Palliative treatment for symptomatic malignant pericardial effusion

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SUMMARY

Consensus has yet to emerge regarding the optimal choice of therapy in the management of malignant pericardial effusion. We review the literature to evaluate the existing evidence on the clinical effectiveness of surgical and interventional cardiological approaches.

A formal literature search for all studies addressing the treatment of pericardial effusion in cancer patients was undertaken using pre-defined keywords. Abstracts were screened, reviewed and data extracted. Data on intervention type, number of patients treated, number of patients surviving the procedure, effusion recurrences, need for further interventions, and procedure-related complications were obtained from each study and collated in a quantitative synthesis.

Of 1181 articles identified, 59 contained sufficient quantitative information to be included in the synthesis. A total of 2322 patients with symptomatic pericardial effusion were identified of which 1399 patients were reported to have underlying malignancy. Three surgical approaches were described in a total of 19 studies with overall success rates ranging from 93.3% to 100% and associated complication rates ranging from 4.5% to 10.3%. The remaining 40 studies reported 4 non-surgical treatment modalities with success rates of 55.1% to 90.4% and complication rates of 5.9% to 32%.

Data from the literature suggest that surgical drainage of the pericardium is superior to non-surgical approaches for symptom relief, effusion recurrence, and morbidity; however, the lack of randomised controlled trials mean that selection bias remains an important limitation to the field and definitive adequately controlled trials should be a priority.

Key words: Malignant Pericardial Effusion, Surgery, Sclerosant

1. INTRODUCTION

The pericardium is a frequent site for neoplastic involvement [1]. Although primary tumours of the pericardium are rare, metastasis to the heart and pericardium have been reported in up to 21% of cancer patients [2]. The majority of these patients remain asymptomatic, but impairment of cardiac function contributing to morbidity occurs in one third of cases [3]. Moreover, the potential for life-threatening cardiac tamponade makes pericardial effusion an important contributor to mortality in cancer patients and can require emergency decompression.

Despite aggressive treatment, the prognosis for patients with malignant pericardial effusion remains poor and is primarily dictated by the underlying disease [4]. The goal of treatment is therefore palliation of symptoms and prevention of effusion recurrence; however, the 'gold standard' treatment for malignant pericardial effusion has yet to be defined. While simple pericardiocentesis is effective in the emergency setting of cardiac tamponade, rapid re-accumulation of pericardial fluid commonly occurs unless more definitive measures are employed [5].

Current guidelines recommend a number of approaches, both interventional cardiological and surgical; however, no randomised controlled trials have been undertaken to determine the relative merits of these treatment modalities [6]. Since this subject was reviewed previously, a number of studies have been published but a consensus has yet to emerge regarding the optimal therapeutic strategy [7-9]. In this systematic review we set out to address the following question:

In patients with malignant pericardial effusion is surgical treatment superior to interventional cardiological management in terms of resolution of symptoms and prevention of effusion recurrence?

2. MATERIALS AND METHODS

2.1 Sources of data

We searched Embase from 1974 to May 2013, Medline from 1946 to May 2013, and the Cochrane Library database in May 2013 using a formal search strategy. Combinations of pre-defined Medical Subject Heading (MeSH) terms and text words related to the treatment of pericardial effusion in cancer patients were used. The search was conservative to retain any likely contributing studies; however, publications in foreign languages were excluded. In addition, we searched the reference lists of publications to identify additional studies of relevance.

2.2 Eligibility criteria

Publications describing the outcomes of patients diagnosed with malignant pericardial effusion by imaging or cytology were considered. Our literature search identified a number of studies reporting mixed patient groups with both neoplastic and non-malignant pericardial effusions. In such cases, data extraction was deemed possible only if the outcomes of patients undergoing treatment for malignant pericardial effusion were reported separately. Studies were included only if they reported outcomes for a single common treatment modality rather than combinations of treatments (Table 1).

2.3 Data extraction

Results from the online search were imported into a reference management program for detection of duplicates. Next, studies were grouped on a spreadsheet for further analysis. For each study, intervention type, number of patients treated, number of patients surviving the procedure, number of effusion recurrences, number of further interventions necessary, and procedure-related complications were extracted. This information was obtained from the body of the text as well as from relevant figures. Data for survival, recurrence and further interventions were presented relative to the total

number of cancer patients reported in each study. Data relating to procedure-related complications and side effects were presented relative to the total number of patients treated in each study (Tables 2-6). An intervention was considered to be successful if the patient survived the initial procedure and did not develop a symptomatic recurrence of their effusion and required no further pericardial interventions.

3. RESULTS

A search on 31 May 2013 yielded a total of 1181 papers. Titles and abstracts were reviewed for relevance. The majority were retrospective cohort studies with a small number of prospective studies. Duplicates, case reports, review articles, studies superseded by later reports from the same institution, and publications containing no quantitative data were excluded. Only 59 papers fulfilled these criteria and were considered further (Fig. 1).

3.1 Single pericardiocentesis

Pericardiocentesis is indicated as an emergency procedure in patients with cardiac tamponade. Before the advent of two-dimensional echocardiography, the procedure was carried out using a blind subxiphoid approach, which oftentimes resulted in serious complications [7]. Because two-dimensional echocardiography permits direct visualisation of cardiac structures and adjacent vital organs, the procedure can now be performed with minimal risk. Two studies reported the use of pericardiocentesis as the definitive treatment for malignant pericardial effusion [10, 11] (Table 2). Apodaca-Cruza et al. treated a total of 100 patients and reported a success rate of 67% [10]. Effusions recurred in the remaining patients, with 29% of patients requiring further intervention. The rate of complications was low at 3% and involved vagal hypotension in all three cases. Lindenberger et al. reported 31 patients treated by pericardiocentesis [11]. Symptomatic relief was achieved in only 45.2% of patients and was associated with a higher rate of procedure-related complications of 8.3%. These included arrhythmias and ventricular puncture. More than half of the patients (54.8%) required further intervention for re-accumulation of pericardial fluid. In neither study were procedure-related deaths reported.

3.2 Extended catheter drainage

To reduce the rate of effusion recurrence following pericardiocentesis extended catheter drainage has been attempted by placement of an indwelling catheter into the pericardial space. Our search identified 6 studies describing the management of malignant pericardial effusion using extended catheter drainage [12-17] (Table 3). Complete resolution of effusion was achieved in only 55.1% of cases. The remainder required further intervention for effusion recurrence. The rate of complications was 12%, arrhythmias being the most common. No fatalities as a direct consequence of the procedure were reported in any of the six studies.

3.3 Pericardial sclerosis

Another well-established approach to reduce the re-accumulation of pericardial fluid is the use of sclerosing agents. These are instilled into the pericardium with the intention to obliterate the potential space by causing adhesions between the pericardial layers. Twenty-two studies described the use of a variety of sclerosants to treat malignant pericardial effusion [18-39] (Table 4). Cisplatin was the most widely employed agent being reported in 5 studies with a total of 176 patients [18, 25, 29, 36, 38]. In 90.3% of these patients, treatment was successful with recurrence of the effusion and procedure-related morbidity in 9.1% and 13.6%, respectively. The intrapericardial instillation of tetracycline was reported in 2 studies totalling 91 patients with a good overall success rate of 87.9% and only 8.8% suffering effusion recurrence, but complications and side effects were high at 45.1% [21, 37]. Thiotepa (N,N'N'-triethylenethiophosphoramide) was used in 3 studies totalling 75 patients [19, 20, 30]. Of those, 90.7% remained symptom-free and only 6.7% suffered complications. Forty-five patients treated with bleomycin were reported in 3 studies [31, 33, 39]. This agent was able to prevent recurrence of effusion in 88.9% of cases, but 26.7% of patients sustained complications, most commonly fever, but in one case constrictive pericarditis caused death. Mitomycin C has been reported in only 2 studies totalling 28 participants [23, 27]. Of those, 19 (67.9%) were treated successfully but there was one case of pericardial constriction (3.6%). Three studies, with a total of

27 patients, reported the use of mitoxantrone in the treatment of malignant pericardial effusion [28, 34, 35]. This agent improved clinical status in 24 patients (88.9%) with no reported complications. The remaining 4 studies employed a range of unique agents to induce pericardial sclerosis [22, 24, 26, 32] (Table 5). These included 2 other tetracycline antibiotics [24, 26] and a second platinum-based chemotherapy, carboplatin [32]. Their results were similar to those of tetracycline and cisplatin respectively. The final agent, OK-432 (penicillin-killed *Streptococcus pyogenes*) was successful in the 3 cases treated, but unsurprisingly caused high fever and pain in each of these [22].

3.4 Surgical intervention

Three surgical approaches to the treatment of malignant pericardial effusion have been described in 19 studies: pericardial fenestration, pericardiectomy, and pericardio-peritoneal shunt insertion [40-58] (Table 5). Pericardial fenestration is the creation of a 'pericardial window' a few centimetres in diameter to enable the drainage of pericardial fluid into the pleural space. Pericardiectomy, the surgical resection of part or all of the pericardium, is a more aggressive approach to achieve a more complete drainage. The insertion of a pericardio-peritoneal shunt involves the placement of a Denver shunt inflow catheter into the pericardial space with the abdominal end tunnelled subcutaneously across the right costal margin through a 3 cm skin incision into the peritoneal cavity. A pumping chamber connected to the shunt is then used for intermittent compression.

The most commonly reported surgical procedure in the literature is pericardial fenestration, which was described in 15 studies [40-44, 46, 48-54, 56, 58]. This technique was associated with an overall success rate of 93.3%. Recurrence was reported in 5.7% and complications occurred in 4.5%. One procedure-related death was reported. Ten out of the 15 studies reported this procedure performed via the subxiphoid approach, whereby a short vertical incision is made over the xiphoid process, allowing the pericardium to be grasped with surgical clamps and incised directly [40, 41, 46, 48, 50-53, 56, 58]. This procedure had a success rate of 93.2%, an effusion recurrence rate of 5.5%, and a complication rate of 3.9%. In 3 studies pericardial fenestration was carried out using video-assisted thoracic

surgery (VATS) [43, 44, 49, 54]. With the patient under general anaesthesia and using single lung ventilation, a thoracoscope is introduced into the thorax. Two further ports are used to grasp and excise a portion of the pericardium to create a pericardial window. This approach was successful in 90.9% of cases with 9.1% recurrence overall. Patients sustained complications in 4.8% of cases. In one study, 26 patients underwent pericardial fenestration by left mini-thoractomy [42]. This achieved control of the effusion in 96.2% of cases with only one patient requiring further treatment due to recurrence (3.8%) and complications observed in 11.3% of patients. Another report described the use of an alternative approach, known as mediastinoscope-controlled parasternal fenestration (MCPF), to create an opening in the pericardium in 22 patients with 100% success and 13.6% complications [54]. Owing to their low numbers, these single reports must be interpreted with caution. Pericardiectomy was the second most commonly reported surgical procedure [45, 47, 55]. All 3 studies that described this approach were performed using VATS with success in all cases and a comparatively higher overall rate of complications of 10.3%. A single study comprising only 4 cases reported the insertion of a pericardio-peritoneal shunt to treat malignant pericardial effusion [57]. This approach was successful in each patient without reported complications, but as before, the small numbers of this series require caution in its interpretation.

3.5 Percutaneous balloon pericardiotomy

Percutaneous balloon pericardiotomy (PBP) requires a guide wire to be is inserted into the pericardial space over which a balloon catheter is passed and inflated to create a window in the pericardium. Typically, fluid passes from the pericardium into the left pleural space. We identified 10 studies reporting the use of this technique to manage malignant pericardial effusion [59-68] (Table 6). In a majority of these the outcomes were good with control of the effusion in 90.4%. The least good outcomes were seen in the smaller studies, suggesting that PBP might best be performed in centres with a higher throughput of patients. There were no procedure-related deaths in any of the 10 studies but complications occurred in 32%, the most common being pleural effusion, fever and pneumothorax.

4. DISCUSSION

Malignant pericardial effusion is an important complication of advanced malignancy that contributes significantly to morbidity and also can hasten death. Although the prognosis of patients with this condition is considered to be poor, therapeutic intervention, if successful, can improve quality of life and prolong survival. Despite this, there have been no randomised controlled trials of therapies and practices differ widely. Immediate drainage of the pericardial cavity prevents tamponade and so relieves symptoms rapidly. Simple pericardiocentesis under local anaesthesia can therefore provide immediate relief. It is a relatively quick and straightforward procedure that can be performed by physicians and radiologists, and provides fluid for cytological diagnosis. The use of echocardiographic-guidance significantly reduces procedure-related complications (5.9%). Despite its usefulness in the acute setting, pericardiocentesis is frequently inadequate in the medium term because of its high rate of recurrence. Even when pericardiocentesis is followed by extended tube drainage the results are poor. Indeed, this approach had only a 55.1% success rate overall when we assessed six individual series and was associated with a higher rate of complication (12%). For this reason, in many patients percardiocentesis must be followed by a more definitive procedure.

The intrapericardial instillation of a sclerosant has been widely performed in cases of recurrent malignant pericardial effusion. Overall, when considering all agents together, this approach has a success rate of 87.8%, but suffers from a high rate of morbidity (20.5%). There appears to be little difference between the individual agents in terms of their effectiveness, although cisplatin and tetracycline have been the most widely reported. The lack of availability of appropriate preparations of tetracycline and its possible higher rate of complications currently make cisplatin a more favourable agent. It may be especially useful for poor surgical candidates.

Surgical decompression of the pericardium appears overall to have a higher success rate of 93.5% and to be associated with fewer complications (4.7%). The subxiphoid approach has the advantage that it can be performed under local anasthaesia in contrast to VATS, which requires general anaesthesia and

single lung ventilation; procedures that can be challenging in critically ill patients. Although surgical treatment options appear to be associated with better clinical outcomes, the lack of adequately controlled studies means that selection bias, with the healthier cases more likely to undergo surgery, remains a real possibility. The published studies reported performance status inconsistently. In only 6 out of 40 papers that reported a medical-cardiological intervention was information on the performance status provided [10, 18, 20, 23, 30, 32], while in only 1 out 19 surgical studies was the performance status available [55]. Since these data include only 11 surgical cases, in contrast to 208 medical cases, statistical comparison would be invalid; however, in both groups the median performance status appeared to be equivalent to 3 using the ECOG scale. Clearly, only with true randomisation will this important question be answered.

Percutaneous balloon pericardiotomy (PBP) was developed to avoid some of the disadvantages associated with surgery, since it can be performed under local anaesthesia and in most cases enables early discharge home. It has a success rate of 90.4% but is associated with more procedure-related complications (32%) when compared with conventional surgery.

Sclerosant therapy is appropriate for those unfit for any surgical intervention, but its high risk of complications suggests that an intervention that promotes pericardial drainage is the treatment of choice for most other cases. What remains unclear is which procedure is truly superior. We conclude that more and higher quality studies are necessary to address the issues that have been raised by this literature review. A head to head comparison, preferably as a randomised controlled trial comparing the two least invasive approaches, pericardial fenestration via the subxiphoid approach versus percutaneous balloon pericardiotomy would be immensely valuable to the field.

Limitations

A number of limitations in the published literature hamper the comparison of the treatment modalities used to treat malignant pericardial effusion. First, short term success rates are difficult to define because survival following a procedure depends significantly on the institution, the clinician, and the patient. Second, metastatic pericardial disease remains a lethal condition. Prognosis is primarily dictated by the non-cardiac progression of the underlying malignancy, thereby making long-term success rates difficult to define. Third, all studies included in this review were observational studies, most of them retrospective. This is an important additional factor that limits the interpretation of observed differences between results.

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CONFLICTS OF INTEREST

None declared.

REFERENCES

[1] Abraham KP, Reddy V, Gattuso P. *Neoplasms metastatic to the heart: review of 3314 consecutive autopsies*. Am J Cardiovasc Pathol 1990;**3**:195-8.

[2] 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 1993;**117**:1027-31.

[3] Thurber DL, Edwards JE, Achor RW. *Secondary malignant tumors of the pericardium*. Circulation 1962;**26**:228-41.

[4] Gornik HL, Gerhard-Herman M, Beckman JA. *Abnormal cytology predicts poor prognosis in cancer patients with pericardial effusion*. Journal of Clinical Oncology 2005;**23**:5211-16.

[5] Shepherd FA. *Malignant pericardial effusion*. Current Opinion in Oncology 1997;**9**:170-74.

[6] Maisch B, Seferovic PM, Ristic AD, Erbel R, Rienmuller R, Adler Y *et al. Guidelines on the diagnosis and management of pericardial diseases executive summary; The Task force on the diagnosis and management of pericardial diseases of the European society of cardiology*. Eur Heart J 2004;**25**:587-610.

[7] Buzaid AC, Garewal HS, Greenberg BR. *Managing malignant pericardial effusion*. Western Journal of Medicine 1989;**150**:174-79.

[8] Press OW, Livingston R. *Management of malignant pericardial effusion and tamponade*. JAMA 1987;**257**:1088-92.

[9] Vaitkus PT, Herrmann HC, LeWinter MM. *Treatment of malignant pericardial effusion*. Journal of the American Medical Association 1994;**272**:59-64.

[10] Apodaca-Cruz A, Villarreal-Garza C, Torres-Avila B, Torres J, Meneses A, Flores-Estrada D *et al. Effectiveness and prognosis of initial pericardiocentesis in the primary management of malignant pericardial effusion*. Interactive Cardiovascular & Thoracic Surgery 2010;**11**:154-61.

[11] Lindenberger M, Kjellberg M, Karlsson E, Wranne B. *Pericardiocentesis guided by 2-D echocardiography: The method of choice for treatment of pericardial effusion*. Journal of Internal Medicine 2003;**253**:411-17.

[12] Buchanan CL, Sullivan VV, Lampman R, Kulkarni MG. *Pericardiocentesis with extended catheter drainage: An effective therapy*. Annals of Thoracic Surgery 2003;**76**:817-20.

[13] Gatenby RA, Hartz WH, Kessler HB. *Percutaneous catheter drainage for malignant pericardial effusion*. Journal of Vascular & Interventional Radiology 1991;**2**:151-5.

[14] Hingorani AD, Bloomberg TJ. *Ultrasound-guided pigtail catheter drainage of malignant pericardial effusions*. Clinical Radiology 1995;**50**:15-9.

[15] Kopecky SL, Callahan JA, Tajik AJ, Seward JB. *Percutaneous pericardial catheter drainage: report of 42 consecutive cases*. American Journal of Cardiology 1986;**58**:633-5.

[16] Medary I, Steinherz LJ, Aronson DC, La Quaglia MP. *Cardiac tamponade in the pediatric oncology population: Treatment by percutaneous catheter drainage*. Journal of Pediatric Surgery 1996;**31**:197-200.

[17] Patel AK, Kosolcharoen PK, Nallasivan M, Kroncke GM, Thomsen JH. *Catheter drainage of the pericardium: Practical method to maintain long-term patency*. Chest 1987;**92**:1018-21.

[18] Bischiniotis TS, Lafaras CT, Platogiannis DN, Moldovan L, Barbetakis NG, Katseas GP. *Intrapericardial cisplatin administration after pericardiocentesis in patients with lung adenocarcinoma and malignant cardiac tamponade*. Hellenic Journal of Cardiology 2005;**46**:324-29.

[19] Bishiniotis TS, Antoniadou S, Katseas G, Mouratidou D, Litos AG, Balamoutsos N. *Malignant cardiac tamponade in women with breast cancer treated by pericardiocentesis and intrapericardial administration of triethylenethiophosphoramide (thiotepa)*. American Journal of Cardiology 2000;**86**:362-4.

[20] Colleoni M, Martinelli G, Beretta F, Marone C, Gallino A, Fontana M *et al. Intracavitary chemotherapy with thiotepa in malignant pericardial effusions: An active and well-tolerated regimen*. Journal of Clinical Oncology 1998;**16**:2371-76.

[21] Davis S, Rambotti P, Grignani F. *Intrapericardial tetracycline sclerosis in the treatment of malignant pericardial effusion: an analysis of thirty-three cases*. Journal of Clinical Oncology 1984;**2**:631-6.

[22] Imamura T, Tamura K, Taguchi T, Makino S, Seita M. *Intrapericardial instillation of OK-432 for the management of malignant pericardial effusion: report of three cases*. Japanese Journal of Medicine 1989;**28**:62-6.

[23] Kaira K, Takise A, Kobayashi G, Utsugi M, Horie T, Mori T *et al. Management of malignant pericardial effusion with instillation of mitomycin C in non-small cell lung cancer*. Japanese Journal of Clinical Oncology 2005;**35**:57-60.

[24] Kawashima O, Kurihara T, Kamiyoshihara M, Sakata S, Ishikawa S, Morishita Y. *Management of malignant pericardial effusion resulting from recurrent cancer with local instillation of aclarubicin hydrochloride*. American Journal of Clinical Oncology 1999;**22**:396-8.

[25] Lafaras C, Mavroudi E, Platogiannis D, Bischiniotis T. *Local chemotherapy with cisplatin in non small lung cancer patients and malignant cardiac tamponade*. Intensive Care Medicine 2009;**35**:S279.

[26] Lashevsky I, Yosef RB, Rinkevich D, Reisner S, Markiewicz W. *Intrapericardial minocycline sclerosis for malignant pericardial effusion*. Chest 1996;**109**:1452-54.

[27] Lee LN, Yang PC, Chang DB, Yu CJ, Ko JC, Liaw YS *et al. Ultrasound guided pericardial drainage and intrapericardial instillation of mitomycin C for malignant pericardial effusion*. Thorax 1994;**49**:594-95.

[28] Lentzsch S, Reichardt P, Gurtler R, Dorken B. *Intrapericardial application of mitoxantrone for treatment of malignant pericardial effusion*. Onkologie 1994;**17**:504-07.

[29] Maisch B, Risti AD, Pankuweit S, Neubauer A, Moll R. *Neoplastic pericardial effusion: Efficacy and safety of intrapericardial treatment with cisplatin*. European Heart Journal 2002;**23**:1625-31.

[30] Martinoni A, Cipolla CM, Cardinale D, Civelli M, Lamantia G, Colleoni M *et al.* Long-term results of intrapericardial chemotherapeutic treatment of malignant pericardial effusions with thiotepa. *Chest*, 2004:1412-6.

[31] Maruyama R, Yokoyama H, Seto T, Nagashima S, Kashiwabara K, Araki J *et al. Catheter drainage followed by the instillation of bleomycin to manage malignant pericardial effusion in non-small cell lung cancer: A multi-institutional phase II trial*. Journal of Thoracic Oncology 2007;**2**:65-68.

[32] Moriya T, Takiguchi Y, Tabeta H, Watanabe R, Kimura H, Nagao K *et al. Controlling malignant pericardial effusion by intrapericardial carboplatin administration in patients with primary non-small-cell lung cancer*. British Journal of Cancer 2000;**83**:858-62.

[33] Moya I, Dalmau E, Segui M, Garcia Y, Bonfill T, Pericay C *et al. Efficacy and safety of intrapericardial bleomycin for malignant pericardial effusion*. Journal of Clinical Oncology 2010;**1)**.

[34] Musch E, Gremmler B, Nitsch J, Rieger J, Malek M, Chrissafidou A. *Intrapericardial instillation of mitoxantrone in palliative therapy of malignant pericardial effusion*. Onkologie 2003;**26**:135-39.

[35] Norum J, Lunde P, Aasebo U, Himmelmann A. *Mitoxantrone in malignant pericardial effusion*. Journal of Chemotherapy 1998;**10**:399-404.

[36] Oida T, Mimatsu K, Kano H, Kawasaki A, Kuboi Y, Fukino N *et al. Pericardiocentesis with cisplatin for malignant pericardial effusion and tamponade*. World Journal of Gastroenterology 2010;**16**:740-44.

[37] Shepherd FA, Morgan C, Evans WK, Ginsberg JF, Watt D, Murphy K. *Medical management of malignant pericardial effusion by tetracycline sclerosis*. American Journal of Cardiology 1987;**60**:1161-66.

[38] Tomkowski WZ, Wisniewska J, Szturmowicz M, Kuca P, Burakowski J, Kober J *et al. Evaluation of intrapericardial cisplatin administration in cases with recurrent malignant pericardial effusion and cardiac tamponade*. Supportive Care in Cancer 2004;**12**:53-57.

[39] Van Belle SJP, Volckaert A, Taeymans Y. *Treatment of malignant pericardial tamponade with sclerosis induced by instillation of bleomycin*. International Journal of Cardiology 1987;**16**:155-60.

[40] Becit N, Unlu Y, Ceviz M, Kocogullari CU, Kocak H, Gurlertop Y. *Subxiphoid pericardiostomy in the management of pericardial effusions: Case series analysis of 368 patients*. Heart 2005;**91**:785-90.

[41] Campbell PT, Van Trigt P, Wall TC, Kenney RT, O'Connor CM, Sheikh KH *et al. Subxiphoid pericardiotomy in the diagnosis and management of large pericardial effusions associated with malignancy*. Chest 1992;**101**:938-43.

[42] Celik S, Celik M, Aydemir B, Tanrikulu H, Okay T, Tanrikulu N. *Surgical properties and survival of a pericardial window via left minithoracotomy for benign and malignant pericardial tamponade in cancer patients*. World Journal of Surgical Oncology 2012;**10**.

[43] Geissbuhler K, Leiser A, Fuhrer J, Ris HB. *Video-assisted thoracoscopic pericardial fenestration for loculated or recurrent effusions*. European Journal of Cardio-thoracic Surgery 1998;**14**:403-08.

[44] Georghiou GP, Stamler A, Sharoni E, Fichman-Horn S, Berman M, Vidne BA *et al. Video-assisted thoracoscopic pericardial window for diagnosis and management of pericardial effusions*. Annals of Thoracic Surgery 2005;**80**:607-10.

[45] Hazelrigg SR, Mack MJ, Landreneau RJ, Acuff TE, Seifert PE, Auer JE. *Thoracoscopic pericardiectomy for effusive pericardial disease*. Annals of Thoracic Surgery 1993;**56**:792-95.

[46] Lajos TZ, Black HE, Cooper RG, Wanka J. *Pericardial decompression*. Annals of Thoracic Surgery 1975;**19**:47-53.

[47] Mack MJ, Landreneau RJ, Hazelrigg SR, Acuff TE. *Video thoracoscopic management of benign and malignant pericardial effusions*. Chest 1993;**103**:390S-93S.

[48] Moores DWO, Allen KB, Faber LP, Dziuban SW, Gillman DJ, Warren WH *et al. Subxiphoid pericardial drainage for pericardial tamponade*. Journal of Thoracic and Cardiovascular Surgery 1995;**109**:546-52.

[49] Neragi-Miandoab S, Linden PA, Ducko CT, Bueno R, Richards WG, Sugarbaker DJ *et al. VATS pericardiotomy for patients with known malignancy and pericardial effusion: Survival and prognosis of positive cytology and metastatic involvement of the pericardium: A case control study*. International Journal of Surgery 2008;**6**:110-14.

[50] Olson JE, Ryan MB, Blumenstock DA. *Eleven years' experience with pericardial-peritoneal window in the management of malignant and benign pericardial effusions*. Annals of surgical oncology : the official journal of the Society of Surgical Oncology 1995;**2**:165-69.

[51] Osuch JR, Khandekar JD, Fry WA. *Emergency subxiphoid pericardial decompression for malignant pericardial effusion*. American Surgeon 1985;**51**:298-300.

[52] Sarigul A, Farsak B, Ates MS, Demircin M, Pasaoglu I. *Subxiphoid approach for treatment of pericardial effusion*. Asian Cardiovascular and Thoracic Annals 1999;**7**:297-300.

[53] Sugimoto JT, Little AG, Ferguson MK, Borow KM, Vallera D, Staszak VM *et al. Pericardial window: mechanisms of efficacy*. Annals of Thoracic Surgery 1990;**50**:442-5.

[54] Toth I, Szucs G, Molnar TF. *Mediastinoscope-controlled parasternal fenestration of the pericardium: definitive surgical palliation of malignant pericardial effusion*. Journal Of Cardiothoracic Surgery 2012;**7**:56.

[55] Uramoto H, Hanagiri T. *Video-assisted thoracoscopic pericardiectomy for malignant pericardial effusion*. Anticancer Research 2010;**30**:4691-94.

[56] Vassilopoulos PP, Nikolaidis K, Filopoulos E, Griniatsos J, Efremidou A. *Subxiphoidal pericardial 'window' in the management of malignant pericardial effusion*. European Journal of Surgical Oncology 1995;**21**:545-47.

[57] Wang N, Feikes JR, Mogensen T, Vyhmeister EE, Bailey LL. *Pericardioperitoneal shunt: an alternative treatment for malignant pericardial effusion*. Annals of Thoracic Surgery 1994;**57**:289-92.

[58] Wilkes JD, Fidias P, Vaickus L, Perez RP. *Malignancy-related pericardial effusion: 127 Cases from the Roswell Park Cancer Institute*. Cancer 1995;**76**:1377-87.

[59] Del Barrio LG, Morales JH, Delgado C, Benito A, Larrache J, Martinez-Cuesta A *et al. Percutaneous balloon pericardial window for patients with symptomatic pericardial effusion*. CardioVascular and Interventional Radiology 2002;**25**:360-64.

[60] Di Segni E, Lavee J, Kaplinsky E, Vered Z. *Percutaneous balloon pericardiostomy for treatment of cardiac tamponade*. European Heart Journal 1995;**16**:184-87.

[61] Galli M, Politi A, Pedretti F, Castiglioni B, Zerboni S. *Percutaneous balloon pericardiotomy, for malignant pericardial tamponade*. Chest 1995;**108**:1499-501.

[62] Jackson G, Keane D, Mishra B. *Percutaneous balloon pericardiotomy in the management of recurrent malignant pericardial effusions*. British Heart Journal 1992;**68**:613-5.

[63] Navarro del Amo LF, Polo MC, Orejas M, Fernandez TL, Mohandes M, Romo AI. *Percutaneous balloon pericardiotomy in patients with recurrent pericardial effusion*. Revista Espanola de Cardiologia 2002;**55**:25-28.

[64] Ovunc K, Aytemir K, Ozer N, Atalar E, Aksoyek S, Nazli N *et al. Percutaneous balloon pericardiotomy for patients with malignant pericardial effusion including three malignant pleural mesotheliomas*. Angiology 2001;**52**:323-29.

[65] Palacios IF, Tuzcu EM, Ziskind AA, Younger J, Block PC. *Percutaneous balloon pericardial window for patients with malignant pericardial effusion and tamponade*. Catheterization & Cardiovascular Diagnosis 1991;**22**:244-9.

[66] Swanson N, Mirza I, Wijesinghe N, Devlin G. *Primary percutaneous balloon pericardiotomy for malignant pericardial effusion*. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2008;**71**:504-07.

[67] Wang HJ, Hsu KL, Chiang FT, Tseng CD, Tseng YZ, Liau CS. *Technical and prognostic outcomes of double-balloon pericardiotomy for large malignancy-related pericardial effusions*. Chest 2002;**122**:893-99.

[68] Ziskind AA, Pearce AC, Lemmon CC, Burstein S, Gimple LW, Herrmann HC *et al. Percutaneous balloon pericardiotomy for the treatment of cardiac tamponade and large pericardial effusions: Description of technique and report of the first 50 cases*. Journal of the American College of Cardiology 1993;**21**:1-5.

Table 1. Treatment modalities in the management of malignant pericardial effusion

Procedure	References	No. of patients with malignancy / total no. of patients treated
Single pericardiocentesis	[10, 11]	131/220
Extended catheter drainage	[12-17]	78/117
Pericardial sclerotherapy	[18-39]	474/474
Surgery	[40-58]	550/1330
Percutaneous balloon pericardiotomy	[59-68]	166/181
Total		**1399/2322**

Table 2. Efficacy of single pericardiocentesis

References	Successfully controlled/ no. of patients with malignancy treated (%)	Side effects and complications related to the procedure (%)
Overall	**81/131[a] (61.8)**	**13/220[b] (5.9)**
Apodaca-Cruza et al., 2010 **[10]**	67/100 (67.0)	vagal hypotension (n=3),
Lindenberger et al., 2003 **[11]**	14/31 (45.2)	arrhythmia (n=6), vasovagal reaction (n=2), ventricular puncture (n=1), breathing difficulties (n=1)

a: number of patients with malignancy
b: total number of patients treated in the study

Table 3. Efficacy of extended catheter drainage

References	Successfully controlled/ no. of patients with malignancy treated (%)	Side effects and complications related to the procedure (%)
Overall	**43/78[a] (55.1)**	**14/117[b] (12.0)**
Buchanan et al., 2003 **[12]**	12/22 (54.5)	cardiac injury (n=2), pneumothorax (n=1)
Gatenby et al., 1991 **[13]**	3/12 (25.0)	transient ventricular arrhythmia (n=1), hypotension (n=1)
Hingorani et al., 1995 **[14]**	8/9 (88.9)	transient atrial fibrillation (n=2), pericardial pain (n=1), erratic drainage (n=1)
Kopecky et al., 1986 **[15]**	5/16 (31.3)	catheter occlusion (n=3), infection (n=1), bradycardia and symptomatic hypotension (n=1)
Medary et al., 1996 **[16]**	9/9 (100)	none reported
Patel et al., 1987 **[17]**	6/10 (60.0)	none reported

a: number of patients with malignancy
b: total number of patients treated in the study

Table 4. Efficacy of pericardial sclerotherapy

Agent	References	Successfully controlled/ no. of patients with malignancy treated (%)	Side effects and complications related to the procedure (%)
Overall		**416/474 (87.8)**	**97/474 (20.5)**
Cisplatin		**159/176 (90.3)**	**24/176 (13.6)**
	Bischiniotis et al., 2005 [18]	23/25 (92.0)	constriction (n=4), transient atrial fibrillation (n=3), non-sustained ventricular tachycardia (n=2)
	Lafaras et al., 2009 [25]	55/56 (98.2)	paroxysmal atrial fibrillation (n=5)
	Maisch et al., 2002 [29]	36/42 (85.7)	myocardial ischaemia (n=1)
	Oida et al., 2010 [36]	7/7 (100)	nausea (n=2)
	Tomkowski et al., 2004 [38]	38/46 (82.6)	transient atrial fibrillation (n=7)
Tetracycline		**80/91 (87.9)**	**41/91 (45.1)**
	Davis et al., 1984 [21]	30/33 (90.9)	mild transient fever (n=12), ventricular arrhythmia (n=5), atrial fibrillation (n=1)
	Shepherd et al., 1987 [37]	50/58 (82.8)	pain (n=9), transient atrial arrhythmia (n=5), fever (n=5), catheter occlusion (n=4)
Thiotepa		**68/75 (90.7)**	**5/75 (6.7)**
	Bischiniotis et al., 2000 [19]	19/19 (100)	atrial fibrillation (n=2), vasovagal reaction (n=1)
	Colleoni et al., 1998 [20]	19/23 (82.6)	transient grade III thrombocytopenia and leukopenia (n=1), grade I leukopenia (n=1)
	Martinoni et al., 2004 [30]	30/33 (90.9)	none reported

Bleomycin		**40/45 (88.9)**	**12/45 (26.7)**
	Maruyama et al., 2007 [31]	21/22 (95.5)	constrictive pericarditis and death (n=1)
	Moya et al., 2010 [33]	14/18 (77.8)	mild fever (n=5), atrial fibrillation (n=3), retrosternal pain (n=1), infection (n=1)
	Van Belle et al., 1987 [39]	5/5 (100)	transient fever (n=1)
Mitomycin C		**19/28 (67.9)**	**1/28 (3.6)**
	Kaira et al., 2005 [23]	7/8 (87.5)	none reported
	Lee et al., 1994 [27]	12/20 (60.0)	pericardial constriction (n=1)
Mitoxantrone		**24/27 (88.9)**	**none reported**
	Lentzsch et al., 1994 [28]	6/6 (100)	none reported
	Musch et al., 2003 [34]	16/16 (100)	none reported
	Norum et al., 1998 [35]	2/5 (40.0)	none reported
Other			
Minocycline	Lashevsky et al., 1996 [26]	10/14 (71.4)	severe chest pain (n=7), pericardial injury (n=2), vasovagal reaction (n=1), transient fever (n=1)
Carboplatin	Moriya et al., 2000 [32]	8/10 (80.0)	none reported
Aclarubicin	Kawashima et al., 1999 [24]	5/5 (100)	none reported
OK-432	Imamura et al., 1989 [22]	3/3 (100)	high fever, chills and chest pain (n=3)

Table 5. Efficacy of surgical approaches

Technique	References	Successfully controlled/ no. of patients with malignancy treated (%)	Side effects and complications related to the procedure (%)
Overall		**514/550[a] (93.5)**	**63/1330[b] (4.7)**
Pericardial fenestration		**474/508[a] (93.3)**	**56/1258[b] (4.5)**
Subxiphoid		*357/383[a] (93.2)*	*42/1079[b] (3.9)*
	Becit et al., 2005 [40]	49/51 (96.1)	myocardial injury (n=3)
	Campbell et al., 1992 [41]	22/25 (88.0)	hypotension (n=1)
	Lajos et al., 1975 [46]	15/15 (100)	none reported
	Moores et al., 1995 [48]	80/82 (97.6)	none reported
	Olson et al., 1995 [50]	18/18 (100)	lobar pneumonia (n=2), atrial fibrillation (n=2), fascial dehiscence (n=1), constrictive pericarditis (n=1), intraoperative entry into left pleural space (n=1)
	Osuch et al., 1985 [51]	6/6 (100)	none reported
	Sarigul et al., 1999 [52]	33/41 (80.5)	cardiac arrest (n= 12), death (n=7), pneumothorax (n=6)
	Sugimoto et al., 1990 [53]	22/24 (91.7)	none reported
	Vassilopoulos et al., 1995 [56]	26/26 (100)	ventricular tachycardia (n=1)
	Wilkes et al., 1995 [58]	86/95 (90.5)	prolonged postoperative ventilation (n=2), infection (n=1), wound dehiscence (n=1), death (n=1)

VATS		*70/77[a] (90.9)*	*5/104[b] (4.8)*
	Geissbuhler et al., 1998 [43]	12/12 (100)	pulmonary embolism (n=1), CVA (n=1), ventricular arrhythmia (n=1)
	Georghiou et al., 2005 [44]	3/3 (100)	supraventricular arrhythmia (n=1)
	Neragi-Miandoab et al., 2008 [49]	55/62 (88.7)	ventilation support (n=1)
Left mini-thoracotomy		*25/26[a] (96.2)*	*6/53[b] (11.3)*
	Celik et al., 2012 [42]	25/26 (96.2)	infection (n=1), ventricular fibrillation (n=1), pneumonia and sepsis (n=1), pulmonary embolism (n=1), heart failure (n=1), prolonged ventilation (n=1)
MCPF		*22/22 (100)*	*3/22 (13.6)*
	Toth et al., 2012 [54]	22/22 (100)	dysrhythmia (n=3)
Pericardiectomy		**38/38[a] (100)**	**7/68[b] (10.3)**
VATS		*38/38 (100)*	*7/68 (10.3)*
	Hazelrigg et al. 1993 [45]	18/18 (100)	atelactasis (n=4), pneumonia (n=2), arrhythmia (n=1)
	Mack et al. 1993 [47]	9/9 (100)	none reported
	Uramoto et al. 2010 [55]	11/11 (100)	none reported
Pericardio-peritoneal shunt		**4/4 (100)**	**none reported**
Denver shunt	Wang et al., 1994 [57]	4/4 (100)	none reported

a: number of patients with malignancy

b: total number of patients treated in the study
VATS: video-assisted thorascopic surgery
MCPF: mediastinoscope-controlled parasternal fenestration

Table 6. Efficacy of percutaneous balloon pericardiotomy

References	Successfully controlled/ no. of patients with malignancy treated (%)	Side effects and complications related to the procedure (%)
Overall	**150/166[a] (90.4)**	**58/181[b] (32.0)**
Del Barrio et al., 2002 **[59]**	8/9 (88.9)	intrapericardial balloon rupture (n=1), right ventricular wall perforation, hypotension and bradycardia (n=1)
Di Segni et al., 1995 **[60]**	7/7 (100)	pain (n=2), profuse bleeding at entry site (n=1), bradycardia (n=1)
Galli et al., 1995 **[61]**	10/10 (100)	none reported
Jackson et al., 1992 **[62]**	1/2 (50.0)	pain (n=1)
Navarro Del Amo et al., 2002 **[63]**	4/4 (100)	mild pleural effusion (n=4)
Ovunc et al., 2001 **[64]**	6/10 (60.0)	pleural effusion (n=2)
Palacios et al., 1991 **[65]**	8/8 (100)	pleural effusion (n=8)
Swanson et al., 2008 **[66]**	25/27 (92.6)	cerebrovascular accident (n=1), pneumopericardium (n=1)
Wang et al., 2002 **[67]**	44/50 (88.0)	fever (n=14), mild pneumothorax (n=3), balloon breakage (n=1)
Ziskind et al., 1993 **[68]**	37/39 (94.9)	fever (n=6), profuse bleeding (n=1), pleural effusion requiring thoracocentesis (n=8), mild pneumothorax (n=2)

a: number of patients with malignancy
b: total number of patients treated in the study

Figure 1. Flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement