Malignant mesothelioma is a tumor of the lining of the lung and chest cavity (pleura) or lining(s) of the abdomen (peritoneum) that is very often related to exposure to carcinogenic mineral fibers such as asbestos and erionite.

There are about 400 mineral fibers in nature. With the exception of palygorskite which was recently proven not to be carcinogenic, all mineral fibers are potentially carcinogenic for humans. Six of them, antophyllite, actinolite, crocidolite, amosite, tremolite and chrysotile were used commercially: thus, millions of people were exposed to them. These six commercial fibers were named collectively “asbestos” and their use has been regulated in the US and in most of Europe since the late 70s 80s. The use of mineral fibers other than those called “asbestos” is not regulated yet, in spite of the fact that some of them, such as erionite, are proven human carcinogens.

Recently, exposure to non-regulated mineral fibers has increased as rural zones containing these minerals are being developed posing a hazard to human health.

According to the Surveillance, Epidemiology and End Results (SEER) Program data, the incidence of mesothelioma in the U.S. is estimated to be between 1-2/million in states with minimal exposure to mineral fibers and 10-15/million in states where large amounts of asbestos were used.

Over 20 million people in the US are at risk of developing mesothelioma due to asbestos exposure, and more due to exposure to other mineral fibers. Mortality rates for mesothelioma are estimated to increase by 5-10% per year in most industrialized countries until about 2020 due to past exposure.

Exposure to asbestos, erionite and other carcinogenic mineral fibers may be occupational or environmental. Environmental exposure to carcinogenic fibrous minerals includes indoor and outdoor contamination caused by both asbestos-containing commercial materials and from naturally occurring asbestos and other fibers. The future effect on mesothelioma mortality due to exposure to non-regulated mineral fibers is unknown.

The latency period, which is the interval between first exposure and the development of mesothelioma, ranges from about 25 to >60 years.

Occasional exposure to asbestos or other mineral fibers does not cause mesothelioma. Prolonged exposures is associated with an increased risk of mesothelioma. For example, no mesotheliomas were recorded in South African crocidolite asbestos miners who worked continuously with asbestos for less than 3 months; most mesotheliomas occurred in miners with >10 years of continuous exposure.

Asbestos and other mineral fibers induce mesothelioma because they are deposited in the pleura and peritoneum where they cause a chronic inflammatory process that is driven by the chronic release of HMGB1 and TNF-α, that over the years may cause malignancy.

Radiation exposure has also been linked to mesothelioma, especially in individuals treated with radiation therapy for lymphoma and other malignancies. SV40 is a DNA tumor virus that causes mesothelioma in animals, that enhances asbestos carcinogenesis and that causes malignant transformation of human mesothelial cells in tissue culture. Whether SV40 may cause human mesothelioma, alone or by enhancing asbestos carcinogenesis remains to be determined.

Genetics influences the risk of developing mesothelioma. For instance, among crocidolite-asbestos miners who worked for over 10 years in South African asbestos mines, 4.6% developed mesothelioma after a period of about 30-40 years, suggesting that some of them were more susceptible to asbestos carcinogenesis.
Several biomarkers to identify individuals exposed to asbestos and/or for early mesothelioma detection have been proposed and are currently being tested for validation: osteopontin, fibulin and HMGB1. Mesothelin, the first mesothelioma biomarker identified, is used to monitor recurrence following therapy, but it is not useful to identify asbestos exposed individuals or for early detection of mesothelioma.

BAP1 is the first, and to date, the only gene that has been linked to familial mesothelioma (i.e., multiple cases of mesothelioma in the same family). All individuals that are born with inherited germline BAP1 mutations have developed one or more malignancies in their life-time, especially mesotheliomas and eye melanomas. Experiments in mice indicate that BAP1 germline mutations lower the threshold amount of asbestos required to induce mesothelioma. These experimental findings suggest that individuals born with BAP1 germline mutations may be susceptible to low doses of asbestos that would not cause mesothelioma in the general population.

Mesotheliomas that develop in individuals carrying germline BAP1 mutations are less aggressive and are often associated with prolonged survival of 5-10 or more years.

The IASLC/IMIG staging system for pleural mesothelioma has been revised recently to include patients who did or did not have surgery. In general, higher stage, non-epithelial histology, older age, male status, palliative vs curative surgery, and the lack of adjuvant therapy was associated with decreased survival.

Low hemoglobin, high white blood cell and platelet count are associated with decreased survival.

MM patients diagnosed and treated in Stage 1 experience survival of 3 or more years. However of the majority of patients are diagnosed at higher stage when median is approximately 12-15 months with first line chemotherapy.

In patients with resectable MM, a tri-modality approach of chemotherapy (systemic, either preoperative or postoperative, or intraoperative), surgery, and postoperative radiation therapy to try to enhance local disease control is recommended in order to delay local recurrence and systemic metastases. In the USA, it is standard practice to administer 2-4 cycles of cisplatin-pemetrexed to multimodality therapy for resectable mesothelioma.

The value of surgery to treat patients with mesothelioma continues to be controversial. The use of extrapleural pneumonectomy has decreased in favor of performing a maximal cytoreduction through a parietal and visceral pleurectomy, along with pericardial and diaphragmatic resection as necessary. Further concordance among mesothelioma surgeons regarding the extent of the resection is necessary, along with novel prospective window of opportunity trials in order to define the utility of new agents for the disease.

The combination of pemetrexed and platinum is the only FDA approved regimen for patients with MPM who are either unresectable or are not otherwise candidates for surgery.

A number of novel treatments for non-resectable MM are in clinical trials. These include several drugs targeting mesothelin such as immunotoxins (SS1P, RG7787), a chimeric monoclonal antibody (Amatuximab)\(^{729}\), an antibody drug conjugate (Anetumab Ravtansine), and a tumor vaccine (CRS-207). The role of checkpoint immunotherapies (PD-1 inhibitor, CTLA4 inhibitor) is under active investigation.