

Cancer Association of South Africa (CANSA)



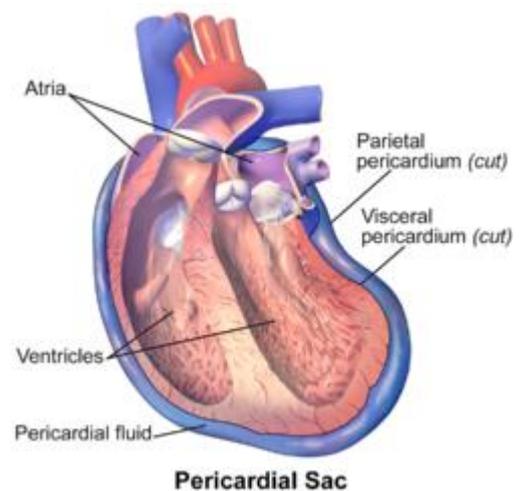
Fact Sheet on Pericardial Effusion Caused by Cancer or Cancer Treatment

Introduction

The pericardium is a double-walled sac containing the heart and the roots of the great blood vessels.

The pericardium has two layers: the fibrous pericardium is the outer layer. It is made from thick connective tissue and is attached to the diaphragm. It holds the heart in place in the chest cavity and protects it from infections; the serous pericardium is the inner layer. It is further divided into two more layers: the visceral (directly part of outer part of the heart) and parietal layers (an outer layer). The serous pericardium helps to lubricate the heart.

[Picture Credit: Pericardium]



The potential space between the two layers contains no more than 50mL of serous fluid under normal circumstances. The pericardium restrains acute dilation of the heart chambers, but it accommodates dilation and fluid accumulation to a certain extent. An abnormal collection of serous fluid in the pericardial space is referred to as pericardial effusion.

Pericardial Effusion

Pericardial effusion, sometimes referred to as "fluid around the heart," is the abnormal build-up of excess fluid that develops between the pericardium, the covering sack around the heart, and the heart itself.

Pericardial effusion may be:

- Transudative effusion (congestive heart failure, myxoedema, nephrotic syndrome),
- Exudative effusion (tuberculosis, spread from empyema)
- Haemorrhagic effusion (trauma, rupture of aneurysms, malignant effusion).
- Malignant effusion (due to fluid accumulation caused by cancer or cancer treatment). Malignant Pericardial Effusion - a condition in which cancer causes extra fluid to collect inside the sac around the heart. The extra fluid causes pressure on the heart, which keeps it from pumping blood normally. Lymph vessels may be blocked, which can cause infection. Malignant pericardial effusions are most often caused by lung cancer, breast cancer, melanoma, lymphoma, and leukaemia.

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

April 2021

Page 1

Chagine, J., Shekhar, S., Mahalwar, G., Imazio, M., Collier, P. & Klein, A. 2021. Pericardial involvement in cancer. *Am J Cardiol.* 2021 Apr 15;145:151-159.

“Despite the monumental advances in the diagnoses and therapeutics of malignancy, several cancer patients have presented with pericardial involvement, including acute pericarditis, constrictive pericarditis, and pericardial effusion. Multiple factors can contribute to acute pericarditis, including direct metastasis to the heart, pericardial hemorrhage, infections due to immunosuppression, and cancer therapies that include chemotherapy, immunotherapy, and radiation. Pericardial effusion, either due to cancer invasion or cancer treatment, is one of the most common incidental findings in cancer patients, which significantly worsens morbidity and mortality. If left untreated, pericardial effusion is known to cause complications such as pericardial tamponade. Constrictive pericarditis can be due to radiation exposure, chemotherapy, or is a sequela of a previous episode of acute pericarditis. In conclusion, early detection, prompt treatment, and understanding of pericardial diseases are necessary to help improve the quality of life of cancer patients, and we aim to summarize the knowledge of pericardial involvement in patients with cancer.”

Canale, M.L., Camerini, A., Casolo, G., Lilli, A., Bisceglia, I., Parrini, I., Lestuzzi, C., Del Meglio, J., Puccetti, C., Camerini, L., Amoroso, D. & Maurea, N. 2020.

Introduction: Cardiovascular toxicity of immunotherapy represents an underreported but potentially fatal side effect. A relatively high incidence of pericardial disease has been noticed in patients with non-small cell lung cancer (NSCLC).

Methods: We retrospectively analyzed a population of patients with advanced NSCLC receiving immune checkpoint inhibitors (ICIs) looking for the presence of pericardial effusion at baseline or during treatment. The study population was compared with a control group treated with chemotherapy. All patients were checked for the presence of concomitant pleural effusion.

Results: We identify 60 patients (36 male/24 female, median age 70 years [range 43-81]). Prevalent histology was adenocarcinoma (65%) followed by squamous cell carcinoma (28%) and large cell or not otherwise specified (NOS) carcinoma (7%). Treatment consisted of nivolumab 3 mg/kg every 14 days (52 cases; 45 as second-line and 7 as third-line treatment) or pembrolizumab 200 mg (8 cases; all first-line treatment) for a total of 302 cycles delivered. Four out of 60 patients (6.7%) developed pericardial effusion during treatment, in two cases (3.3%) without concomitant pleural effusion, compared to 2 out of 60 (3.3%) in the control group in one case without concomitant pleural effusion (1.6%). Median time of onset was 40 days. Myocarditis was not observed.

Conclusion: Our findings confirm pericardial effusion as a relatively frequent side effect of immunotherapy in NSCLC. Clinicians should be aware of this specific toxicity in patients with metastatic NSCLC receiving immunotherapy and refer to a cardiologist for a multidisciplinary approach.

Signs and Symptoms of Pericardial Effusion

Signs and symptoms of pericardial effusion may include:

- Chest pain
- Feeling of pressure in the chest
- Discomfort feeling in the chest
- Light-headedness
- Syncope
- Palpitations
- Cough
- Dyspnoea

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

April 2021

- Hoarseness
- Anxiety and confusion
- Hiccoughs

Causes and Risk Factors of Pericardial Effusion

Causes of pericardial effusion may include:

Inflammation of the pericardium following heart surgery or a heart attack. Autoimmune disorders, such as rheumatoid arthritis or lupus. Spread of cancer (metastasis), particularly lung cancer, breast cancer, melanoma, leukaemia, non-Hodgkin's lymphoma or Hodgkin's disease (which is serious and should be diagnosed and treated promptly)

The extra fluid causes pressure on the heart, which keeps it from pumping blood normally. Lymph vessels may be blocked, which can cause infection. Malignant pericardial effusions are most often caused by lung cancer, breast cancer, melanoma, lymphoma, and leukaemia.

In most cases, inflammation of the pericardial sac, a condition called pericarditis, leads to the effusion. As it becomes inflamed, more fluid is produced.

Viral infections are one of the main causes of the inflammation and the effusions it leads to. These infections include:

- Cytomegalovirus
- Coxsackieviruses
- Echoviruses
- Human Immunodeficiency Virus (HIV)

Other conditions that can cause pericardial effusions include:

- Cancer
- Injury to the sac or heart from a medical procedure
- Heart attack
- Severe kidney failure, also called uremia
- Autoimmune diseases (lupus, rheumatoid arthritis, and others)
- Bacterial infections, including tuberculosis

In many cases, no cause can be found. One's doctor may call these 'idiopathic pericardial effusions'.

Takata, N., Kataoka, M., Hamamoto, Y., Tsuruoka, S., Kanzaki, J., Uwatsu, K., Nagasaki, K. & Mochizuki, T. 2018.

"Pericardial effusion is an important late toxicity after concurrent chemoradiotherapy (CCRT) for locally advanced esophageal cancer. We investigated the clinical and dosimetric factors that were related to pericardial effusion among patients with thoracic esophageal cancer who were treated with definitive CCRT using the two opposed fields technique (TFT) or the four-field technique (FFT), as well as the effectiveness of FFT. During 2007-2015, 169 patients with middle and/or lower thoracic esophageal cancer received definitive CCRT, and 94 patients were evaluable (51 FFT cases and 43 TFT cases). Pericardial effusion was observed in 74 patients (79%) and appeared at 1-18.5 months (median: 5.25 months) after CCRT. The 1-year incidences of pericardial effusions were 73.2% and 76.7% in the FFT and TFT groups, respectively (P = 0.6395). The mean

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

April 2021

doses to the pericardium were 28.6 Gy and 31.8 Gy in the FFT and TFT groups, respectively ($P = 0.0259$), and the V40 Gy proportions were 33.5% and 48.2% in the FFT and TFT groups, respectively ($P < 0.0001$). Grade 3 pericardial effusion was not observed in patients with a pericardial V40 Gy of <40%, or in patients who were treated using the FFT. Although the mean pericardial dose and V40 Gy in the FFT group were smaller than those in the TFT group, the incidences of pericardial effusion after CCRT were similar in both groups. As symptomatic pericardial effusion was not observed in patients with a pericardial V40 Gy of <40% or in the FFT group, it appears that FFT with a V40 Gy of <40% could help minimize symptomatic pericardial effusion.”

Diagnosis of Pericardial Effusion

If one’s doctor suspects someone to suffering from a pericardial effusion, he or she will do a series of tests to look for it, identify possible causes in order to determine treatment.

Medical examination - The doctor will perform a medical examination, including listening to the heart with a stethoscope.

Echocardiogram - An echocardiogram uses sound waves to create real-time images of the heart. With this procedure, a cardiologist can see the extent of pericardial effusion based on the amount of space between the two layers of the pericardium. An echocardiogram can also show decreased heart function due to pressure on the heart (tamponade).

A cardiologist might be able to see whether one or more chambers of the heart have collapsed and how efficiently the heart is pumping blood. There are two types of echocardiograms:

- Transthoracic echocardiogram - this test uses a sound-emitting device (transducer) that is placed on the chest over the heart.
- Transoesophageal echocardiogram - a tiny transducer on a tube is put down the part of the digestive tract that runs from the throat to the stomach (oesophagus). Because the oesophagus lies close to the heart, having the transducer placed there often provides a more-detailed image of the heart.

Electrocardiogram - an electrocardiogram — also called an ECG or EKG — records electrical signals as they travel through the heart. A cardiologist can look for patterns that suggest tamponade.

Chest X-ray - this can show an enlarged heart silhouette if the amount of fluid in the pericardium is large.

Other imaging technologies - computerized tomography (CT) scans and magnetic resonance imaging (MRI) are imaging technologies that can detect pericardial effusion, although they're not generally used to look for the disorder. However, pericardial effusion may be diagnosed when these tests are done for other reasons.

Other tests - if there is evidence of pericardial effusion, the doctor may order blood tests or other diagnostic tests to identify the cause.

Examination findings in patients with pericardial effusion may include the following:

- Classic Beck triad of pericardial tamponade: Hypotension, muffled heart sounds, jugular venous distention
- Pulsus paradoxus
- Pericardial friction rub
- Tachycardia

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

April 2021

Page 4

- Hepatojugular reflux
- Tachypnoea
- Decreased breath sounds
- Ewart sign: Dullness to percussion beneath the angle of left scapula
- Hepatosplenomegaly
- Weakened peripheral pulses, oedema, and cyanosis

The following lab studies may be performed in patients with suspected pericardial effusion:

- Electrolytes - To assess for metabolic abnormalities (e.g., renal failure)
- Complete blood count (CBC) with differential - Leukocytosis for evidence of infection, as well as cytopenias, as signs of underlying chronic disease (e.g., cancer, HIV)
- Cardiac biomarkers
- Other markers of inflammation, such as erythrocyte sedimentation rate and C-Reactive protein - While these do not aid in identifying specifics, they can be used to potentially assess the need for anti-inflammatory agents (i.e., corticosteroids, colchicine, NSAIDs), especially in the setting of recurrent effusions
- Thyroid-stimulating hormone - Thyroid-stimulating hormone screen for hypothyroidism
- Blood cultures in the presence of systemic inflammatory response syndrome (SIRS) or fever; in general, specific viral studies are low yield and therefore not recommended
- Rheumatoid factor, immunoglobulin complexes, antinuclear antibody test (ANA), and complement levels (which would be diminished) - In suspected rheumatologic causes
- Specific infectious disease testing, based upon clinical suspicion, such as (1) tuberculin skin testing or QuantiFERON-TB assay; (2) rickettsial antibodies if there is a high index of suspicion for tick-borne disease; and HIV serology

Kalogeraki, A., Lazopoulos, G., Papadakis, G.Z., Tamiolakis, D., Karvela-Kalogeraki, I., Karvelas-Kalogerakis, M., Segredakis, J. & Chalkiadakis, G.E. 2016.

BACKGROUND: Malignant pericardial effusion occurs in one tenth of all cancers. It is a very serious disorder that is mainly a secondary process due to metastasis because primary neoplasms of the pericardium such as mesotheliomas, sarcomas being exceedingly rare [corrected]. Pericardial effusion specimens are uncommon and to the best of our knowledge the current study is the largest systematic evaluation of pericardial fluid cytology performed to date.

MATERIAL AND METHODS: Pericardial effusion specimens from 145 patients collected over a 25 [corrected] year period were studied by cytology [corrected]. The minimum pericardial fluid volume used for adequate cytologic diagnosis in these patients was more than 60 mL.

RESULTS: Cytological diagnosis revealed malignant pericardial exudates in 100% of the studied patients [corrected].

CONCLUSIONS: Cytology provides an immediate and accurate means of diagnosis. Immunocytology is very important in the diagnostic evaluation.

Treatment of Pericardial Effusion

Treatment of pericardial effusion is based on the underlying condition that is causing it and if the effusion is leading to severe symptoms, such as shortness of breath or difficulty breathing.

The goal of medical management for pericardial effusions is to treat the underlying cause. Medical therapies for pericardial effusions may include:

- Non-steroidal anti-inflammatory medications (NSAIDs) can be used to treat pericardial effusions caused by inflammation.
- Diuretics and other heart failure medications can be used to treat pericardial effusions caused by heart failure.
- Antibiotics are used to treat pericardial effusions caused by an infection.
- If a pericardial effusion is related to the presence of cancer, treatment may include chemotherapy, radiation therapy, or medication infused within the chest.

Large pericardial effusions may be drained through:

- Ultrasound-guided pericardiocentesis, a safe and effective procedure to remove excess fluid from the pericardium. This is most common followed by fluoroscopy.
- Video-assisted thoracoscopic surgery (VATS), also known as thoracoscopy is a minimally-invasive technique performed under general anaesthesia. VATS allows for visual evaluation of the pericardium and is used when the diagnosis of pericardial effusion has remained undiagnosed despite previous, less-invasive tests. It is also used to drain the excess fluid and prevent its re-accumulation.

Palaskas, N., Morgan, J., Daigle, T., Banchs, J., Durand, J.B., Hong, D., Naing, A., Le, H., Hassan, S.A., Karimzad, K., Mouhayar, E., Kim, P., Lopez-Mattei, J., Thompson, K., Yusuf, S.W. & Ilescu, C. 2019.

“Targeted cancer therapies with pericardial effusions requiring pericardiocentesis focusing on immune checkpoint inhibitors. *Am J Cardiol.* 2019 Apr 15;123(8):1351-1357. doi: 10.1016/j.amjcard.2019.01.013. Epub 2019 Jan 25. PMID: 30765065

“Case reports have reported immune checkpoint inhibitors (ICI), especially nivolumab, are associated with recurrent pericardial effusions. Our objective was to determine how often patients being treated with ICI develop hemodynamically significant pericardial effusion requiring pericardiocentesis compared with other cancer therapeutics and whether the survival of patients who underwent pericardiocentesis differs according to ICI use versus standard cancer therapeutics. Our institutional review board approved catheterization laboratory data collection for all pericardiocenteses performed and all patients receiving ICI from January 1, 2015 to December 31, 2017. Retrospective review of the electronic medical record was performed to identify cancer therapeutics given preceding pericardiocentesis. Log-rank analysis was performed to compare survival in patients requiring pericardiocentesis between those on ICI and those not on ICI. Overall, 3,966 patients received ICI of which only 15 pericardiocenteses were required, including 1 repeat pericardiocentesis in a patient on nivolumab. The prevalence of pericardiocentesis among patients on ICI was 0.38% (15/3,966). Eleven pericardiocenteses were performed after nivolumab infusion, 3 after pembrolizumab, and 1 after atezolizumab, with pericardiocentesis prevalences for each agent of 0.61% (11/1,798), 0.19% (3/1,560), and 0.32% (1/309), respectively. One hundred and twenty pericardiocenteses were performed on patients receiving other cancer therapeutics although no therapeutic agent was associated with more pericardiocenteses than nivolumab. In conclusion, the prevalence of hemodynamically significant pericardial effusions and ICI administration is uncommon, and survival durations after pericardiocentesis for patients receiving ICI and those not receiving ICI are similar, suggesting that frequent echocardiographic monitoring for pericardial effusions is not necessary.”

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst the Cancer Association of South Africa (CANSA) has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.



Sources and References Consulted and/or Utilised

Burazor, I., Imazio, M. Markel, G. & Adler, Y. 2013. Malignant pericardial effusion. *Cardiology*. 2013;124(4):224-32. doi: 10.1159/000348559. Epub 2013 Apr 5.

Canale, M.L., Camerini, A., Casolo, G., Lilli, A., Bisceglia, I., Parrini, I., Lestuzzi, C., Del Meglio, J., Puccetti, C., Camerini, L., Amoroso, D. & Maurea, N. 2020. Incidence of Pericardial Effusion in Patients with Advanced Non-Small Cell Lung Cancer Receiving Immunotherapy. *Adv Ther*. 2020 Jul;37(7):3178-3184.

Chagine, J., Shekhar, S., Mahalwar, G., Imazio, M., Collier, P. & Klein, A. 2021. Pericardial involvement in cancer. *Am J Cardiol*. 2021 Apr 15;145:151-159.

Hoit, B.C. 2017. Pericardial effusion and cardiac tamponade in the new millennium. *Curr Cardiol Rep*. 2017 Jul;19(7):57. doi: 10.1007/s11886-017-0867-5.

Istomin, V., Blondheim, D.S., Meisel, S.R., Frimerman, A., Lapidot, M. & Rachmilevitch, R. 2016. Pericardial effusion due to primary malignant pericardial mesothelioma: a common finding but an uncommon cause. *Case Reports in Medicine*. Volume 2016, Article ID 4810901.

Jama, G.M., Scarci, M., Bowden, J., Marciniak, S.J. 2014. Palliative treatment for symptomatic malignant pericardial effusion. *Interact Cardiovas Thorac Surg*. 2014 Dec;19(6):1019-26. doi: 10.1093/icvts/ivu267. Epub 2014 Aug 20.

Kalogeraki, A., Lazopoulos, G., Papadakis, G.Z., Tamiolakis, D., Karvela-Kalogeraki, I., Karvelas-Kalogerakis, M., Segredakis, J. & Chalkiadakis, G.E. 2016. Cytology of pericardial effusion due to malignancy. *Rom J Intern Med*. 2016 Sep 1;54(3):179-183. doi: 10.1515/rjim-2016-0026.

Niclauss, L., Montemurro, M. & Prêtre, R. 2015. Survival after surgical drainage of malignant pericardial effusion. *World J Surg*. 2015 Jul;39(7):1767-72. doi: 10.1007/s00268-015-3025-5.

Palaskas, N., Morgan, J., Daigle, T., Banchs, J., Durand, J.B., Hong, D., Naing, A., Le, H., Hassan, S.A., Karimzad, K., Mouhayar, E., Kim, P., Lopez-Mattei, J., Thompson, K., Yusuf, S.W. & Iliescu, C. 2019. Targeted cancer therapies with pericardial effusions requiring pericardiocentesis focusing on immune checkpoint inhibitors. *Am J Cardiol*. 2019 Apr 15;123(8):1351-1357. doi: 10.1016/j.amjcard.2019.01.013. Epub 2019 Jan 25. PMID: 30765065

Pericardial Effusion

<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/malignant-pericardial-effusion>

<https://www.webmd.com/heart-disease/guide/pericardial-effusion#1>

<https://www.mayoclinic.org/diseases-conditions/pericardial-effusion/diagnosis-treatment/drc-20353724>

Researched and Authored by Prof Michael C Herbst

[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]

Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

April 2021

Page 7

<https://www.uptodate.com/contents/diagnosis-and-treatment-of-pericardial-effusion>
<https://emedicine.medscape.com/article/157325-overview>
<https://emedicine.medscape.com/article/157325-workup#c8>
<https://my.clevelandclinic.org/health/diseases/17351-pericardial-effusion/diagnosis-and-tests>

Pericarditis

<https://www.webmd.com/heart-disease/guide/pericardial-effusion#1>

Pericardial Effusion Following Cancer Treatment

<https://www.webmd.com/heart-disease/guide/pericardial-effusion#1>

Pericardium

<https://en.wikipedia.org/wiki/Pericardium>

Rousseau-Bussac, G., Crequit, P., Alifano, M. & Chouaid, C. 2014. Management of malignant pericardial effusion in lung cancer. *Rev Mal Respir.* 2014 Oct;31(8):746-53. doi: 10.1016/j.rmr.2014.02.011. Epub 2014 Apr 24.

Takata, N., Kataoka, M., Hamamoto, Y., Tsuruoka, S., Kanzaki, J., Uwatsu, K., Nagasaki, K. & Mochizuki, T. 2018. Risk factors for pericardial effusion after chemoradiotherapy for thoracic esophageal cancer-comparison of four-field technique and traditional two opposed fields technique. *J Radiat Res.* 2018 May 1;59(3):291-297. doi: 10.1093/jrr/rry029.

Tsang, T.S.M., Seward, J.B., Barnes, M.E., Bailey, K.R., Sinak, L.J., Urban, L.H. & Hayes, S.N. 2000. Outcomes of Primary and Secondary Treatment of Pericardial Effusion in Patients With Malignancy. <https://doi.org/10.4054/75.3.248>.

Vakamudi, S., Ho, N. & Cremer, P.C. 2017. Pericardial effusions: causes, diagnosis, and management. *Prog Cardiovasc Dis.* 2017 Jan - Feb;59(4):380-388. doi: 10.1016/j.pcad.2016.12.009. Epub 2017 Jan 4.