Cancer Association of South Africa (CANSA)

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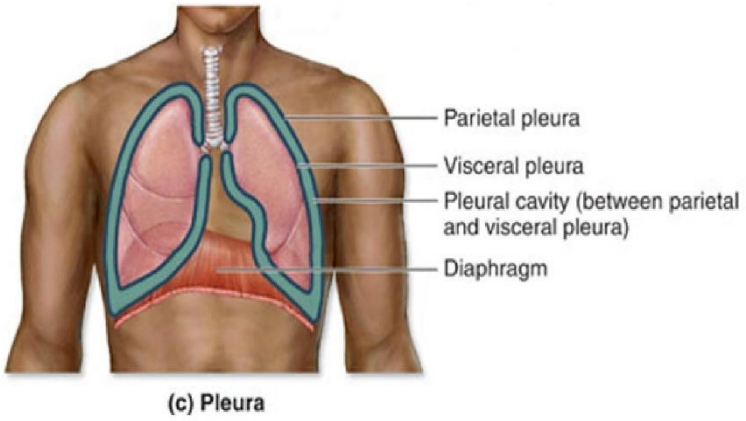
Fact Sheet
on
Pleural Cancer

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 (2014) 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.

Marsh, G.M., Riordan, A.S., Keeton, K.A. & Benson, S.M. 2017.
OBJECTIVE: To conduct an updated literature review and meta-analysis of studies of pleural malignant mesothelioma (PMM) risk among persons exposed to asbestos non-occupationally (household and neighbourhood).
METHODS: We performed a literature search for articles available in the National Center for Biotechnology Information's PubMed database published between 1967 and 2016. Meta-analyses were conducted to calculate pooled PMM risk estimates, stratifying for household or neighbourhood exposure to asbestos and/or predominant asbestos fibre type (chrysotile, amphibole or mixed).
RESULTS: Eighteen studies in 12 countries comprising 665 cases met the meta-analysis inclusion criteria. We identified 13 estimates of PMM risk from neighbourhood exposures, 10 from household and one from

mixed exposure, and combined the estimates using random-effects models. The overall meta-relative risk (meta-RR) was 5.9 (95% CI 4.4 to 8.7). The meta-RRs for household and neighbourhood exposures were 5.4 (95% CI 2.6 to 11.2) and 6.9 (95% CI 4.2 to 11.4), respectively. We observed trends in risk in relation to fibre type for both household and neighbourhood studies. For chrysotile, mixed and amphibole fibres, respectively, meta-RRs for neighbourhood studies were 3.8 (95% CI 0.4 to 38.4), 8.4 (95% CI 4.7 to 14.9) and 21.1 (95% CI 5.3 to 84.5) and meta-RRs for household studies were 4.0 (95% CI 0.8 to 18.8), 5.3 (95% CI 1.9 to 15.0) and 21.1 (95% CI 2.8 to 156.0).
CONCLUSIONS: PMM risks from non-occupational asbestos exposure are consistent with the fibre-type potency response observed in occupational settings. By relating our findings to knowledge of exposure-response relationships in occupational settings, we can better evaluate PMM risks in communities with ambient asbestos exposures from industrial or other sources.

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.

Sakuma, K., Yamashiro, T., Moriya, H., Murayama, S. & Ito, H. 2017.
PURPOSE: Using 4-dimensional dynamic-ventilatory scanning by a 320-row computed tomography (CT) scanner, we performed a quantitative assessment of parietal pleural invasion and adhesion by peripheral (subpleural) lung cancers.
METHODS: Sixteen patients with subpleural lung cancer underwent dynamic-ventilation CT during free breathing. Neither parietal pleural invasion nor adhesion was subsequently confirmed by surgery in 10 patients, whereas the other 6 patients were judged to have parietal pleural invasion or adhesion. Using research software, we tracked the movements of the cancer and of an adjacent structure such as the rib or aorta, and converted the data to 3-dimensional loci. The following quantitative indices were compared by the Mann-Whitney test: cross-correlation coefficient between time curves for the distances moved from the inspiratory frame by the cancer and the adjacent structure, the ratio of the total movement distances (cancer/adjacent structure), and the cosine similarities between the inspiratory and expiratory vectors (from the cancer to the adjacent structure) and between vectors of the cancer and of the adjacent structure (from inspiratory to expiratory frames).
RESULTS: Generally, the movements of the loci of the lung cancer and the adjacent structure were similar in patients with parietal pleural invasion/adhesion, while they were independent in patients without. There were significant differences in all the parameters between the two patient groups (cross-correlation coefficient and the movement distance ratio, $P<0.01$; cosine similarities, $P<0.05$).

CONCLUSION: These observations suggest that quantitative indices by dynamic-ventilation CT can be utilized as a novel imaging approach for the preoperative assessment of parietal pleural invasion/adhesion.

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.

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."

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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