Cancer Association of South Africa (CANSA)

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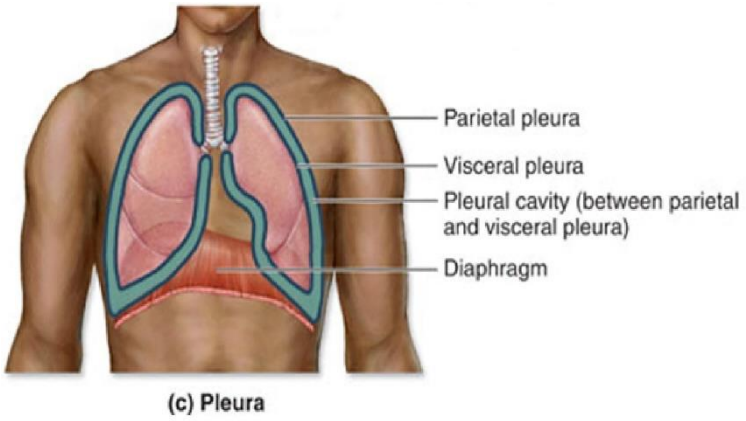
Fact Sheet
on
Pleural Cancer

Introduction

The pleura is a serous membrane that lines the Mediastinum, pericardium, diaphragm and thoracic wall (parietal pleural), and the lungs.

{Picture Credit: Pleura]



(c) Pleura

Pleural Cancer

Pleural cancer occurs outside the lungs in the chest or pleural cavity and along the pleural lining, the membrane that surrounds the lungs and covers the inside of the chest cavity.

Cancer that occurs in the pleural cavity has most often spread (metastasised) to the pleura from somewhere else in the body. For this reason, the disease is sometimes referred to as unknown primary pleural cancer. It has most commonly spread to the pleural space from the lung but can come from the breast, ovary, pancreas, colon, and other locations.

With lung cancer, the pleural tissue is a common area affected by metastasis. Cancer cells from primary tumours migrate to the pleura through the blood stream or spread through the lymphatic system. Cancer cells may also transfer to the pleura through simple contact, as the lungs press directly against this tissue. Once in the pleura, cancer cells may develop into one or multiple tumours.

Primary pleural cancer is cancer that develops in the pleural cavity itself, such as malignant pleural mesothelioma, but this type is less common.

Determining the cancer's origin and degree of involvement often requires special diagnostic testing and procedures.

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Incidence of Pleural Cancer in South Africa
The National Cancer Registry (2017) does not provide any information regarding Pleural Cancer.

Signs and Symptoms of Pleural Cancer
Individuals diagnosed with Pleural Cancer may not have any symptoms. Signs and symptoms are most often found when the patient's chest is being X-rayed for other purposes. But metastatic pleural tumours produce symptoms similar to those of lung cancer or other serious chest ailments.

They include:
- Shortness of breath when active
- Chest pain
- General discomfort or uneasiness
- Cough
- Unintended weight loss

Risk Factors for Pleural Cancer
A risk factor is anything that increases your chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be changed. Others, like a person's age or family history, can't be changed. But having a known risk factor, or even many, does not mean that you will get the disease. And some people who get the disease may have few or no known risk factors.

The most common form of pleural cancer is Pleural Mesothelioma. The main risk factor for pleural mesothelioma is exposure to asbestos. In fact, most cases of pleural mesothelioma have been linked to high levels of asbestos exposure, usually in the workplace.

Asbestos is a group of minerals that occur naturally as bundles of tiny fibres. These fibres are found in soil and rocks in many parts of the world.

When asbestos fibres in the air are inhaled, they can get into the lungs. Fibres that stay in the lungs can travel to the ends of the small airways and enter the pleural lining of the lung and chest wall. These fibres can then injure the cells of the pleura, and, over time, cause mesothelioma. Asbestos fibres can also damage cells of the lung and result in asbestosis (scar tissue in the lung) and/or lung cancer.

Barone-Adesi, F., Ferrante, D., Chellini, E., Merler, E., Pavone, V., Silvestri, S., Miligi, L., Gorini, G., Bressan, V., Girandi, P., Ancona, L., Romeo, E., Luberto, F., Sala, O., Scarnato, C., Menegozzo, S., Oddone, E., Tunesi, S., Perticaroli, P., Pettinari, A., Cuccaro, F., Curti, S., Baldassarre, A., Cena, T., Angelini, A., Marinaccio, A., Mirabelli, D., Musti, M., Pirastu, R., Ranucci, A., Magnani, C. & Working Group. 2019.
Objectives: Models based on the multistage theory of cancer predict that rates of malignant mesothelioma continuously increase with time since first exposure (TSFE) to asbestos, even after the end of external exposure. However, recent epidemiological studies suggest that mesothelioma rates level off many years after first exposure to asbestos. A gradual clearance of asbestos from the lungs has been suggested as a possible explanation for this phenomenon. We analysed long-term trends of pleural and peritoneal cancer mortality in subjects exposed to asbestos to evaluate whether such trends were consistent with the clearance hypothesis.

Methods: We used data from a pool of 43 Italian asbestos cohorts (51 801 subjects). The role of asbestos clearance was explored using the traditional mesothelioma multistage model, generalised to include a term representing elimination of fibres over time.
Results: Rates of pleural cancer increased until 40 years of TSFE, but remained stable thereafter. On the other hand, we observed a monotonic increase of peritoneal cancer with TSFE. The model taking into account asbestos clearance fitted the data better than the traditional one for pleural (p=0.004) but not for peritoneal (p=0.09) cancer.
Conclusions: Rates of pleural cancer do not increase indefinitely after the exposure to asbestos, but eventually reach a plateau. This trend is well described by a model accounting for a gradual elimination of the asbestos fibres. These results are relevant for the prediction of future rates of mesothelioma and in asbestos litigations.

Diagnosis of Pleural Cancer
Imaging techniques used to diagnose pleural cancer might include:

- Chest X-ray**:** This type of imaging is used to visualise abnormalities in the pericardium.
- Contrast-enhanced or multi-detector computed tomography (CT) scan: CT technology helps physicians visualise the location and extent of unknown primary pleural cancer.
- Magnetic resonance imaging (MRI)**:** MRI helps physicians identify suspicious areas that could indicate unknown primary pleural cancer and learn if and how far it has spread.
- Positron emission tomography (PET) scan**:** Cancer cells absorb large amounts of radioactive sugar used in this technique, and a special camera creates images of that radioactivity, enabling physicians to identify cancerous cells in the pleura.
- Endoscopic ultrasonography: This technology maps sound waves to help physicians visualize pleural cancer.

Additional testing may also include a tissue sample (biopsy) of the pleural tissue.

Kastelik, J.A., Bhowmik, A. & Park, J. 2019.
"Lung and pleural malignancies remain common in the UK with poor survival rates due, at least in part, to late stage diagnosis. Diagnostic pathways aim to reduce the time taken for patients to reach a diagnosis and treatment, with the use of positron emission tomography and endobronchial ultrasound to provide staging information alongside diagnostics. Advances in molecular phenotyping of tumours and the development of treatments to target these have provided new therapeutic options which can be individualised to patients. In the UK, screening for lung cancer remains in its infancy, but provides a promising possibility for capturing curative disease. We provide an overview of the diagnostic process, therapeutic options and potential future screening programmes in pleural and pulmonary malignancies."

Salaroglio, I.C., Kopecka, J., Napoli, F., Pradotto, M., Maletta, F., Costardi, L., Gagliasso, M., Milosevic, V., Ananthanarayanan, P., Bironzo, P., Tabbò, F., Cartia, C.F., Passone, E., Comunanza, V., Ardissone, F., Ruffini, E., Bussolino, F., Righi, L., Novello, S., Di Maio, M., Papotti, M., Scagliotti, G. & Riganti, C. 2019.
INTRODUCTION: A comprehensive analysis of the immune-cell infiltrate collected from pleural fluid and from biopsies of malignant pleural mesothelioma (MPM) may contribute to understand the immune-evasion mechanisms related to tumor progression, aiding in differential diagnosis and potential prognostic stratification. Till now such approach has not routinely been verified.
METHODS: We enrolled in 275 patients with an initial clinical diagnosis of pleural effusion. Specimens of pleural fluids and pleural biopsies used for the pathological diagnosis and the immune-phenotype analyses

were blindly investigated by multi-parametric flow cytometry. The results were analyzed by Kruskal-Wallis test. The Kaplan-Meier and log-rank tests were used to correlate immune-phenotype data with patients' outcome.
RESULTS: The cut-offs of intra-tumor T-regulatory (Treg; >1.1%) cells, M2-macrophages (>36%), granulocytic and monocytic myeloid-derived suppressor cells (MDSC; >5.1% and 4.2%, respectively), $CD4^+PD1^+$ (>5.2%) and $CD8^+PD1^+$ (6.4%) cells, $CD4^+LAG\text{-}3^+$ (>2.8%) and $CD8^+LAG\text{-}3^+$ (>2.8%) cells, $CD4^+TIM\text{-}3^+$ (>2.5%) and $CD8^+TIM\text{-}3^+$ (>2.6%) cells discriminated MPM from pleuritis with 100% sensitivity and 89% specificity. The presence of intra-tumor MDSC contributed to the anergy of tumor-infiltrating lymphocytes (TILs). The immune-phenotype of pleural fluid cells had no prognostic significance. By contrast, the intra-tumor Treg and MDSC levels significantly correlated with progression-free and overall survival, the $PD\text{-}1^+/LAG\text{-}3^+/TIM\text{-}3^+$ $CD4^+$TILs correlated with overall survival.
CONCLUSIONS: A clear immune-signature of pleural fluids and tissues of MPM patients may contribute to better predict patients' outcome.

Wijmans, L., Baas, P., Sieburgh, T.E., de Bruin, D.M., Ghuijs, P.M., van de Vijver, M.J., Bonta, P.I. & Annema, J.T. 2019.
BACKGROUND: Pleural biopsies in patients with suspected malignant pleural mesothelioma (MPM) are often inconclusive featuring fibrosis, resulting in repeat diagnostic procedures. Confocal laser endomicroscopy (CLE) enables real-time imaging on a cellular level. We investigated pleural CLE imaging as a biopsy guidance technique to distinguish malignant from benign pleural disease.
METHODS: Prospective, multi-center study in patients with (suspected) MPM based on (PET)-CT imaging who were scheduled for pleural biopsies. Patients received 2.5ml fluorescein intravenously preceding the procedure. In-vivo -through the needle- CLE-imaging of the pleura and ex-vivo CLE-imaging of the biopsies were correlated with histology. CLE characteristics for various pleural entities were identified and their interpretability was tested by CLE-video scoring by multiple blinded raters.
RESULTS: CLE imaging was successfully obtained in 19 from 20 diagnostic pleural biopsy procedures (thoracoscopy (n=3), surgical excision (n=3) CT- (n=4) , ultrasound- (n=9), EUS-guided (n=1)) in 15 patients. CLE videos (n=89) and corresponding pleural biopsies (n=105) were obtained. No study related adverse events occurred. Tumor deposits of malignant pleural mesothelioma were distinguished from pleural fibrosis based on CLE imaging and recognized by raters (n=3). (IOA: 0.56 (95%CI 0.49-0.64).
CONCLUSIONS: CLE imaging was feasible and safe regardless of the biopsy method. Real-time visualization of pleural abnormalities in epithelial and sarcomatoid MPM, could be distinguished from pleural fibrosis. Therefore, CLE has potential as a guidance biopsy tool, to reduce the current substantial rate of repeat biopsy procedures, by identification of areas with malignant cells in vivo (smart needle).

Yamamoto, N., Watanabe, T., Yamada, K., Nakai, T., Suzumura, T., Sakagami, K., Yoshimoto, N., Sato, K., Tanaka, H., Mitsuoka, S., Asai, K., Kimura, T., Kanazawa, H., Hirata, K. & Kawaguchi, T. 2019.
BACKGROUND: Ultrasound (US)-guided percutaneous needle biopsy is a useful diagnostic technique with short examination time and real-time monitoring at the bedside. However, there are only a few studies that report on thoracic lesions, whereas the computed tomography (CT)-guided biopsy is well established. There is also limited data comparing US- and CT-guided biopsy. We aimed to clarify the efficacy and safety of US-guided biopsy for thoracic lesions adjacent to the chest wall.
METHODS: We retrospectively enrolled consecutive patients who underwent US- or CT-guided percutaneous biopsies for thoracic lesions adjacent to the chest wall between April 2012 and December 2017. Clinical characteristics, lesion size, lesion-pleura contact arc length (LPCAL), diagnostic rate, and complications were compared between the 2 groups.
RESULTS: This study enrolled 61 US-guided and 70 CT-guided biopsies. No significant difference was found in age or sex. The lesion size and LPCAL in the US-guided group were significantly larger than those in the CT-guided group ($P<0.0001$). The diagnostic rate was marginally higher in the US-guided group (93.4%) than in

the CT-guided group (84.3%) (P=0.101). When the median cut-off of the LPCAL was defined as 40 mm in all cases, the diagnostic rate for lesion size >40 mm was significantly higher in the US-guided group than in the CT-guided group (P=0.009). Complication rates were significantly lower in the US-guided group (3.3%) than in the CT-guided group (24.3%) (P<0.001).
CONCLUSIONS: US-guided percutaneous needle biopsy for thoracic lesions adjacent to the chest wall is a feasible technique compared with CT-guided biopsy because of its higher diagnostic rate with a longer LPCAL and reduced complications.

Treatment of Pleural Cancer
Unfortunately pleural cancer can be very difficult to treat as it is often found when it is advanced. Nearly all treatment aims to control it for as long as possible and keep symptoms under control.

Some people with early stage pleural cancer may have surgery. This is followed by chemotherapy or radiotherapy or a combination of both.

People with more advanced pleural cancer might have chemotherapy to shrink it and reduce symptoms. Chemotherapy can help some people live weeks or months longer. Radiotherapy might also shrink the cancer and control the symptoms.

Patients may have chemotherapy for early stage pleural cancer, alongside surgery and radiotherapy. Chemotherapy can also help to shrink or control advanced pleural cancer for some time.

Walker, S., Mercer, R., Maskell, N. & Rahman, N.M. 2020.
"With no cure for malignant pleural effusion, efforts are focused on symptomatic management. Historically, this symptomatic management was achieved with the instillation of a sclerosant agent into the pleural space to achieve pleurodesis. The development of the tunnelled indwelling pleural catheter and ambulatory pleural drainage changed the management of malignant pleural effusion, not solely by offering an alternative management pathway, but by challenging how health-care providers view success in a palliative condition. Furthermore, with additional treatment options available, increased imperative exists to better characterise patients to enable a personalised approach to their care. We have done a review of the scientific literature and clinical trial registries to provide an overview of the current and ground-breaking research published in the past 10 years."

Scagliotti, G.V., Gaafar, R., Nowak, A.K., Nakano, T., van Meerbeeck, J., Popat, S., Vogelzang, N.J., Grosso, F., Aboelhassan, R., Jakopovic, M., Ceresoli, G.L., Taylor, P., Orlandi, F., Fennell, D.A., Novello, S., Scherpereel, A., Kuribayashi, K., Cedres, S., Sørensen, J.B., Pavlakis, N., Reck, M., Velema, D., von Wangenheim, U., Kim, M., Barrueco, J. & Tsao, A.S. 2019.
BACKGROUND: Nintedanib targets VEGF receptors 1-3, PDGF receptors α and β, FGF receptors 1-3, and Src and Abl kinases, which are all implicated in malignant pleural mesothelioma pathogenesis. Here, we report the final results of the phase 3 part of the LUME-Meso trial, which aimed to investigate the efficacy and safety of pemetrexed plus cisplatin combined with nintedanib or placebo in unresectable malignant pleural mesothelioma.
METHODS: This double-blind, randomised, placebo-controlled phase 3 trial was done at 120 academic medical centres and community clinics in 27 countries across the world. Chemotherapy-naive adults (aged ≥18 years) with unresectable epithelioid malignant pleural mesothelioma and ECOG performance status 0-1 were randomly assigned 1:1 via an independently verified random number-generating system to receive up

to six 21-day cycles of pemetrexed (500 mg/m^2) plus cisplatin (75 mg/m^2) on day 1, then nintedanib (200 mg twice daily) or matched placebo on days 2-21. Patients without disease progression after six cycles received nintedanib or placebo maintenance on days 1-21 of each cycle. The primary endpoint was progression-free survival (investigator-assessed according to mRECIST) in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of their assigned study drug. This study is registered with ClinicalTrials.gov, number NCT01907100.
FINDINGS: Between April 14, 2016, and Jan 5, 2018, 541 patients were screened and 458 were randomly assigned to either the nintedanib group (n=229) or the placebo group (n=229). Median treatment duration was 5·3 months (IQR 2·8-7·3) in the nintedanib group and 5·1 months (2·7-7·8) in the placebo group. After 250 events, progression-free survival was not different between the nintedanib group (median 6·8 months [95% CI 6·1-7·0]) and the placebo group (7·0 months [6·7-7·2]; HR 1·01 [95% CI 0·79-1·30], p=0·91). The most frequently reported grade 3 or worse adverse event in both treatment groups was neutropenia (73 [32%] in the nintedanib group vs 54 [24%] in the placebo group). Serious adverse events were reported in 99 (44%) patients in the nintedanib group and 89 (39%) patients in the placebo group. The only serious adverse event occurring in at least 5% of patients in either group was pulmonary embolism (13 [6%] vs seven [3%]).
INTERPRETATION: The primary progression-free survival endpoint of the phase 3 part of LUME-Meso was not met and phase 2 findings were not confirmed. No unexpected safety findings were reported.

MacRae, R.M., Ashton, M., Lauk, O., Wilson, W., O'Rourke, N., Simone, C.B. 2nd & Rimner, A. 2019.
"Radiation remains an important component of mesothelioma treatment in 2018. Its use as a treatment modality continues to evolve as the technology for planning and delivery continues to improve. Use of radiation to improve local control in the involved hemithorax has been a common adjuvant treatment post extrapleural pneumonectomy for many years. Modern treatment options with advanced planning techniques including protons and intensity modulated radiation therapy lead to new potential options for treatment post lung-sparing surgery or in the unresectable setting. Presentations and discussions on the implementation of these strategies for palliation, treatment of oligometastatic recurrence or unresectable disease were the focus of a session dedicated to the role of radiation therapy at the 14th International Conference of the International Mesothelioma Interest Group and are reviewed in this article. Preclinical data to better understand how to integrate radiation and the delivery of novel systemic therapy approached like check point inhibitors are also presented."

Van Gerwen, M., Alpert, N., Wolf, A., Ohri, N., Lewis, E., Rosenzweig, K.E., Flores, R. & Tajoli, E. 2019.
Malignant pleural mesothelioma (MPM) is a rare disease with a very poor prognosis. Previous studies have indicated that women experience longer survival compared with men. We analyzed 16 267 eligible patients (21.3% females) in the National Cancer Database to evaluate which clinical factors are independently predictive of longer survival. After adjusting for all covariates, survival was significantly better in females compared with males [HRadj: 0.81, 95% confidence interval (CI): 0.77-0.85]. Other factors significantly associated with better survival were younger age at diagnosis, higher income, lower comorbidity score, epithelial histology, earlier stage and receipt of surgical or medical treatment. After propensity matching, survival was significantly better for females compared with males [hazard ratio (HR): 0.86, 95% CI: 0.80-0.94]. After propensity matching within the epithelial group, survival remained significantly better for females compared with males (HR: 0.85, 95% CI: 0.74-0.97). This study adds information to the known significant gender survival difference in MPM by disentangling the effect of gender from the effect of age and histology, two known independent factors affecting survival. Circulating estrogen, present in young but not older women, and higher expression of the estrogen receptor beta in epithelial mesothelioma have been suggested to play a role in gender survival differences. These findings may lead to exploring new therapeutic options, such as targeting estrogen receptor beta, and considering hormonal therapy including estrogens for patients with otherwise limited prognosis.

Murthy, V., Katzman, D & Sterman, D.J. 2019.

Objectives: Malignant pleural mesothelioma and malignant pleural effusions are a major therapeutic challenge, and are associated with impairment in quality of life and increased mortality. Advances in systemic therapies of malignant pleural mesothelioma have demonstrated limited clinical benefit and there is ongoing interest in intrapleural immunotherapies which have been demonstrated to be well tolerated overall with variable clinical responses. We have reviewed the literature to provide a comprehensive summary of novel intrapleural immunotherapeutic paradigms, including oncolytic virus therapy, gene-mediated cytotoxic immunotherapy, direct cytokine-mediated immunotherapies, innate immunomodulators and adoptive transfer of intrapleural chimeric antigen receptor T-cell therapy.

Data sources: A review of PubMed for original manuscripts and conference reports published between 1998 and 2018 pertaining to intrapleural immunotherapy, as well as examination of reference lists from reviewed manuscripts.

Study selection: Human clinical trials on intrapleural immunotherapies in subjects with malignant pleural mesothelioma or malignant pleural effusion were included in this review, including some relevant preclinical studies and anticipated ongoing trials reported on Clinicaltrials.gov.

Results: Twenty-six clinical trials were identified, in addition to three trials currently in progress.

Conclusion: Intrapleural immunotherapies for pleural malignancy have demonstrated promise with regard to generating durable tumor-specific immune responses with possible clinical benefits which merit further investigation as part of multimodal chemotherapeutic and immunotherapeutic regimens.

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Pleura
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Pleural Cancer
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