



PLEURAL  
MESOTHELIOMA



# PLEURAL MESOTHELIOMA

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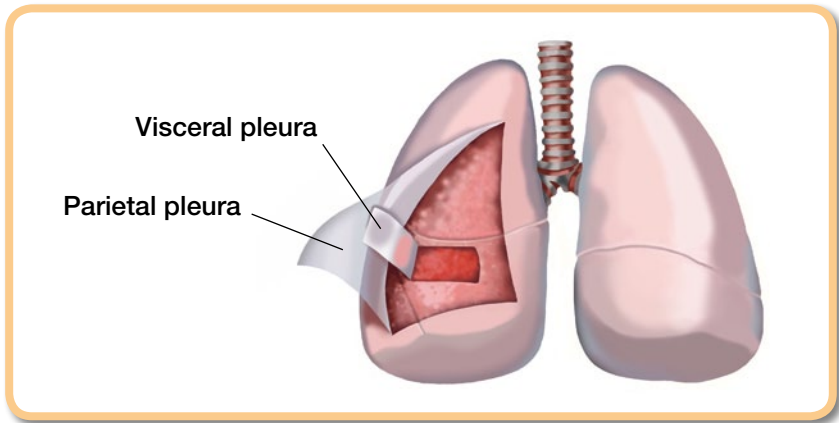
# PLEURAL MESOTHELIOMA



# 1. Introduction

The lungs are the organs that enable the red blood cells to resupply themselves with oxygen. By means of the red blood cells, oxygen circulates in the blood stream and is then released in organs and other structures to support their function and various activities. The lungs are contained in the thoracic cavity and are covered by a thin, transparent membrane that is called the visceral pleura.

Likewise, the inside of the thoracic cavity (or rib cage) is also lined with the same membrane, but in this case it is called the parietal pleura. These two pleural layers, the visceral pleural and the parietal pleura, are in continuity with each other, separated only by a virtual space that contains small amounts of liquid (pleural fluid) that allows one layer to slide over the other, almost like a lubricant.



In normal conditions, when the lungs expand to breathe in air, the two pleuras slide over each other easily, making this continuous, vital mechanism fluid and smooth. The cells that make up the pleura are called **mesothelial cells**.

The pleura can be affected by a variety of pathologies, some of which can remain hidden, to the extent that there are no outward signs of their

presence (pleural plaques or parietal fibrosis, diffuse pleural fibrosis, asbestosis), and very often localised pleural thickenings, although numerous, retain benign characteristics. **Pleural mesothelioma** is a rare form of tumour that originates from the mesothelial cells of the pleura. It is not the only known type of mesothelioma, since the same type of disease can arise in other structures of the human body that are lined with mesothelial cells as well, like the **peritoneum (peritoneal mesothelioma)**, the **pericardium (pericardial mesothelioma)** and the serous membrane that lines the testicle, in the male.

Of these, pleural mesothelioma is definitely the most widespread, making up some 80% of all mesotheliomas, while peritoneal mesothelioma accounts for 20% and the other forms are rare. In the United States around 3,000 cases of mesothelioma are recorded every year and the ratio between men and women is five to one. One of the peculiarities of this disease is the long **latency period** between exposure to possible causes and the appearance of the disease, which ranges from 20 to 40 years. The age at which it strikes most often is around 60.

Mesothelioma patients have a median survival that is in close correlation with the microscopic characteristics of the tumour and proper classification of its extent (staging).

Unfortunately, there is currently no screening test (i.e., early diagnosis method) for mesothelioma that is universally approved and applicable at least in patients with known exposure.

Some studies have been conducted in order to ascertain the possible existence of “exposure markers”, that is, “spies” that, by means of a simple blood sample, make it possible to identify persons with exposure to asbestos and likely to be more at risk of developing this cancerous disease. Among these markers, the most widely studied is undoubtedly **mesotheline**, which has shown itself to be higher in subjects exposed to asbestos who later developed mesothelioma. In itself this is not sufficient, however, and biopsy or examination of the pleural fluid (see p. 16) remain fundamental for diagnosis. Application of this marker as a screening test is still to be confirmed.



## 2. Causes of Mesothelioma

Mesothelioma is one of the forms of cancer in which a close correlation has been clearly shown with the factors that cause it, first and foremost exposure to **asbestos fibres**. Asbestos fibres are extremely fine and penetrate through the airways - fibres with diameters of less than 0.5  $\mu\text{m}$  can reach the **pulmonary alveoli**. The deposited fibres lead to activation of the local immune system (our defence system) and cause a foreign-body inflammatory reaction. Macrophages (the human body's "cleaning cells") phagocytise or surround these fibres and stimulate the fibroblasts (worker cells) to produce connective tissue. The result of all this is the development of **interstitial fibrosis**.

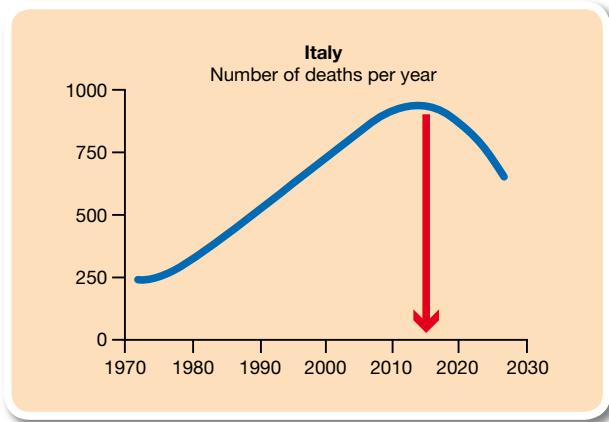
The asbestos fibres also reach the pleura and exert their fibrogenic and carcinogenic action there as well.



*Asbestos fibres*

As stated earlier, mesothelioma does not present itself immediately after exposure to asbestos; it usually takes over 20 years following exposure for the disease to develop. This means that the numerous prevention campaigns undertaken already many years ago, aimed at prohibiting the






use of asbestos and disposal of the sources present, have not yet made it possible to see a decrease in the incidence of this disease. In Italy, the peak of greatest incidence (that is, the number of new cases of disease in a year) is expected in around 2015.



*Cases per one million inhabitants in Italy*



*Distribution of the incidence of pleural mesothelioma in the various regions*

-  Less than 252
-  252 - 495
-  496 - 740
-  741 - 984
-  985 - 1229



As can be seen on the preceding page, there are some Italian regions in which there is a decidedly higher incidence than in other regions, including Lombardy, Piedmont, Liguria, Puglia and Sicily. Each of these regions has identified the sites and the causes of this higher incidence, setting up special registers for monitoring the disease.

In addition, data exist that have shown that in three small Turkish towns a higher incidence of mortality due to mesothelioma (chiefly pleural) and **erionite** fibres have been identified in the lung tissue of the persons affected by mesothelioma. Erionite is a mineral that is part of the zeolite family. It can be found in clay and kaolin quarries and mines; in the manufacture of refractory materials and products; in the manufacture of prefabricated products and elements made of concrete, cement, artificial stones, elements in light, expanded, blown conglomerates; in water purification, sterilisation and depollution plants; in construction finishing work; in the production of bricks, tiles and other building products; and in general services for the petrochemical industry.



*Erionite fibres*

Erionite is rarely encountered in the pure form, as it is mostly found together with other zeolites. Mineral deposits have been reported in 40 countries around the world, with a prevalence in the western United States (Arizona, California, Idaho, Nevada, New Mexico, Oregon, Texas, Utah and Wyoming).

# 3. What is asbestos?

Asbestos deposits and mines exist in numerous countries around the world, including Italy, which was the largest European producer. It presents itself in various chemical forms: **chrysotile** or serpentine (**white asbestos**), which alone represents over 90% of the extracted and utilised material, and **amphiboles**, like crocidolite (**blue asbestos**) and amosite (**brown asbestos**), which make up less than 10% of the asbestos used.

## 3.1 Why was it used so much in the past?

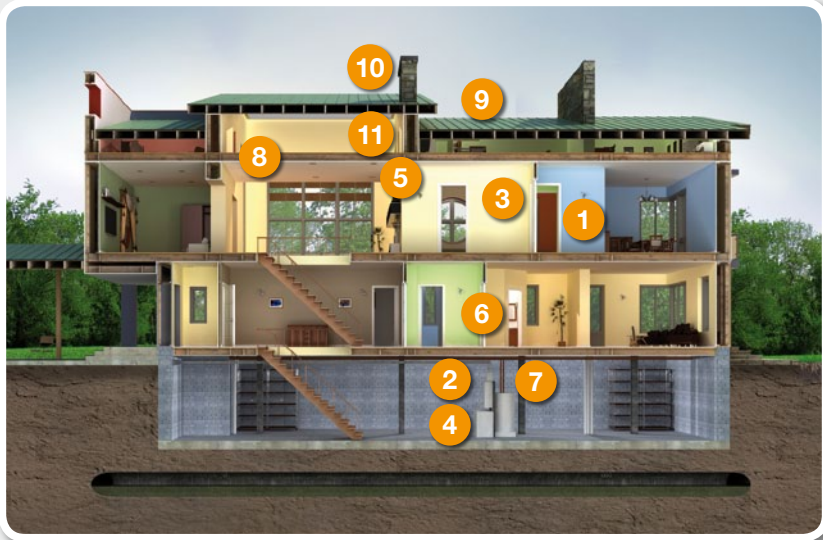
Thanks to its low thermal conductivity, good resistance to chemical agents and extraordinary strength, asbestos offers high insulating power. Very widespread in nature, it can also be spun or woven, with exceptional fire resistance and non-conductivity characteristics (thermal, electrical or acoustic insulating capacity).



*Within the space of one centimetre, the following can be placed side by side:*  
*250 human hairs*  
*500 nylon fibres*  
*350,000 asbestos fibres*

## 3.2 Where was asbestos used most frequently?

The next page lists just SOME of the products that contained asbestos in its various forms.

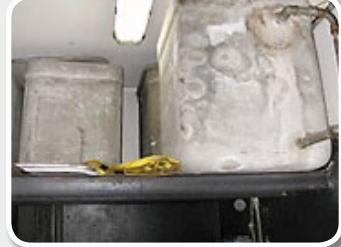


- |                         |                         |
|-------------------------|-------------------------|
| 1. Plaster              | 7. Water pipes          |
| 2. Stove gaskets        | 8. Insulating materials |
| 3. Panels               | 9. Roofing sheets       |
| 4. Pipe insulation      | 10. Chimneys            |
| 5. Fireplace lining     | 11. Water tanks         |
| 6. Household appliances |                         |

During work on buildings, plants or structures, it is still possible to come across materials made of asbestos or treated with asbestos. They can be either friable or non-friable. Friable materials can be crumbled between the fingers; those that can be crumbled only with the help of mechanical tools (*like a drill*) are non-friable. Materials like insulating panels or partitions, roofing made of flat or corrugated sheets (*like Eternit*), chimneys, some linoleum floorings and water tanks are non-friable. Friable materials tend to release asbestos fibres into the environment more easily; non-friable materials release fibres only if they are scraped, drilled or broken up.



*Roofing sheets*



*Water tanks*



*Chimneys*



*Pipes*



*Spray-on plasters applied to coat surfaces (such as ceilings or metal structures or trusses) in order to increase their fire resistance*



*Coatings on pipes for transporting fluids at high temperatures, made up of windings with asbestos-containing fabrics or chalky pastes*

**In 80% of mesotheliomas, exposure to asbestos is identified as the cause of the tumour**, even if only 5% of people exposed to asbestos fibres contract mesothelioma, which leads to the belief that there may also be other contributing causes of the disease. It has been hypothesised that another cause of mesothelioma may be a virus, named SV 40, which can cause mesothelioma in rats, and viral sequences have been identified in mesothelioma samples in humans. It is also possible that the two factors act jointly and that asbestos may favour the carcinogenic action of the virus. It should also be stressed that the pathogenic role of the virus (i.e., whether it is able to actually intervene in the development of mesothelioma and how) has yet to be definitively proven.



*Electron microscope image of the virus SV 40*

Asbestosis (a chronic lung disease resulting from the inhalation of asbestos fibres) is actually a disease that has been known since 1930, even if its correlation with lung tumours dates from 1955, while the first report of a close link between asbestos and mesothelioma came in 1960, when 57 cases of mesothelioma were described in South African workers who worked in asbestos mines. Since then the reports pointing to this close correlation have become ever more frequent and **today pleural mesothelioma is considered an environmental disease.**

As already said, exposure to asbestos occurs by breathing in the fibres dispersed in the air. This can happen for various reasons: perhaps because the person's job involved working with it, or because he or she was living in an area with a high rate of environmental pollution from asbestos. The people most commonly affected (obviously we are talking here about jobs in past years since asbestos was prohibited in 1992) are shipyard workers, workers in the building industry, automotive workers and mechanics (especially those involved in working on brake linings), workers handling insulating materials and piping and installing heating systems, and flooring and roofing workers.

In addition, for persons exposed to asbestos who are also smokers, the risk increases exponentially. Studies have demonstrated that asbestos workers who are also smokers have a probability of dying from mesothelioma that is 55 times higher than non-smokers who were not exposed to asbestos.

Exposure to asbestos undoubtedly remains the primary cause of malignant mesothelioma in the majority of patients.

**There is no minimum exposure level that can be considered safe.**

If a person is aware of having been exposed to asbestos, **his or her doctor should be informed**, especially if symptoms like chest oppression, shortness of breath, chest pain and coughing are present. Even if these symptoms **do not indicate** presence of the disease, they are the most common ones and should be explored if they are present in a person who has been exposed to asbestos.



# 4. Pleural mesothelioma: histology

Malignant mesothelioma is **subdivided into three categories** according to the characteristics of the cells that constitute it: **epithelioid, sarcomatoid and biphasic** mesothelioma. Within each of these types of tumour there are further subtypes, and many mesothelioma patients present different characteristics in the framework of the same tumour.

## **EPITHELIOID MESOTHELIOMA**

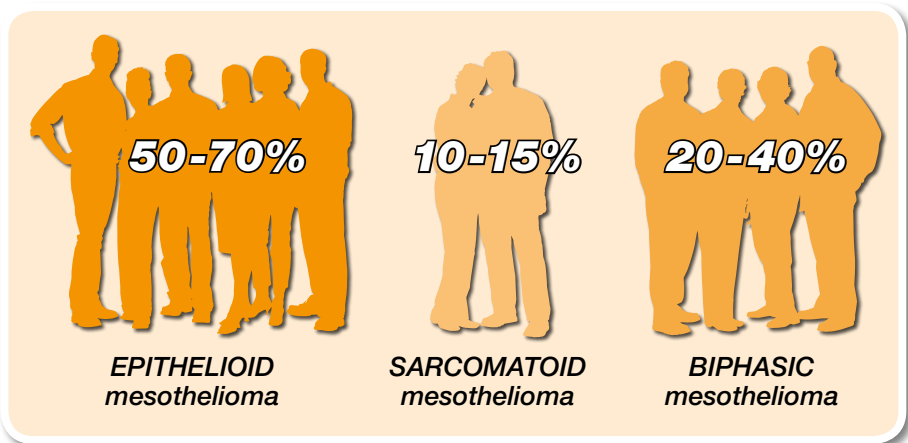
This is the most common type and constitutes approximately 50-70% of all malignant mesotheliomas.

## **SARCOMATOID MESOTHELIOMA**

This is the least common form of mesothelioma (10-15% of cases) but is the one most resistant to treatment.

## **BIPHASIC MESOTHELIOMA**

Some 20-40% of mesotheliomas fall within the biphasic category, which is a combination of the sarcomatoid and epithelioid types.



# 5. Diagnosis

Very often the diagnosis is reached when the disease is already in an advanced stage, both because the clinical symptoms are often underestimated or not recognised and because it is hard to correlate them with an exposure to a harmful substance that occurred so many years earlier. For the diagnosis of mesothelioma, performing only a chest X-ray or other radiological tests is not sufficient as different types of tumour may be present in the thoracic cavity and also as what is visible on a specific radiological image may not necessarily be a tumour. The images may show something SIMILAR to a tumour in nature but do not make it possible to identify the type of tumour. **The indispensable test to diagnose mesothelioma is a tissue biopsy and/or analysis of the pleural fluid.**

## 5.1 Biopsy

Almost all mesothelioma diagnoses are made as a result of a biopsy, that is, **taking a small sample of tissue** from the disease site, which is then sent to the pathologist (a doctor specialised in observing tumour cells under the microscope), who is tasked with making the definitive diagnosis.

It is not always easy to reach a diagnosis right away and often the pathologist must undertake a number of specific investigations (**immunohistochemistry**) that are aimed at differentiating the normal mesothelial cells from the tumoral cells, as well as at distinguishing tumoral cells originating in the pleura (characterised, for example, by positivity to markers like certain cytokeratins, calretinin, vimentin...) or in other organs. The diagnosis is generally achieved by introducing a small instrument into the cavity between the parietal and visceral pleura and using it to pinch off a tiny fragment of pleural tissue that seems to display the characteristics of the disease.

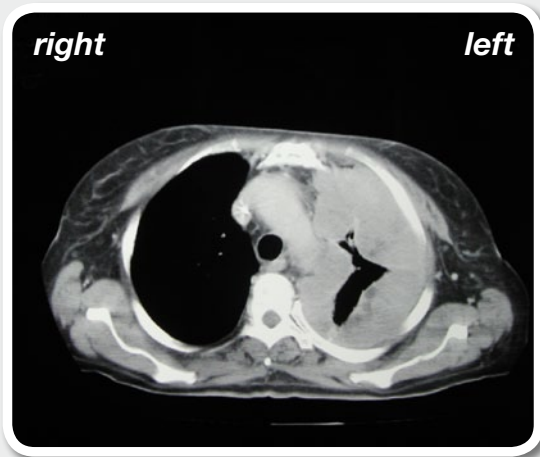




# 6. Staging

The term “staging” refers to the determination of the extent of the disease, that is, what parts of the body are affected and how severely. Chest X-rays and other radiological investigations are necessary to describe the appearance and the extent of the disease, identifying the sites of thickening of the pleura and the possible presence of pleural effusion (fluid).

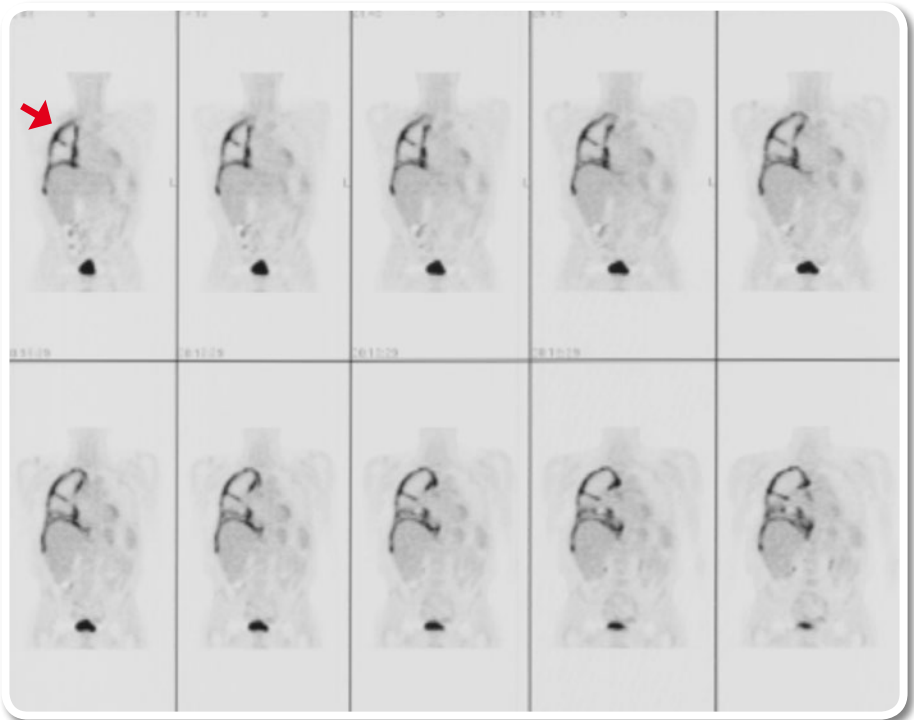
## *CT evaluation of pleural mesothelioma*



*On the right* the lung (in the photo it looks like a black bean) has a thin, well-defined profile, that is, the pleura lining has its normal shape.

*On the left* the lung is reduced to a small central part, while the whole grey part is “thickened” pleura. A biopsy in this site led to a diagnosis of mesothelioma.

More recently, positron-emission tomography (**PET**) has also begun to be used as a diagnostic investigation tool for evaluating the extent of the disease.



*An example of a PET image with right pleural mesothelioma*

The staging most used today for mesothelioma is the staging used by the International Mesothelioma Interest Group (IMIG), which can be summed up as follows:

**Stage I:** *tumour confined to the parietal pleura or parietal and part of the visceral pleura on the same side, without involvement of lymph nodes.*

**Stage II:** *tumour still confined to the parietal and visceral pleura on the same side, but more widespread. There is no involvement of lymph nodes at this stage either.*

**Stage III:** *in this stage the disease extensively affects the parietal and visceral pleura (and can also involve other structures like the pericardium or tissues of the chest wall) and in addition there is involvement of the lymph nodes.*

**Stage IV:** *this stage entails involvement of the contralateral pleura or the presence of pleural fluid containing tumour cells or the involvement of bone structures (ribs or spinal column) or of other organs outside the rib cage.*

The above is a schematisation of the IMIG staging, which actually provides a very detailed description, delineating subtle differences that make it possible to get a precise picture of the disease, which can guide the physician in the choice of the most appropriate therapy. In 2010 a new staging system for mesothelioma was introduced, proposed by the IASLC (International Association for the Study of Lung Cancer), which together with a change in lung tumour classification also proposed a few modifications for mesothelioma.

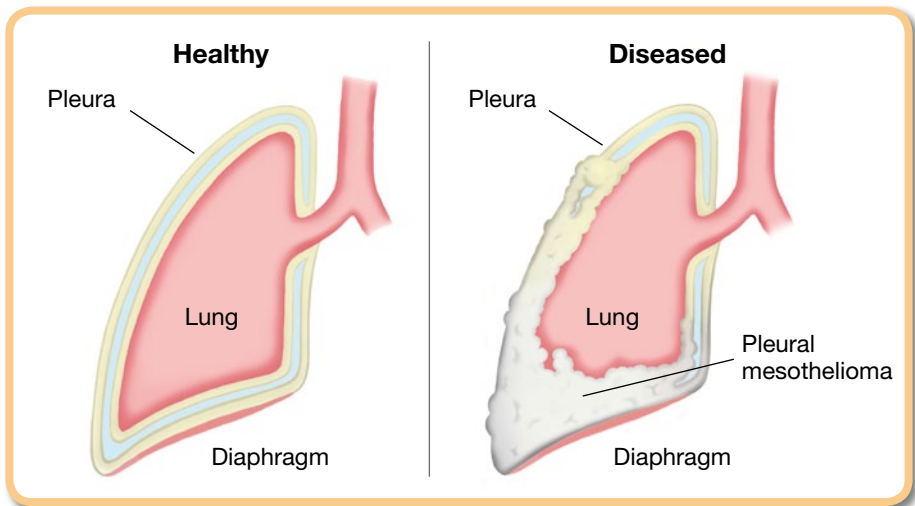


# 7. Symptoms

The symptoms of mesothelioma are not specific to this disease. In other words, there are no “signals” that present themselves only in those who have this form of tumour. The same “signals” can be set off by other illnesses as well.

In general the first symptoms **begin to appear 25-35 years after exposure to asbestos**, and often those who present symptoms don't make the connection with an exposure to a harmful substance that took place several decades before and perhaps even for a limited period of time.

The symptoms of mesothelioma depend on the extent of the disease, on the organs affected and on the presence of pleural fluid.



The most common symptoms are a sensation of “**shortness of breath**” (or dyspnoea), **chest pain** and persistent **cough**, most often a dry cough (non-productive cough). Less frequently, fevers and weight loss can manifest themselves. There are also patients who, although presenting signs of the disease radiologically, are practically symptom-free.

# 8. Treatment

Essentially two types of treatment can be distinguished: the traditional treatment (which is the most tested and which has already demonstrated its effectiveness and is part of common clinical practice) and the new treatments (which involve new therapeutic approaches that are still in the study phase and are possible only in the framework of clinical studies). The traditional treatment includes various possibilities which can be either used individually or in combination, depending on the extent of the disease and the patient's general condition.



The proper course of therapy is in any case decided by the reference oncologist or pulmonologist on the basis of the patient's characteristics (general health conditions, age, concomitant illnesses, respiratory function, prior treatments) and the degree of extent of the disease. This means that different treatments may be proposed to patients with similar characteristics and with diseases that differ only in their extent. In the same way, patients with the same disease by type and extent but with a different state of health may receive different therapies.

Pleural mesothelioma can be treated with surgery, radiotherapy and chemotherapy, possibly in combination with each other.

**Role of surgery:** surgically resectable disease is an indication that is given by a thoracic surgeon on the basis of the extent of the disease, the general condition of the patient and the respiratory function tests. The surgical techniques that can be used are pleurectomy/decortication, which entails removal of the tumour mass and of the pleura affected by disease, or extrapleural pneumonectomy, a more extensive intervention that also involves removal of the lung in addition to other thoracic structures.

Normally, where possible, depending on the spread of the disease and the patient's condition, extrapleural pneumonectomy is used.

It should be pointed out, however, that this intervention is highly incapacitating and carries high rates of mortality and post-surgical complications. In addition, recovery from the disease is not 100% guaranteed to patients undergoing either of the two operations, and the risk of recurrence of the disease remains high even after surgery.

Surgery has other roles in this pathology: thoracoscopy, for example, it can facilitate a correct diagnosis. This involves making a small incision in the thoracic wall for examination purposes and possibly performing biopsies at the site.

Talc pleurodesis is another useful surgical manoeuvre that is often used in mesotheliomas with abundant pleural effusion. This technique consists of draining the fluid and then inserting a substance meant to prevent new formation. This intervention can be done in day surgery or with a short hospitalisation.

**Role of radiotherapy:** in itself radiation therapy is not particularly effective on mesothelioma. It can play a role in certain cases (for example, to manage pain in some patients), however it is mostly used in supplementing other therapeutic approaches.

The extent of the field of treatment, as well as the radiation dosage, are at the discretion of the radiotherapist and in relation to the patient's condition and the results obtained with the surgery (if the patient has been operated on). Even patients who cannot be treated surgically can benefit



from radiation treatment, if they present disturbances linked to involvement of the bones or brain by the disease, for instance. In these cases radiotherapy can help to reduce the reported symptoms. New radiotherapy techniques exist which are not however part of clinical practice but are for the most part still the subject of study.

**Role of chemotherapy:** chemotherapy can be administered in combination with radiotherapy or without it, either before the surgical intervention, with the aim of facilitating it, or after, for the purpose of consolidating its effects.

It is the elective treatment for patients who are inoperable or have extensive disease. In this situation, where possible, it is preferable to use a combination of two drugs, but once again the therapeutic choice is at the discretion of the oncologist, who will take account of the patient's condition, age, kidney and liver function, and associated pathologies. The most commonly used drugs are cisplatin and pemetrexed: these two chemotherapeutics are those that have proven to be the most effective in treating this type of disease over the years. Four or six intravenous administrations of these drugs are generally provided, repeated every three weeks and alternated with periodic radiological reassessments that make it possible to evaluate the response. Pemetrexed requires vitamin and steroid premedication throughout the therapy period. Pemetrexed can also be administered alone or in combination with carboplatin.



In the event that there is no response (i.e., stoppage of the advance of the disease or its regression) to the aforementioned chemotherapeutics, or should the disease progress, there are at the moment no drugs that have demonstrated sufficiently persuasive efficacy to convince the regulatory agencies to register them. This means that there is no **second line** therapeutic standard for mesothelioma, although common experience, together with some literature data, suggests that certain drugs such as vinorelbine or gemcitabine may have a degree of efficacy.

There are currently no biological therapies that have demonstrated effectiveness in systemic treatment of mesothelioma.

Pleural mesothelioma still remains a difficult disease to treat and innovative therapies (like new biologic drugs and chemotherapeutic agents and new radiotherapy methods) are under study. It is therefore important to ask one's oncologist if there are clinical studies in which it is possible to participate at the centre where one is being treated and what advantages and disadvantages are connected with them.



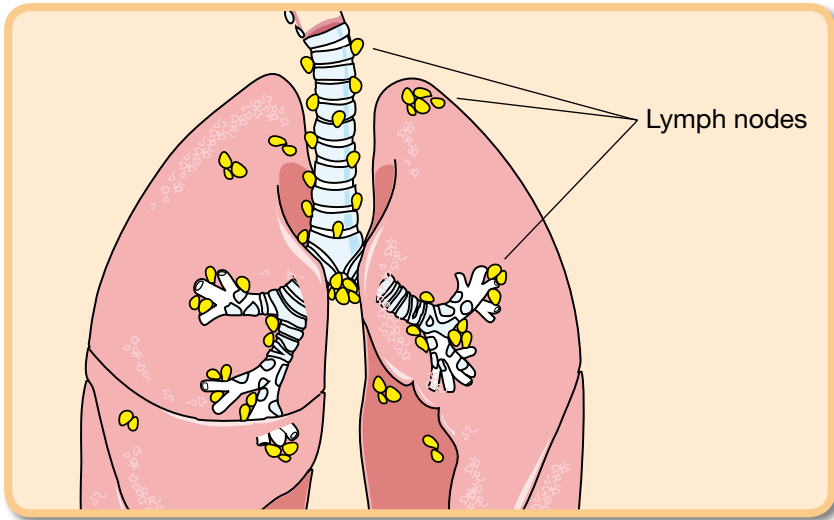


# 9. Glossary

- **Amphiboles:** family of minerals present in eruptive rocks after the cooling of silicate magmas; together with serpentines they make up asbestos.
- **Asbestos fibres:** name of a group of highly fibrous minerals that can be found naturally in the environment.
- **Chrysotile:** a mineral belonging to the class of the silicates. It is one of the minerals of the asbestos group, by far the one most extracted. Much sought after for its fibrous properties, incombustibility and low thermal conductivity, it has grave consequences on the human organism precisely because of its fibrous nature.
- **Immunohistochemistry:** investigation technique that makes it possible to analyse sections of tissue or cells taken from the patient, to identify whether they are tumour cells and to characterise them further in order to plan the treatment.
- **Interstitial fibrosis:** a lung pathology, very often of unknown origin or linked to exposure to fibrosing agents (such as asbestos), characterised by a thickening of the pulmonary interstitium. This causes a reduction of the lung's ability to expand, limits respiratory capacity and causes respiratory insufficiency.
- **Latency period:** this is the period of apparent inactivity that extends between an episode (in this case an exposure) and an event (in this case the appearance of disease).

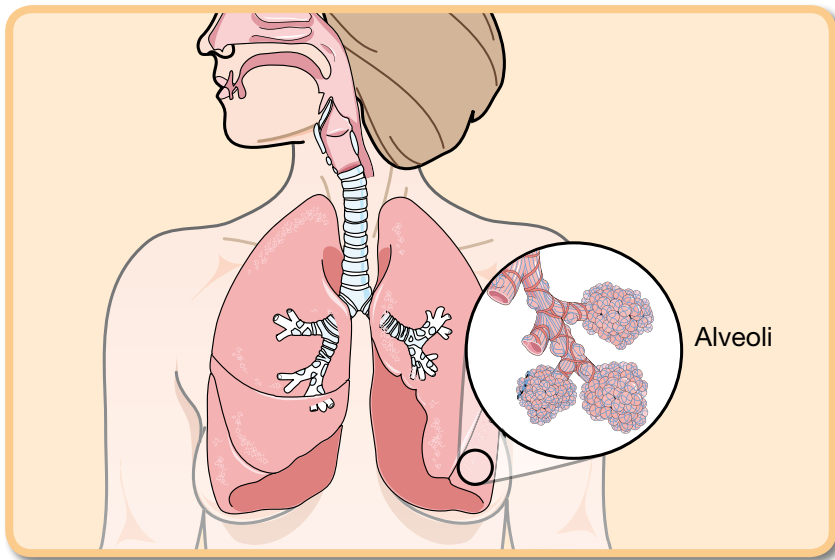


- **Lymph nodes:** small nodules of tissue, made up of immune system cells, that are able to capture and destroy the bacteria carried by the lymph.



- **Pericardium:** thin serous membrane that encloses the heart and the first portion of the large blood vessels.
- **Peritoneum:** serous membrane comprised of two distinct layers: the “parietal layer”, which lines the wall of the abdominal cavity, and the “visceral layer”, which encloses the organs of the abdomen and the pelvis, facilitating their movement without any friction occurring between them. The peritoneum is the most extensive serous membrane of the human body.

- **PET:** abbreviation that stands for positron-emission tomography. This is a diagnostic examination in which the images are obtained after intravenous administration of radiopharmaceuticals (like FDG, fluoro-deoxyglucose) that emit positrons (electrical particles with a positive charge). The principal difference with respect to CT scanning and magnetic resonance imaging is that it provides functional images, that is, images that reflect the metabolic activity present in a certain area of the body (“how active the disease is”).
- **Pulmonary alveoli:** these constitute the extreme ramification of the bronchial tree and the site where all the gas exchanges between inhaled air and the blood take place.



- **Second line:** second-line therapy is the treatment that is administered in a patient who has already received a previous treatment for that disease, if there are signs of resumption and/or of non-response to the first line.



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