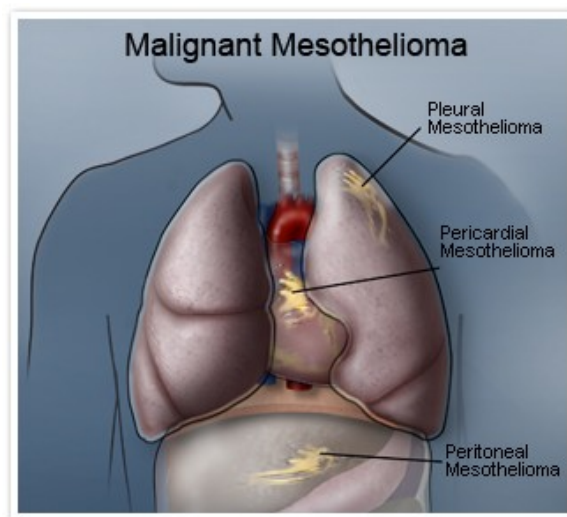


Mesothelioma: From Discovery to Treatment
By Debra Gordon, MS



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Metastatic mesothelioma is very aggressive cancer that affects cells in the **pleura**, a membrane that enfolds your lungs and prevents them from sticking to other tissues during breathing. The disease can also affect the abdominal lining, the **peritoneum**, and often spreads into the abdominal area.

Mesothelioma is a disease that barely existed 100 years ago. In fact, it wasn't formally identified until the 1930s. Today, however, the incidence of the disease, although still rare, is increasing in many countries.[1](#), [2](#)

Unlike most cancers, we know exactly what causes most cases of metastatic mesothelioma: exposure to **asbestos**, naturally occurring fiber-like minerals that have unique fire- and heat-resistant properties. The mineral has been known since ancient times, but only became common in the industrial world beginning around the 1890s.

Its remarkable properties (resulting in the moniker "magic mineral") led to extensive use of asbestos in soundproofing, fire protection, and insulation. For decades, asbestos-containing materials were incorporated into roofing shingles, ceiling and floor tiles, paper and cement products, automobile parts, heat-resistant fabrics, packaging, gaskets, and coatings. Navy and Merchant Marine ships were loaded with the mineral after World War II to prevent fires at sea,

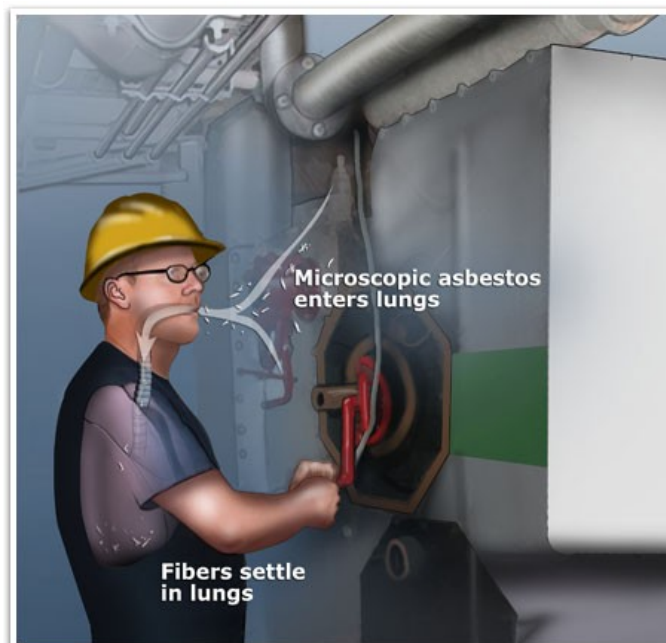
which is why so many men who built those ships or served on them have developed asbestos-related lung diseases, including mesothelioma. But the industrial world wasn't the only place for asbestos. Many asbestos-containing products were installed in homes, schools, and other buildings built before the 1980s; the "indestructible material" was even used in oven hot pad gloves![1](#)

History of Malignant Mesothelioma

In the late 1950s/early 1960s, pathologists in South Africa began noticing strange lesions and lung tumors in people who worked in the asbestos mining industry there. Although public health experts throughout the world had earlier identified an increased risk of lung cancer in people who worked in industries in which asbestos was used, without autopsies or modern diagnostic tools, these people were never officially diagnosed with mesothelioma.

The true nature of the risk didn't really become apparent until the 1960s, when a series of case studies (in which cancer rates of people who worked in asbestos-related industries were compared to those who worked in other fields) demonstrated a clear correlation between asbestos exposure and lung diseases. Over the next 20 years, hundreds of studies in animals and humans confirmed the link between the disease and the mineral.

In 1972, the Occupational Health and Safety Administration (OSHA) began regulating the use of asbestos in the workplace; but it wasn't until July 12, 1989 that the Environmental Protection Agency (EPA) issued its final rule banning most asbestos-containing products, a regulation that was overturned in Federal court two years later. Thus, although many asbestos-containing materials are banned, including certain papers and flooring felt, and although products that never contained asbestos cannot now be manufactured with asbestos, the mineral can still be used in some cases.



Although the mineral is rarely used in most industrialized countries today, it continues to be extensively used in developing countries. In addition, because it can take up to 50 years between exposure to asbestos and development of the metastatic mesothelioma, people exposed decades ago are just now being diagnosed.[6](#)

For instance, in the United Kingdom today, more people die from mesothelioma than from

malignant melanoma, or uterine or cervical cancers.⁶ The UK, Belgium, and Australia have the highest reported incidence rates in the world.⁷ In the US, the incidence has nearly doubled between 1970 and 1999: from less than one per 100,000 people to nearly two per 100,000.¹ In Japan, where asbestos was extensively used until 2000, a significant number of mesothelioma cases and deaths are expected in the coming decades.⁷

Who Develops Mesothelioma?³

About 80% of those diagnosed with mesothelioma are men older than 50, primarily because they were more likely to work in industries that used asbestos, such as shipping and plumbing.⁴ However, there is also evidence that it develops in women who were exposed by their husbands or fathers, and people who live in areas with high levels of natural asbestos also have a higher risk of developing the disease. There is some thought that radiation therapy for other cancers, particularly breast cancer, Hodgkin's lymphoma, cervical cancer, or Wilm's tumor, could contribute to the risk of developing mesothelioma, but the evidence remains unclear.⁵

However, because only a very small number of people exposed to asbestos develop the cancer, it's obvious that something else is going on. Indeed, researchers suspect that certain genetic differences may predispose some individuals to developing the disease when exposed to the mineral. Other studies suggest that diets high in antioxidants (fruits and vegetables, in particular) may protect exposed people from mesothelioma. There is even some thought that viruses, particularly [simian virus 40](#), might trigger the development of mesothelioma when coupled with asbestos exposure.⁷

Symptoms

The most common symptoms of pleural malignant mesothelioma are shortness of breath and chest pain (which is why the disease is often misdiagnosed as heart disease), both of which get worse as the disease progresses.⁶

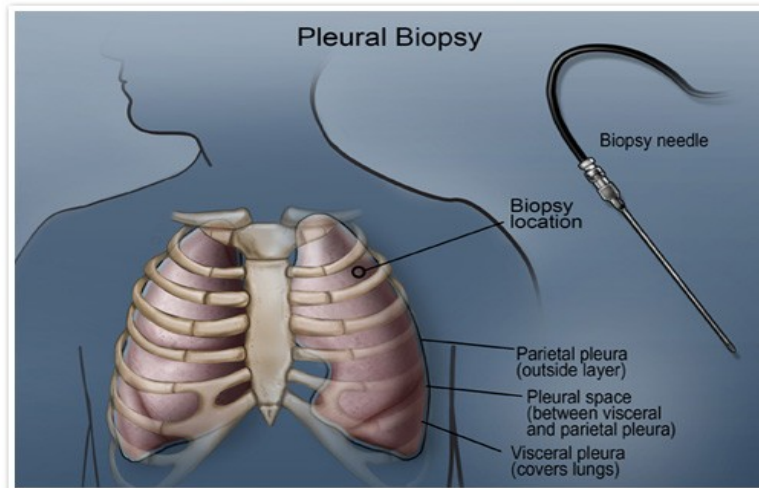
A chest x-ray rarely, but sometimes, shows fluid build up between the lungs and the pleura, but most patients are diagnosed after more extensive imaging with CT, MRI or PET scan.

Other symptoms include:

- Pain
- Cough
- Loss of appetite
- Fatigue
- Sleep problems
- Sweating

In most cases, the disease begins in one lung, typically the lower lobe of the right lung.

Diagnosis



Malignant mesothelioma is very difficult to diagnose. Thus, you may see several doctors and undergo numerous tests before you are conclusively diagnosed and begin treatment.

When your doctor examines you, he/she may:

- Feel a mass on your chest wall
- Hear a dull sound when tapping (**percussing**) your chest, an indication of fluid buildup
- Observe bone curvature on the right side of the tumor

Conditions that you might think are unrelated to cancer may also be evidence, including:

- Blood clotting abnormalities
- Anemia
- Low blood sugar
- High blood levels of calcium

There is also no single “best” way to diagnosis the disease, and several tests may be used, including:

PET-CT: Positron emission tomography, or a PET scan, involves injecting small amounts of radioactive material called radiopharmaceuticals or radiotracers into your vein. It takes about an hour for the material to collect in the lungs. The PET scan picks up the energy released from dye and creates pictures showing the structure and function of the lungs and surrounding tissue. Meanwhile, a CT scan conducted at the same time provides a crisp, 3-dimensional image. The amount of radiation used is low, and unless you are allergic to the dye, there should be no complications.

One often-cited study found a 93 percent overall accuracy in diagnosing mesothelioma with the PET-CT. [8](#) In addition to diagnosis, PET-CT is also being used to stage the disease, described below.

FDG-PET: This is a form of PET scan that uses a dye containing glucose (fluorine-18-2-fluoro-2-deoxy-D-glucose). This dye collects in greater amounts in cancer cells than normal cells. It is used both for diagnosis and to see how your tumor responds to treatment.

MRI (magnetic resonance imaging): An MRI uses magnetic energy, not radiation, to provide

images of tissues and organs. Although people used to have to lie very still in an enclosed space during an MRI, today many hospitals offer “open” MRIs that are less claustrophobic. Magnetic resonance is typically used to see if the tumor can be surgically removed; it can also help determine the tumor subtype, described below.

Chest CT: A computed tomography scan is really just a fancy x-ray. It uses much more radiation than a typical x-ray, however, although it provides far better images, including three-dimensional views that can assist in diagnosis. A chest CT is used to see if the tumor has spread to the chest wall, ribs, and other tissues.

A recent review of several studies on the diagnosis of mesothelioma found that PET-CT works better than any other imaging option to correctly diagnosed the disease. However, surgical biopsy is still considered the gold standard for a definitive diagnosis and to stage the disease.⁹

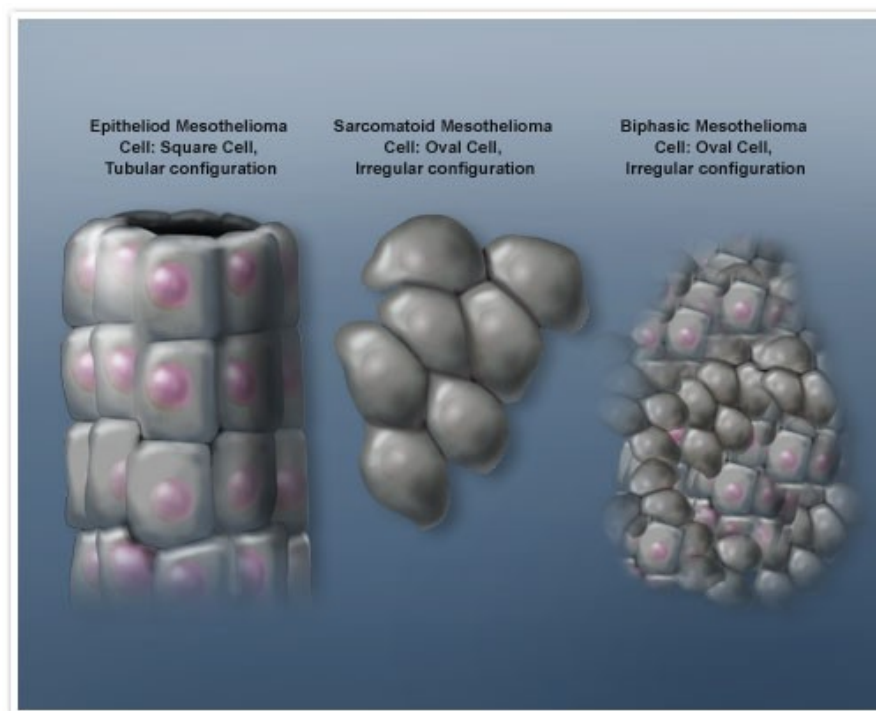
Other Tests

Other tests that are increasingly being used to diagnose mesothelioma include:

Mediastinoscopy, a surgical procedure to examine the space between and in front of the lungs called the mediastinum. The surgeon makes a small cut in your neck just above your breastbone, then inserts a thin scope called a mediastinoscope through the opening to visualize the area. The scope can also be used to take a tissue sample. It is used to see if the cancer has spread to the mediastinal lymph nodes. You are anesthetized during the procedure, and should only have some mild discomfort in your neck afterwards.

Pulmonary function tests. With these tests, you blow into a machine to measure how well your lungs work. They are typically performed to see if the tumor is preventing the lung from inflating properly.

Types of Mesothelioma



The surgeon sends a tissue sample from the biopsy to a pathologist to identify the subtype of

mesothelioma. This helps stage the disease and determine treatment. It will also become more important as cancer treatments become increasingly personalized based on the genetic and molecular characteristics of tumors.

There are three main subtypes:

- **Epithelioid**. This is the most common form, occurring in about 60 percent of all mesothelioma tumors. Subtypes within this category are:
 - Tubulopapillary
 - Acinar (glandular)
 - Adenotoid
 - Solid epithelial
- **Sarcomatoid**. A subtype is desmoplastic mesothelioma.
- **Biphasic (mixed)**. These tumors have epithelioid and sarcomatoid features.

In addition to identifying the type of mesothelioma, researchers are trying to find other markers that might help determine which drugs to use. These include measuring blood levels of hyaluronic acid, mesothelin, osteopontin, and vascular endothelial growth factor (VEGF), as well as levels of hyaluronidase in the lung cavity.

Staging the Disease

Tumors are “staged” as a means of identifying how far they have progressed so you and your doctor can identify the best treatment for your tumor. As with many cancers, doctors use the T (tumor), N (node), M (metastasis) staging system for malignant pleural and abdominal mesothelioma.

Each letter is followed by a number, determining how far that particular component of the tumor has progressed. For instance, a T3 pleural mesothelioma means that the tumor has spread in the chest cavity but might still benefit from surgery. An N0 stage means that there is no evidence of spread into the regional lymph nodes, while M1 means the cancer has spread far from the lungs, or **metastasized**.

The three components are then considered together to stage the disease: I-IV. Stages I-III describe tumors that could still be surgically removed (at least partly); stage IV means the cancer has spread to distant parts of the body and surgery is not an option (unless it's used to help you breathe better).

Prognosis

The reality is that there is no cure for mesothelioma. Even people diagnosed in the early stages of the disease have a median survival (meaning half of people live longer and half live less) of about a year to 18 months. However, the growing incidence of the disease, coupled with an explosion of new therapies for other cancers, is, for the first time, offering at least the potential of hope for people with metastatic mesothelioma.

While the stage at which your cancer is diagnosed is most important for determining your prognosis, certain clinical signs that can also provide prognostic information.

Contributors to Good Prognosis

- Epithelial form of the disease
- Stage I disease
- Age under 65 years
- Good performance status, a classification that refers to how well you are able to manage daily activities
- Lack of chest pain
- Symptoms for more than six months prior to diagnosis

Contributors to Poor Prognosis

- Increased number of blood platelets (thrombocytosis), white blood cells (leukocytosis), or anemia
- Fever unrelated to a specific infection
- Sarcomatous or mixed cancer type
- Age older than 65 years
- Poor performance status
- Male

Disease Progression

Most mesotheliomas start in the chest and gradually fill the chest cavity, often metastasizing, or spreading, to the other lung, spinal vertebrae, and abdominal cavity. This is why it becomes so hard to breathe.

In the abdomen, mesothelioma results in a significant accumulation of fluid, called **ascites**. The tumors also spread to the surfaces of major organs and the peritoneal wall, the membrane that surrounds the abdominal organs.

Finding the Right Doctor

Because mesothelioma is so rare, few doctors have much experience treating it. That's why it is so important to find a physician who specializes in the disease. You can usually find such doctors at large cancer centers.

Living with Mesothelioma

Mesothelioma has a tremendous impact on nearly every aspect of life. Interviews with people who have the disease and their family members find that people often feel that the disease results in:⁶

- A loss of identity
- Loss of ability to live a normal life

- Frustration and anger at the physical limitations
- Caregivers feeling helpless and unsupported
- Significant impact on their relationship with their partner

People often feel that they did something to cause the disease, leading to feelings of guilt, anger, and remorse. However, few people were ever aware of the risks of exposure to asbestos—one study found that just two out of seven people exposed to asbestos ever received any reliable information about the cancer risk—and most didn't even know that they were exposed to asbestos when the exposure occurred.⁶ In other words, *this is not your fault*.

Nonetheless, the disease will likely affect you emotionally nearly as bad—or even worse—as it does physically. In fact, at least one study found that people with mesothelioma experience more psychological distress than people with lung cancer.¹⁰

Overall, researchers find that people with the disease report high rates of:

- Anxiety
- Depression
- Fear

Many patients also say they feel socially isolated, as people they used to interact disappear or change how they behave towards them.¹¹

“I can't do the job I did, the job I loved, so that is different. I'm different, so life is totally different. That's why I get so frustrated . . . I feel guilty about (how it affects my family), but it's not my fault, but I still feel responsible for it and how it affects them . . . They should get on with their lives and I'll get on with mine, because there's no telling how long it will be.”

--- Patient explaining to researcher the effect of the disease¹¹

As the disease progresses, you may feel angry at its affect on your life, your deteriorating physical ability, changes in your body, and fear of the future. You may also feel a sense of hopelessness, which is understandable given the seriousness of the diagnosis.⁶ If possible, try to focus on the present, the moment you are in, rather than trying to look into the future. Finding a support group of other cancer patients can also help, since people who are undergoing similar experiences may be better able to understand what you're going through.

You might also consider asking your doctor for a referral to a mental health professional, particularly if you find that your fear, anxiety and depression are affecting your quality of life.

Caring for Someone with Mesothelioma

Caring for someone with mesothelioma can take a tremendous toll. Most caregivers report that they are angry about the diagnosis and, sometimes, at their loved one. Other studies find that eight out of 10 caregivers report anxiety, depression, and feelings of isolation, with more than half saying they felt fear. And while 71 percent of patients in one study said they felt peace or acceptance towards their diagnosis, just 23 percent of caregivers did.⁶

You may also experience a loss of intimacy, which isn't unusual when one partner has cancer.¹¹

The message here is that you should not go it alone. Counseling and support groups can go a long way towards helping you cope with your own issues around your loved one's diagnosis.

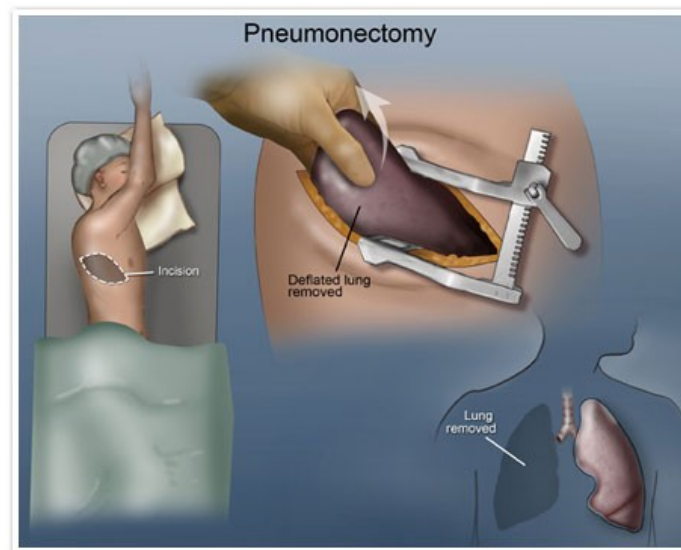
Treatment

Unlike many cancers, there is no single primary protocol for treating mesothelioma. That's due, in part, to its relative rarity. With only about 3,000 patients a year diagnosed in the US, it's very difficult to run the kind of large-scale research studies needed to determine which therapies work best at various disease stages.

There is also no cure. Thus, a major goal of treatment is to reduce pain and suffering and prolong your life as long as possible while providing you with the highest quality of life possible.

The most important consideration in treating mesothelioma is the cancer stage and type. Treatment decisions also depend on whether the cancer is localized to the chest or has spread to the chest wall, diaphragm, or lymph nodes, your age and overall health, and the center where you're being treated.

As with most solid tumors, doctors turn to surgery, radiation and chemotherapy to manage mesothelioma.



Surgery¹²

Only about one in five patients with metastatic pleural mesothelioma undergo surgery, although studies find that most people who survive longest have had surgery. That's likely because the earlier the disease is diagnosed, the more likely you are to be eligible for surgery and the better your prognosis to begin with.

If your doctor does recommend surgery, ask which type. There are two types of surgery:

- **Pleurectomy/decortication.** In this procedure, the surgeon tries to remove as much of the tumor from around the lung as possible. It has traditionally had a higher failure rate than pneumonectomy (described below), with the tumor recurring in the chest cavity 50 to 80 percent of the time. However, that rate may change with improved radiotherapy techniques, which is typically performed following the procedure.
- **Radical extrapleural pneumonectomy.** This procedure involves removing the entire

affected lung, followed by radiation to destroy any remaining tumor cells. Studies find it prevents tumor recurrence in the chest in 80 to 85 percent of patients who have the surgery. However, it is a long, intensive operation with a 55 percent complication rate and a 3 percent risk of death, higher in some institutions. Thus, it is typically only performed in patients whose cancer has not spread throughout the chest. It is also typically performed in younger patients who have the epithelial form of the disease, no obvious lymph gland involvement, and are otherwise healthy enough to withstand the rigor of the procedure.

Because your doctor won't know how far the disease has progressed until you are in surgery, he/she may not make the decision about which procedure to perform until seeing the condition of your lung and chest cavity.

While the risk of recurrence is lower with pneumonectomy, studies find no difference in survival rates between the two surgeries. One major reason is that the cancer has often spread to other parts of the body by the time it's diagnosed.

Chemotherapy¹³

Chemotherapy, also known as systemic therapy, uses oral or infusion-based medications to kill cancer cells throughout your body. Chemotherapy is used both before (neoadjuvant) and after (adjuvant) surgery, as well as in people who don't qualify for surgery. It is also used in the palliative setting to reduce pain and improve quality of life.

The most commonly used **chemotherapy drugs for mesothelioma** are:

- Cisplatin
- Pemetrexed (Alimta®)
- Raltitrexed (Tomudex)
- Oxaliplatin (Eloxatin)
- Irinotecan (Camptosar)
- Mitomycin
- Gemcitabine
- Carboplatin

These drugs are used in various combinations for first- and second-line treatment. The traditional combination is cisplatin with pemetrexed, gemcitabine, or vinorelbine. If you can't manage combination therapy, your doctor may start you on just one drug.

Unfortunately, unlike most other cancers, mesothelioma appears to be unusually resistant to traditional chemotherapy, even newer targeted biologic agents.¹⁴

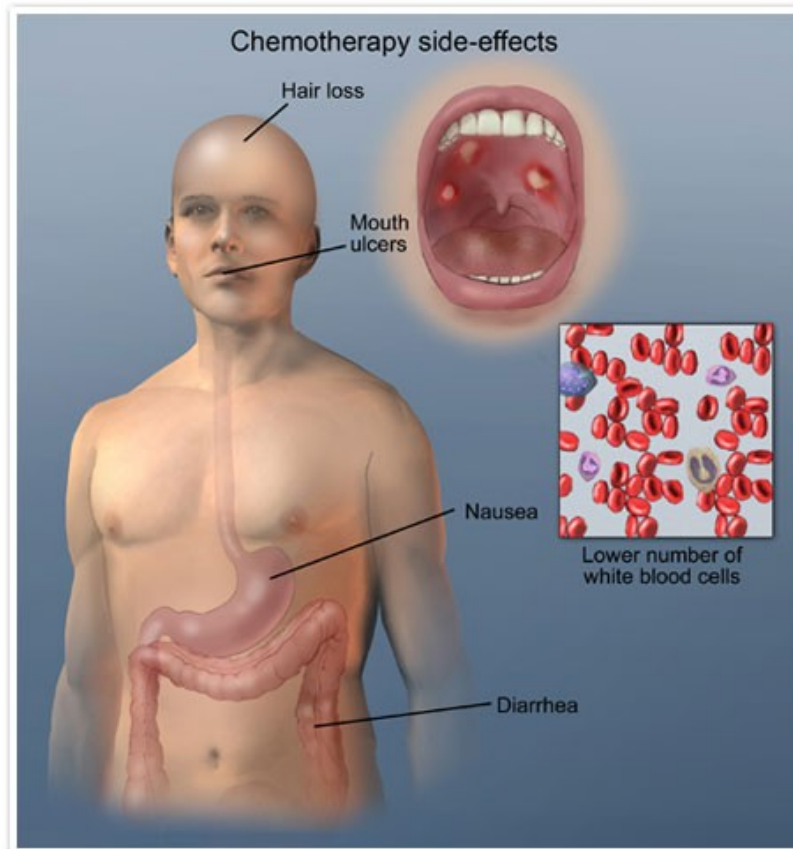
Cisplatin and Pemetrexed

The newest chemotherapy combination is cisplatin and pemetrexed. A study comparing the combination to cisplatin alone found that patients who weren't eligible for surgery who received the combination survived a median 12 months versus nine months for those who received cisplatin alone. These patients were not eligible for surgery. Adding oral folate and B-12 injections not only reduced the combination's side effects, but improved how it worked.¹⁵ A similar study comparing cisplatin alone to a combination of cisplatin and carboplatin found similar results.

One way to try and overcome that resistance is by infusing the medication directly into your

chest cavity, a procedure called pleural chemotherapy. If the cancer has spread to the abdomen, infused chemotherapy is called intraperitoneal chemotherapy.

Some centers are beginning to provide intraperitoneal or pleural chemotherapy before surgery, followed by chemotherapy shortly after surgery.



Radiotherapy

Radiation is an important part of mesothelioma treatment. The problem is that because the cancer is near the heart and lungs, it's challenging to provide the kind of high-dose, intensive therapy needed to shrink the tumor. However, a newer option, intensity-modulated radiotherapy (IMRT), which can more accurately target cancer cells and avoid healthy tissue, may provide better results when performed by experienced clinicians.

Radiotherapy is also used in the palliative setting to improve breathing and reduce pain.

Palliative Care¹⁶

At some point, the management of your disease will shift from trying to cure the disease to trying to keep you as comfortable as possible for as long as possible. This is the palliative care stage, when many people enter a [hospice](#) program.

This doesn't mean treatment stops; radiation, for instance, may continue to shrink the tumor so you can breathe easier. Medication to help with pain, breathing, and other symptoms is a mainstay. So is emotional and spiritual support for you and your family.

Investigational Therapies

There are more than 50 studies on new therapies for mesothelioma in the US that are looking for volunteers. These include:

- **Immunotherapy.** This approach harnesses the power of the immune system to fight the disease. A very small study presented at the American Society of Clinical Oncology (ASCO) in May 2011 suggested that giving patients an immunotoxin called SS1P together with pemetrexed and cisplatin resulted in greater tumor shrinkage than might be expected.¹⁷ The drug is an antibody attached to a toxic substance that hones in on a protein expressed on tumor cells called mesothelin. Thus, unlike standard chemotherapy, which tends to target all fast-growing cells, this therapy would kill only cancer cells, theoretically resulting in fewer side effects.
- **Phototherapy.** This approach involves injecting you with a drug that bonds to cancer cells and is activated by high-intensity light. A big advantage is that it can be administered during lung-sparing pleurectomy. Although it is approved for several other cancer types, it is still considered experimental for mesothelioma.¹⁴
- **Unique drug delivery systems.** These include using nanotechnology to deliver drug molecules directly into the nucleus of the cancer cell.¹⁴
- **Genetic therapies.** This approach identifies unique genetic markers within the tumor itself and target therapies to those genetic mutations or differences. For instance, a recent study suggested that patients with a *BRCA1* mutation (the same gene implicated in some breast cancers) might respond better to the chemotherapy agent vinorelbine.¹⁸ In addition, researchers are investigating the use of bevacizumab (Avastin) for mesothelioma. Avastin blocks vascular endothelial growth factor (VEGF), a protein required to make blood vessels. Studies find that mesothelioma cells express high amounts of VEGF.¹⁹
- **Novel radiotherapy techniques.** This includes approaches like TomoTherapy, in which the radiation is delivered to individual “slices” of the tumor rather than to the entire tumor, to treat the disease.

You can find a clinical trial to participate in [here](#).

Alternative Therapies

Complementary and alternative medicine (CAM) includes such therapies as massage, acupuncture, and meditation. They can be a powerful part of your overall management plan, helping you better manage the stress and anxiety of the disease and conventional treatments.

Conclusion

With new agents being explored for the disease, new biomarkers identified, and new combinations of existing therapies being tried there is hope that the median survival rate in mesothelioma patients will increase in the future. Today, however, it continues to be a very serious disease with poor prognosis and low survival rates. Early detection, working with top mesothelioma treatment providers and finding the right emotional support to help maintain a positive mindset can contribute to greater longevity and improved quality of life.

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