarditis is usually associated with radiation doses to the cardiac window exceeding 3,000 cGy [10] and occurs most frequently in patients who have received mediastinal radiation for Hodgkin disease or breast cancer.[10] Doxorubicin and cyclophosphamide have been associated with the development of acute pericarditis with effusions.[11,12] Other drugs that may cause acute pericarditis include procainamide, hydralazine, isoniazid, methysergide, phenytoin, and anticoagulants.

Clinical manifestations of pericardial effusion are highly dependent upon the rate of accumulation of fluid in the pericardial sac. Rapid accumulation of pericardial fluid may cause elevated intrapericardial pressures with as little as 80 mL of fluid, while slowly progressing effusions can grow to 2 L without symptoms

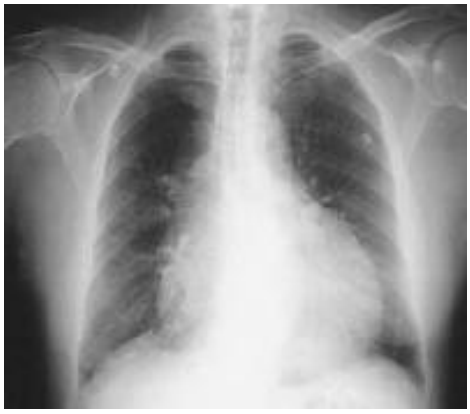
Pericardial tamponade results from progressive fluid accumulation in the pericardial sac, causing elevated intrapericardial pressure, diminished stroke volume, decreased cardiac output, progressive decrease in cardiac diastolic filling, and hemodynamic compromise resulting in death if not treated. Hemodynamic compromise occurs when the normal amount of pericardial fluid (approximately 15–50 cc) increases to 200 cc to 1,800 cc. [15,18] When fluid accumulates rapidly, as little as 250 cc of fluid can result in tamponade.[11,19]

Dyspnea occurs in 93% of patients with pericardial effusions. [6] Cough, chest pain, and orthopnea (discomfort with breathing while lying flat) are common symptoms. Other symptoms of pericardial effusion include upper abdominal distention or pressure due to downward hepatic distention, hiccups due to pressure on the diaphragm, or pleuritic pain due to stretching of the pericardium (especially when lying flat). Signs of effusion include

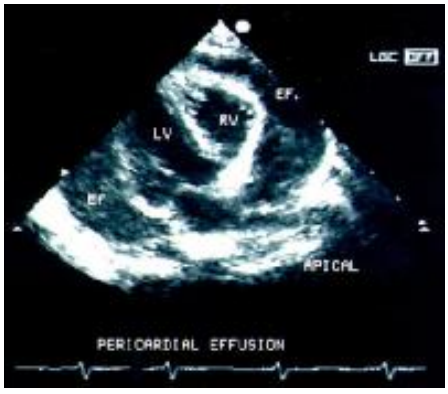
Kussmaul's sign (increased distention of jugular veins with inspiration), Freidreich's sign (rapid diastolic descent of the venous pulse), and pulsusparadoxus (decrease of more than 10 mm Hg in the diastolic pressure on inspiration). Pericardial friction rubs and fever are more commonly associated with nonmalignant causes of pericardial effusions than malignant etiologies. [9] Signs of pericardial tamponade include tachycardia, pulsusparadoxus, elevated jugular venous pressure, and hypotension; however, some patients may develop tamponade without this clinical pattern. [4]

Diagnosis

Chest radiography may show widening of the cardiac silhouette [7] if the amount of pericardial fluid collection exceeds 250 cc. [20] Chest x-ray cannot determine the degree of cardiac dysfunction or tamponade. Loculated pericardial effusions may not be apparent on standard posterior/anterior or lateral chest radiographic views.[15]



Transthoracic echocardiography using apical, subxiphoid, and parasternal views can evaluate the presence, quantity, and quality of suspected pericardial effusions as well as associated pericardial masses and inflammation. Moderate effusions on echocardiography show an echo-free space of 10 mm to 20 mm during diastole in M-mode or 2-dimensional echocardiography, whereas severe effusions have an echo-free space exceeding 20 mm. [21,22] Echocardiography can also determine right and left ventricular function and the possibility of right ventricular or atrial diastolic collapse. [7] Left ventricular collapse due to large pleural effusion without clinically significant pericardial effusions has been reported;[4,16,23,24] however, transesophageal echocardiography may be useful for loculated effusions due to adhesions adjacent to the atria, where the thinness of the atrial wall may not be well visualized on transthoracic echocardiography.[4,16]



Echocardiography in pericardial effusion with tamponade shows right atrial or right ventricular compression, or left atrial compression, decreased left ventricular dimension, and absence of collapse of the inferior vena cava on deep inspiration.[6,25] Echocardiography findings predictive of pericardial tamponade have been reported.[26] Right atrial collapse has a sensitivity of 55% to 60% and a specificity of 50% to 68%. Right ventricular diastolic collapse has a lower sensitivity of 38% to 48% but a higher specificity ranging from 84% to 100%. Because neither finding provides 100% sensitivity and specificity, patients who are clinically

symptomatic should have a diagnostic pericardiocentesis, even in the absence of definitive findings on echocardiography.[4,27] One study found right atrial collapse present in only 42% of patients and right ventricular collapse in 62%.[27] Nonetheless, 80% of patients with malignant pericardial effusions had symptomatic relief following pericardiocentesis.

The most definitive test for the diagnosis of cardiac tamponade is equalization of diastolic pressures between all cardiac chambers on right-heart cardiac catheterization.[7] This invasive technique, however, is not necessary to diagnose tamponade.

Electrocardiograms in patients with pericardial effusions typically show diminished QRS amplitude in all leads. A classic but uncommonly seen finding in large effusions with pericardial tamponade is variation in the amplitude of the P wave and QRS complex in successive beats on EKG, referred to as electrical alternans. This finding results from movement of the heart within the pericardial sac.[6] Electrocardiography is not sufficiently sensitive to diagnose pericardial effusions.

Pericardial fluid cytology has an accuracy of 80% to 90% in diagnosing malignant pericardial effusion.[6,28] Lymphomas and mesothelioma have higher false-negative detection rates on cytology evaluation.[6,29] Pericardial fluid cytology has a specificity of up to 100%, but sensitivity ranges from 57% to 100% in patients with a known cancer diagnosis and pericardial fluid. Because nonmalignant causes of pericardial effusion can occur in 42% to 62% of patients with cancer and pericardial fluid, a negative cytology examination of pericardial fluid does not help distinguish malignant from nonmalignant causes. The use of more than one cytological preparation (such as concentrating the sample via cytospin, using special markers, or analyzing DNA content) increases the yield over a single preparation; however, multiple samples using the same technique did not significantly increase the diagnostic yield in a retrospective study of 215 patients.[30] In a survey of 80 samples, measurement of DNA index via flow cytometry of pericardial fluid has a sensitivity of 94.8% and a specificity of 100%, compared with routine cytology with a sensitivity of 98.5% and a specificity of 92.3% Pericardial biopsy may increase the sensitivity of diagnosing pericardial effusions of malignant origin. Because pericardial effusions usually occur in advanced disease and portend a shorter survival than do other sites of metastatic involvement, however, the relief of symptoms rather than diagnosis should be the overriding factor in determining the extent of the evaluation and the course of treatment. Two studies failed to show a difference in survival in cancer patients with pericardial effusion dependent on the results of fluid cytology. [10,32]

Treatment

No large controlled, randomized, prospective clinical trials demonstrate the optimal management of malignant pericardial effusions or tamponade. Treatment should therefore be individuallized to maximize symptom relief with minimal impact on quality of life.

Treatment options include percutaneous pericardiocentesis, pericardial sclerosis, subxiphoid pericardial window, pericardiectomy, or pericardotomy by thoracotomy or video-assisted thoracoscopy. Considerations in the choice of therapeutic option should include relief of tamponade, minimal invasiveness, cost, morbidity, safety,

shortened hospitalization for patients with advanced disease, and patient's prognosis. [33]

Large symptomatic malignant pericardial effusions are managed by draining the fluid, unless the goals of therapy dictate a less invasive, conservative approach with concomitant shorter survival that should be balanced against quality-of-life concerns. If treatment is indicated for management of tamponade, percutaneous subxiphoid pericardiocentesis is the treatment of choice in the acute setting. Echocardiography is recommended for catheter guidance.[6,34] Catheter drainage is recommended for large effusions to prevent rapid reaccumulation of fluid and subsequent tamponade and for the anticipated survival of the patient.

Recurrent pericardial effusion occurs in 21% [35] to 50% [33,34] of patients following pericardiocentesis. Limited case series suggest rates of pericardial fluid reaccumulation at 30 days ranging from 5% to 33% after pericardial drainage followed by intrapericardial treatment with sclerosing agents or phosphorus-colloid versus more than 50% of those treated with pericardial drainage alone.[33,34] Treatment options to prevent reaccumulation include intrapericardial sclerosis to obliterate the space within the pericardial sac, or pericardotomy to increase the quantity of fluid drained from the pericardium. The most effective sclerosing agent for malignant pericardial effusions had been tetracycline, with success rates of up to 80 %;[6] however, this agent is no longer available as an intravenous drug in the United States. Alternative sclerosants that have been used include doxycycline,[36] bleomycin, thiotepa,[34];[37] carboplatin, mitoxantrone,[39] docetaxel, and radionuclide chromic phosphate. Most cases may require 3 or more treatments to achieve adequate sclerosis.[6] Significant pain is reported by 16% of patients undergoing pericardial sclerosis. [6] Consideration must be given to the side effects of various sclerosing agents, e.g., chest pain and arrhythmias. Of patients undergoing pericardial sclerotherapy, 70% to 80% have no fluid reaccumulation within 30 days of the procedure.[34]

A retrospective comparison of pericardiocentesis with sclerotherapy to open surgical drainage among 60 patients showed similar rates for treatment complications, incidence of recurrent effusion, and survival following treatment in both treatment groups.[40] A retrospective review of 59 patients also found similar success rates, whether patients were managed with surgical subxiphoid pericardial window or by pericardiocentesis with or without sclerosis.[33] Patients who underwent pericardiocentesis followed by pericardial window had the longest survival, with a median of 6 months; however, selection bias toward patients with better performance status undergoing more aggressive surgical techniques may contribute to the reported survival advantage. The surgical procedure group had significantly higher average costs of $4,830 compared with $1,625 for patients managed with pericardiocentesis.[33] Other studies have reported mortality, recurrence, and survival rates for sclerosis that are similar to or slightly lower than those for subxiphoid window or video-assisted thoracoscopy.[40,41];(Pericardiocentesis with or without sclerotherapy should be considered over more invasive procedures in patients with advanced disease or poor functional status.[43]

Transcutaneous balloon pericardiostomy is another technique that is less invasive than open surgical approaches, which include subxiphoid pericardial windows, thoracotomy with

pericardiopleural window formation,[44] and thoracotomy with pericardectomy.

Video pericardioscopy has a diagnostic sensitivity of 97% for detecting malignant effusions.[45]

Pericardioscopy also is useful for drainage of loculated effusions.[46]

Video-assisted thoracoscopy is preferable to more invasive surgical management and should be considered for patients requiring repeated pericardiocentesis for control of symptomatic effusions.[43]

N.B: The main topic of information is derived from the national Cancer Institute-USA

References

1. Lam KY, Dickens P, Chan AC: Tumors of the heart. A 20-year experience with a review of 12,485 consecutive autopsies. Arch Pathol Lab Med 117 (10): 1027-31, 1993. (PUBMED Abstract)
2. Silvestri F, Bussani R, Pavletic N, et al.: Metastases of the heart and pericardium. G Ital Cardiol 27 (12): 1252-5, 1997. (PUBMED Abstract)
3. Galli M, Politi A, Jemoli R, et al.: Transcatheter management of cardiac and pericardial metastatic involvement. G Ital Cardiol 28 (6): 687-90, 1998. (PUBMED Abstract)
4. Shepherd FA: Malignant pericardial effusion. Curr Opin Oncol 9 (2): 170-4, 1997. (PUBMED Abstract)
5. Bisel HF, Wroblewski F, Ladue JS: Incidence and clinical manifestations of cardiac metastases. J Am Med Assoc 153 (8): 712-5, 1953. (PUBMED Abstract)
6. Fiocco M, Krasna MJ: The management of malignant pleural and pericardial effusions. Hematol Oncol Clin North Am 11 (2): 253-65, 1997. (PUBMED Abstract)
7. DeCamp MM Jr, Mentzer SJ, Swanson SJ, et al.: Malignant effusive disease of the pleura and pericardium. Chest 112 (4 Suppl): 291S-295S, 1997. (PUBMED Abstract)
8. García-Riego A, Cuiñas C, Vilanova JJ: Malignant pericardial effusion. Acta Cytol 45 (4): 561-6, 2001 Jul-Aug. (PUBMED Abstract)
9. Warren WH: Malignancies involving the pericardium. Semin Thorac Cardiovasc Surg 12 (2): 119-29, 2000. (PUBMED Abstract)
10. Wang PC, Yang KY, Chao JY, et al.: Prognostic role of pericardial fluid cytology in cardiac tamponade associated with non-small cell lung cancer. Chest 118 (3): 744-9, 2000. (PUBMED Abstract)
11. Chiles C, Woodard PK, Gutierrez FR, et al.: Metastatic involvement of the heart and pericardium: CT and MR imaging. Radiographics 21 (2): 439-49, 2001 Mar-Apr. (PUBMED Abstract)
12. Posner MR, Cohen GI, Skarin AT: Pericardial disease in patients with cancer. The differentiation of malignant from idiopathic and radiation-induced pericarditis. Am J Med 71 (3): 407-13, 1981. (PUBMED Abstract)
13. Ang P, Tan EH, Leong SS, et al.: Primary intrathoracic malignant effusion: a descriptive study. Chest 120 (1): 50-4, 2001. (PUBMED Abstract)
14. Guberman BA, Fowler NO, Engel PJ, et al.: Cardiac tamponade in medical patients. Circulation 64 (3): 633-40, 1981. (PUBMED Abstract)
15. Beauchamp KA: Pericardial tamponade: an oncologic emergency. Clin J Oncol Nurs 2 (3): 85-95, 1998. (PUBMED Abstract)
16. D'Cruz IA, Kanuru N: Echocardiography of serous effusions adjacent to the heart. Echocardiography 18 (5): 445-56, 2001. (PUBMED Abstract)
17. White CS: MR evaluation of the pericardium and cardiac malignancies. Magn Reson Imaging Clin N Am 4 (2): 237-51, 1996. (PUBMED Abstract)
18. Celermajer DS, Boyer MJ, Bailey BP, et al.: Pericardiocentesis for symptomatic malignant pericardial effusion: a study of 36 patients. Med J Aust 154 (1): 19-22, 1991. (PUBMED Abstract)
19. Hancock EW: Neoplastic pericardial disease. Cardiol Clin 8 (4): 673-82, 1990. (PUBMED Abstract)
20. Mercé J, Sagristà-Sauleda J, Permanyer-Miralda G, et al.: Correlation between clinical and Doppler echocardiographic findings in patients with moderate and large pericardial effusion: implications for the diagnosis of cardiac tamponade. Am Heart J 138 (4 Pt 1): 759-64, 1999. (PUBMED Abstract)
21. Weitzman LB, Tinker WP, Kronzon I, et al.: The incidence and natural history of pericardial effusion after cardiac surgery--an echocardiographic study. Circulation

69 (3): 506-11, 1984. (PUBMED Abstract)
22. Sagristà-Sauleda J, Mercé J, Permanyer-Miralda G, et al.: Clinical clues to the causes of large pericardial effusions. Am J Med 109 (2): 95-101, 2000. (PUBMED Abstract)
23. Kisanuki A, Shono H, Kiyonaga K, et al.: Two-dimensional echocardiographic demonstration of left ventricular diastolic collapse due to compression by pleural effusion. Am Heart J 122 (4 Pt 1): 1173-5, 1991. (PUBMED Abstract)
24. Kaplan LM, Epstein SK, Schwartz SL, et al.: Clinical, echocardiographic, and hemodynamic evidence of cardiac tamponade caused by large pleural effusions. Am J Respir Crit Care Med 151 (3 Pt 1): 904-8, 1995. (PUBMED Abstract)
25. Himelman RB, Kircher B, Rockey DC, et al.: Inferior vena cava plethora with blunted respiratory response: a sensitive echocardiographic sign of cardiac tamponade. J Am Coll Cardiol 12 (6): 1470-7, 1988. (PUBMED Abstract)
26. Chong HH, Plotnick GD: Pericardial effusion and tamponade: evaluation, imaging modalities, and management. Compr Ther 21 (7): 378-85, 1995. (PUBMED Abstract)
27. Cooper JP, Oliver RM, Currie P, et al.: How do the clinical findings in patients with pericardial effusions influence the success of aspiration? Br Heart J 73 (4): 351-4, 1995. (PUBMED Abstract)
28. Meyers DG, Meyers RE, Prendergast TW: The usefulness of diagnostic tests on pericardial fluid. Chest 111 (5): 1213-21, 1997. (PUBMED Abstract)
29. Thurber DL, Edwards JE, Achor RW: Secondary malignant tumors of the pericardium. Circulation 26: 228-41, 1962. (PUBMED Abstract)
30. Garcia LW, Ducatman BS, Wang HH: The value of multiple fluid specimens in the cytological diagnosis of malignancy. Mod Pathol 7 (6): 665-8, 1994. (PUBMED Abstract)
31. Decker D, Stratmann H, Springer W, et al.: Benign and malignant cells in effusions: diagnostic value of image DNA cytometry in comparison to cytological analysis. Pathol Res Pract 194 (11): 791-5, 1998. (PUBMED Abstract)
32. Okamoto H, Shinkai T, Yamakido M, et al.: Cardiac tamponade caused by primary lung cancer and the management of pericardial effusion. Cancer 71 (1): 93-8, 1993. (PUBMED Abstract)
33. Anderson TM, Ray CW, Nwogu CE, et al.: Pericardial catheter sclerosis versus surgical procedures for pericardial effusions in cancer patients. J Cardiovasc Surg (Torino) 42 (3): 415-9, 2001. (PUBMED Abstract)
34. Martinoni A, Cipolla CM, Civelli M, et al.: Intrapericardial treatment of neoplastic pericardial effusions. Herz 25 (8): 787-93, 2000. (PUBMED Abstract)
35. Tsang TS, Seward JB, Barnes ME, et al.: Outcomes of primary and secondary treatment of pericardial effusion in patients with malignancy. Mayo Clin Proc 75 (3): 248-53, 2000. (PUBMED Abstract)
36. Vaitkus PT, Herrmann HC, LeWinter MM: Treatment of malignant pericardial effusion. JAMA 272 (1): 59-64, 1994. (PUBMED Abstract)
37. Colleoni M, Martinelli G, Beretta F, et al.: Intracavitary chemotherapy with thiotepa in malignant pericardial effusions: an active and well-tolerated regimen. J Clin Oncol 16 (7): 2371-6, 1998. (PUBMED Abstract)
38. Moriya T, Takiguchi Y, Tabeta H, et al.: Controlling malignant pericardial effusion by intrapericardial carboplatin administration in patients with primary non-small-cell lung cancer. Br J Cancer 83 (7): 858-62, 2000. (PUBMED Abstract)
39. Norum J, Lunde P, Aasebø U, et al.: Mitoxantrone in malignant pericardial effusion. J Chemother 10 (5): 399-404, 1998. (PUBMED Abstract)
40. Girardi LN, Ginsberg RJ, Burt ME: Pericardiocentesis and intrapericardial sclerosis: effective therapy for malignant pericardial effusions. Ann Thorac Surg 64 (5): 1422-7; discussion 1427-8, 1997. (PUBMED Abstract)
41. Maher EA, Shepherd FA, Todd TJ: Pericardial sclerosis as the primary management of malignant pericardial effusion and cardiac tamponade. J Thorac Cardiovasc Surg 112 (3): 637-43, 1996. (PUBMED Abstract)
42. Liu G, Crump M, Goss PE, et al.: Prospective comparison of the sclerosing agents doxycycline and bleomycin for the primary management of malignant pericardial effusion and cardiac tamponade. J Clin Oncol 14 (12): 3141-7, 1996. (PUBMED Abstract)
43. Lin JC, Hazelrigg SR, Landreneau RJ: Video-assisted thoracic surgery for diseases within the mediastinum. Surg Clin North Am 80 (5): 1511-33, 2000. (PUBMED Abstract)

44. Olson JE, Ryan MB, Blumenstock DA: Eleven years' experience with pericardial-peritoneal window in the management of malignant and benign pericardial effusions. Ann Surg Oncol 2 (2): 165-9, 1995. (PUBMED Abstract)
45. Porte HL, Janecki-Delebecq TJ, Finzi L, et al.: Pericardoscopy for primary management of pericardial effusion in cancer patients. Eur J Cardiothorac Surg 16 (3): 287-91, 1999. (PUBMED Abstract)
46. Millaire A, Wurtz A, de Groote P, et al.: Malignant pericardial effusions: usefulness of pericardioscopy. Am Heart J 124 (4): 1030-4, 1992. (PUBMED Abstract)