CURE PRESENTS

understanding mesothelioma

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Published by
CURE Media Group
3102 Oak Lawn, Suite 610
Dallas, Texas 75219
www.curetoday.com

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Library of Congress Control Number: 2009906317

ISBN 978-0-980130829

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Printed in the United States of America

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curemediagroup

Dallas, Texas

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[introduction]

SINCE mesothelioma is a rare cancer, occurring in approximately one in 150,000 people in the United States, diagnosis and treatment can be a great challenge to patients and their families. Understanding this disease is important in making decisions about your care and treatment. With the availability of many sources of mesothelioma information, patients and family members may have difficulty deciding what is credible and what is not. Created by the staff of nationally recognized, award-winning *CURE* magazine, we hope this guide will provide you with the information you need to understand mesothelioma and the journey ahead.

What Is Mesothelioma?

Mesothelioma is a medical condition in which a tumor forms in the mesothelium, a protective membrane covering internal organs. The mesothelium is made up of two layers of cells—one surrounding the organ itself and the other forming an outer sac. Between the layers is a lubricating fluid that lessens friction between the membranes and permits the organs to glide smoothly against each other. This is particularly important to the heart and lungs, because they produce significant movement as they function.

Mesothelioma can be either malignant (cancerous)

or benign (non-cancerous). Solitary fibrous tumors or benign mesothelioma are uncommon, accounting for only 10 percent of all cases. Because solitary fibrous tumors are contained in one location in the body, it is generally easy to treat with surgery, and the expected outcome for patients is excellent. However, this is not the case with malignant mesothelioma—this disease is extremely aggressive, and patients with malignant mesothelioma are expected to live, on average, approximately one year after diagnosis.

Mesothelioma is defined by the site of the primary tumor. Pleural mesothelioma, in which cancer cells are found surrounding the lungs and/or lining the chest wall, is the most common type, accounting for about 85 percent of malignant mesotheliomas. Most of the remaining cases are peritoneal or in tissues that cover the abdominal organs. Pericardial (tissues surrounding the heart) and testicular (tissues surrounding the testicles) mesothelioma are both exceedingly rare—comprising about 1 percent of cases.

Pleural mesothelioma differs from lung cancer. The most significant difference is the locations of the cancers—whereas mesothelioma is present in the surrounding lining (pleura) of the lungs, most other lung cancers are found in the interior linings of the airways. Thus, while smoking causes lung cancer, it does not increase the risk of mesothelioma. On the other hand, mesothelioma has a close linkage to asbestos exposure; approximately 70 percent of pleural mesothelioma patients have had some exposure to this mineral.

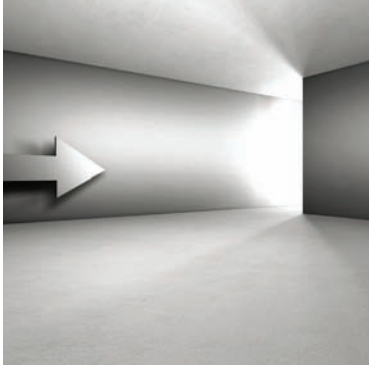
All of the mesothelioma subtypes (pleural, peritoneal, pericardial, and testicular) combined equal only 1 percent of the total thoracic cancers in the United States. Most mesothelioma patients are men age 60 and older, although women, children, and younger adults can contract the disease. This demographic imbalance toward older men is due to male-dominated occupations, such as mining, construction, and shipbuilding, related to asbestos exposure. Also, because mesothelioma can take decades to develop, most patients will be older at diagnosis.

The geographic distribution of this disease is not uniform across the United States, with the highest death rates appearing in the Northeastern states, along the Pacific Coast, and in Illinois, Florida, Wyoming, and Colorado. As with the demographic imbalance, the geographic distribution can also be explained by asbestos exposure—the regions with the highest death rates are (or were) home to either factories that manufactured asbestos-containing products or shipbuilding facilities (asbestos materials were commonly used as insulation in ships).


chapter 1
causes

causes of mesothelioma

WHILE asbestos is far and away the most common cause of mesothelioma, there are theories of other causes of the disease, such as viruses, radiation exposure, and genetic predisposition. Asbestos also causes other thoracic diseases, some with symptoms similar to mesothelioma.



Asbestos ›

Asbestos exposure is the most common cause of mesothelioma. Six minerals, all of which are present in nature as bundles of fibrous crystals, comprise asbestos. The favorable properties of these crystals—heat and chemical resistance, strength, flexibility, and low electrical conductivity—make them useful in numerous residential and commercial applications, such as roofing materials, ship insulation, pipe insulation, and acoustic ceiling tiles. These are just some of the 3,000 estimated products manufactured during the peak of asbestos usage in the late 1960s and early 1970s.

Three types of asbestos are commonly used in the United States. Chrysotile, or white asbestos, is the most widely used because its fibers are curled, a property that makes it less likely to fragment than the other asbestos types. This is an important fact because if asbestos is easily crushed, it remains airborne longer, which increases the likelihood of inhaling the fibers that cause mesothelioma.

The other two types, crocidolite (blue asbestos) and amosite (brown asbestos), are typically used in limited, specialized applications due to their needle-like structure, which makes them highly susceptible to fragmenting.

Asbestos-Related Mesothelioma

Asbestos is catergorized as a carcinogen (a substance that causes cancer) by the U.S. Department of Health and Human Services, the U.S. Environmental Protection Agency, and the International Agency for Research on Cancer. Studies have shown that asbestos exposure may increase the risk of mesothelioma and lung cancer. Although asbestos-related mesothelioma is most often attributed to occupational asbestos exposure, this is not always the case; there are also cases of asbestos-induced mesothelioma in women who laundered the work clothes of their husbands who were exposed to asbestos and cases of other environmental exposures.

Generally, it takes 20 to 40 years or more for mesothelioma to develop following asbestos exposure. The association between asbestos exposure and both pleural and peritoneal mesotheliomas has been well established. Since pericardial and testicular mesotheliomas are rare, their linkage to asbestos exposure is unclear.

How Asbestos Causes Mesothelioma

The exact means by which asbestos causes cancer has not yet been fully determined, but it is known when

asbestos is inhaled, about two-thirds of the fibers are eliminated from the body by coughing or swallowing. The remaining fibers travel through the airways, and some may reach the alveoli, the tiny air sacs in the lungs. Although the method by which asbestos fibers arrive at the mesothelium is not certain, it is likely that this journey takes years, a belief that fits with the extended period of time necessary to develop mesothelioma.

One theory is that the shape of the fibers affects the ability to cause mesothelioma. This theory proposes that longer fibers are too big to be eliminated through the actions of certain immune system cells called macrophages. Mesothelial cells may take in asbestos fibers, and the presence of fibers inside the cells can interfere with chromosomal division that takes place as cells reproduce. This interference may be the cause of the chromosomal abnormalities that are frequently documented in mesothelioma cells. Asbestos fibers can also initiate numerous cellular events, including the generation of free radicals, the initiation of inflammation, and other signals of cellular distress. Taken together, these processes likely induce a number of genetic changes, which ultimately lead to the development of mesothelioma.

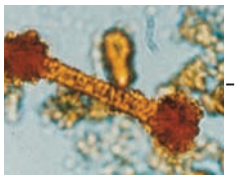
Asbestos Safety

It has never been established if there are any "safe" levels of asbestos exposure. Currently, the acceptable level of asbestos exposure requiring no protective gear has been set by the Occupational Safety and Health Administration at 0.1 fiber per cubic centimeter of air per eight-hour day. This standard covers only those

Mesothelioma: Cause & Effect

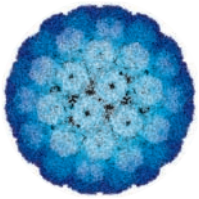
CAUSES

A

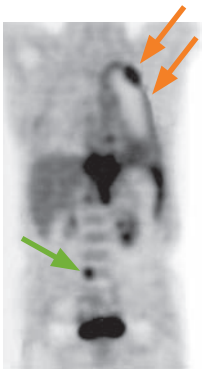


While **asbestos** (A) has been proven to cause more than 80 percent of mesothelioma cases, a **DNA virus known as SV40** (B) has also been implicated.

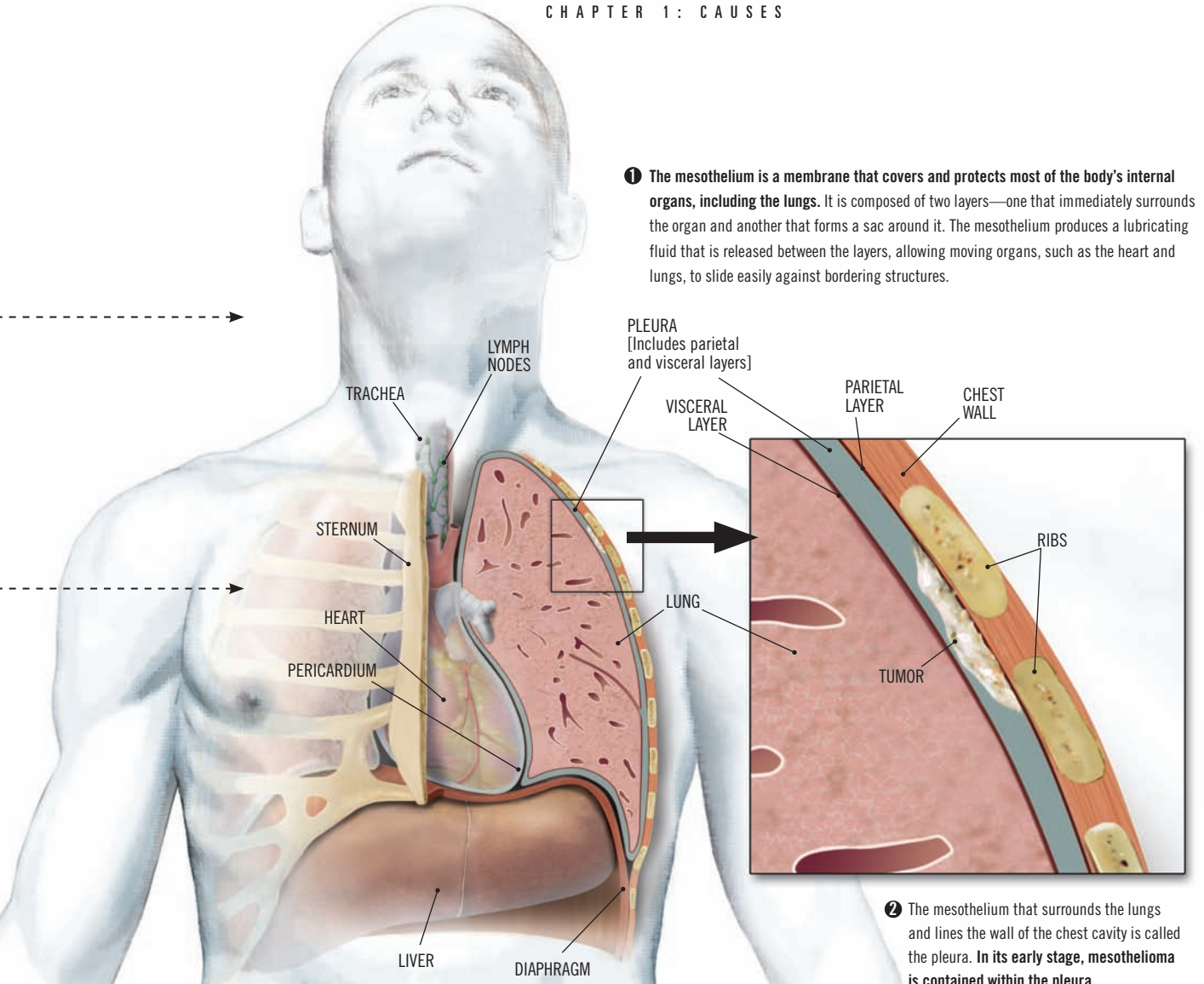
B



DIAGNOSTIC



Positron emission tomography (PET) scan of a patient with stage 4 mesothelioma showing disease in the superior part of the lung (orange arrows) and a metastatic lesion in the abdomen (green arrow).



❶ **The mesothelium is a membrane that covers and protects most of the body's internal organs, including the lungs.** It is composed of two layers—one that immediately surrounds the organ and another that forms a sac around it. The mesothelium produces a lubricating fluid that is released between the layers, allowing moving organs, such as the heart and lungs, to slide easily against bordering structures.

❷ The mesothelium that surrounds the lungs and lines the wall of the chest cavity is called the pleura. **In its early stage, mesothelioma is contained within the pleura.**

❸ **As the cancer becomes more advanced, it can spread** from the chest lining into the outer lining of the lung, into the diaphragm, or into the lung and other areas.

ILLUSTRATION BY **PAM CURRY**

chapter 2

diagnosis

diagnosis

DIAGNOSING mesothelioma can be a complicated process. Symptoms are vague, and many tests may be needed to reach a proper diagnosis. Once a final diagnosis is made, the stage of the disease will be determined, and a course of treatment can be decided.

Symptoms ›

Symptoms of mesothelioma do not typically arise until the disease has reached the late stages. When they do arise, most are nonspecific in nature, including weight loss, fatigue, and night sweats. Depending on the type of mesothelioma, other organ-specific symptoms may be present. For instance, most patients with pleural mesothelioma begin to experience lung-related symptoms, such as consistent chest pain and progressively worsening shortness of breath. The pain is typically caused by invasion of cancer into the chest wall, and the shortness of breath is often caused by pleural effusion (excess fluid in the pleural linings of the lungs). The presence of cough, or coughing up blood, can occasionally occur with pleural mesothelioma.

Patients with peritoneal mesothelioma often report abdominal pain or bloating. A change in bowel habits (diarrhea or constipation), nausea, and vomiting can also develop. Even fewer symptoms are present in pericardial mesothelioma, making it difficult to diagnose. Because the tumor is present in the linings of the heart, patients with pericardial mesothelioma generally have symptoms related to cardiac function, including chest pain, heart palpitations, and difficulty breathing. The only known symptom of testicular mesothelioma is testicular lumps.

Diagnosis ›

Because of the nonspecific nature of mesothelioma symptoms, proper diagnosis requires a combination of physical, radiological, and pathological examinations, as well as an accurate patient history, including potential asbestos exposure and identification of asbestos-related occupations. Obtaining an accurate history of asbestos exposure can be challenging because in most cases, patients must be able to recall exposure that occurred 20 or more years in the past.

For those patients with pleural effusions, a sample of the pleural fluid is taken and sent to a pathologist, who examines the sample for the presence of malignant cells. In most cases, even when a pleural fluid sample is available, a biopsy of the pleural tissue is required to make a diagnosis. A biopsy can be obtained

Symptoms of mesothelioma do not typically arise until the disease has reached the late stages.

Mesothelioma staging, or determining the extent of the disease, is used both to predict a patient's outcome and to determine the best course of treatment.

by needling the pleural mass. The optimal method, however, involves surgical biopsy, such as a thoracoscopy, a procedure in which a tube with a camera on the end is inserted into the chest.

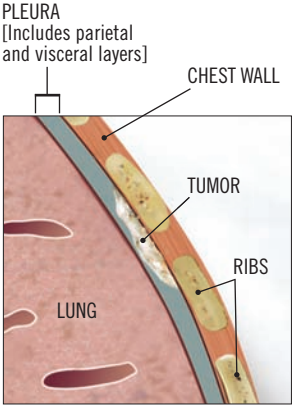
Radiological analysis using contrast-enhanced computed tomography (CT) scan provides a three-dimensional view of the entire pleural surface. It can help determine the extent of disease and can aid the physician in finding the desired tissue for biopsy. Two other radiological tests, magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, may also be used to evaluate patients with mesothelioma. PET scan provides information regarding how active the tumor is by measuring its metabolic activity, and can also assess whether the cancer has spread to other parts of the body.

The pathological examination of the biopsy samples includes immunohistochemistry tests, in which the samples are processed in a way that allows the pathologist to look for specific signs, called markers, of mesothelioma. There are no known markers that correspond to mesothelioma alone, so in order to diagnose mesothelioma, the pathologist generally evaluates the presence or absence of several different markers. The pathologist also uses the biopsy samples to classify the type of mesothelioma: epithelioid, sarcomatoid, or biphasic. About 50 to 60 percent of mesotheliomas are of epithelioid origin, and these tend to be associated with better outlooks than the other two types. Approximately 10 to 20 percent of mesotheliomas are sarcomatoid, or fibrous, in nature, and the remaining cancer cells are biphasic, or mixed, containing both epithelioid and sarcomatoid areas.

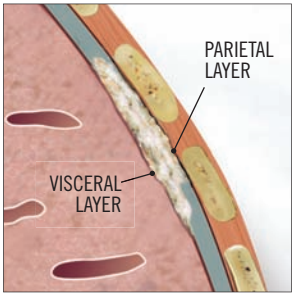
Staging ›

Once a diagnosis of mesothelioma has been reached, the disease stage is also evaluated. As with any type of cancer, mesothelioma staging, or determining the extent of the disease, is used both to predict a patient's outcome and to determine the best course of treatment. There are several different types of staging systems by which pleural mesothelioma can be evaluated, but the one used by most major cancer centers in the United States has been developed by the American Joint Committee on Cancer and is called a TNM staging system, because is takes into account Tumor location and involvement with surrounding tissues, disease spread to lymph Nodes, and presence or absence of Metastases (disease spread to other organs). There are

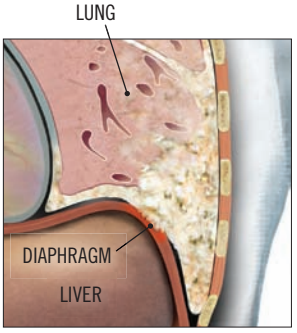
Stages of Mesothelioma



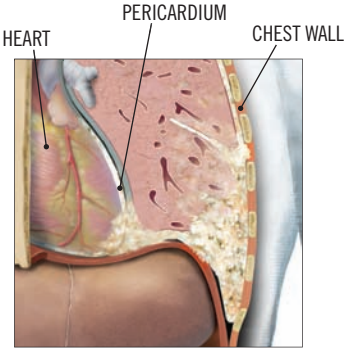
STAGE 1A: Tumor is confined to the parietal pleura, the external layer of the pleura.



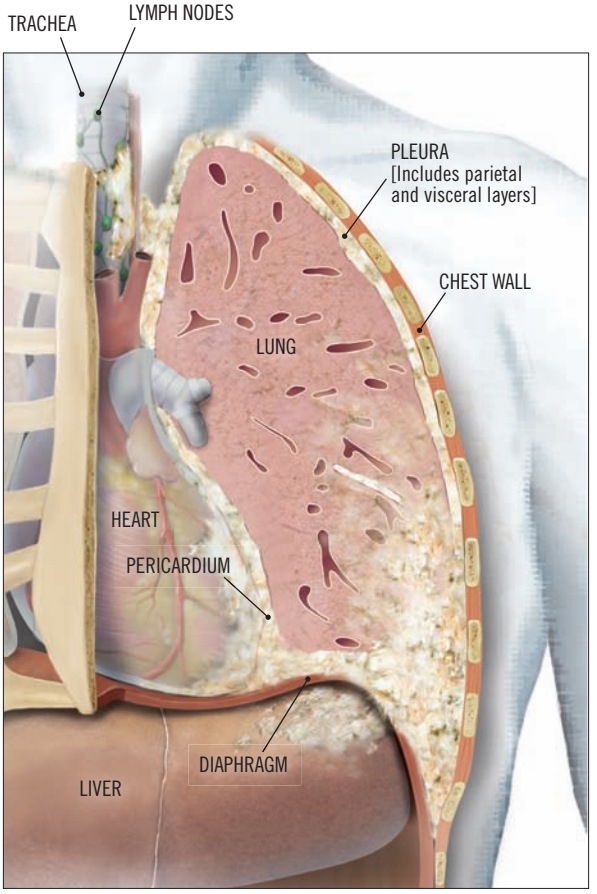
STAGE 1B: Tumor occupies the parietal pleura and the visceral pleura, the internal layer of the pleura that covers the lung.



STAGE 2: Tumor expands into the lung or diaphragm.



STAGE 3: Tumor extends into the chest wall, the tissue surrounding the heart (pericardium), and/or the lymph nodes in the chest.



STAGE 4: Tumor invades multiple areas, penetrates the pericardium or diaphragm, extends into lymph nodes outside the chest, and/or spreads to at least one other organ, such as the heart, esophagus, liver, or opposite lung.

ILLUSTRATION BY **PAM CURRY**

chapter 4

treatment options

treatment options

TREATMENT options for mesothelioma vary because it is rarely curable and clinical trial research is limited due to small patient enrollment caused by the rarity of the disease. Few well-controlled clinical trials have been conducted in which mesothelioma therapies can be compared for both effectiveness and tolerability. Nonetheless, improvements in treatment have been made in recent years, giving mesothelioma patients a ray of hope for their futures.

Surgery ›

Although complete surgical removal of the mesothelial tumor is desired, this is rarely achievable for most patients, as microscopic tumor tissue is generally left behind during surgery. However, surgery is still being used to treat patients with the goal of removing the vast bulk of the tumor and thus alleviating symptoms. Three surgical procedures are used: video-assisted thoracoscopic (VATS) talc pleurodesis, pleurectomy/decortication (P/D), and extrapleural pneumonectomy (EPP). Each procedure has distinguishing characteristics that can help a physician to determine which is best for a particular patient.

VATS Talc Pleurodesis

This procedure is primarily used to treat pleural effusions, but a biopsy can be obtained at the same time for diagnostic purposes. With VATS talc pleurodesis, a camera is inserted into the pleura through a small incision in the chest, and surgical instruments are inserted through two other incisions. The camera allows the surgeon to maneuver instruments into the pleural space, where the surgeon first drains the excess fluid and then blows talc (similar to common talcum powder, but sterilized), causing an inflammatory reaction that literally glues the lung to the inner surface of the rib cage. Eventually, scar tissue forms, creating permanent bonds that eliminate the space in which fluid can develop. This procedure should relieve the shortness of breath that accompanies pleural effusions. Because VATS talc pleurodesis does not reduce the size of the tumor, it does not by itself improve the expected survival of patients with mesothelioma, but it may permit patients who are too frail to undergo more aggressive therapy to later be treated with chemotherapy. By eliminating the shortness of breath caused by pleural effusions, this procedure may also improve the quality of life of mesothelioma patients.

P/D

The goal of this procedure is to remove as much of the tumor as possible. To accomplish this, part of the pleura is removed, as is the fibrous covering of the lungs, which may restrict the expansion of the lungs. This procedure can be performed by VATS or through a larger incision on the side of the chest. A P/D is considered major surgery, and a small percentage of patients die as a result of this surgery. Nonetheless, it is less invasive than EPP and is considered preferable for frail patients. A P/D may also be considered for patients with very early-stage disease in an effort to keep the lungs intact.

Although the majority of the tumor is removed during a P/D, visible tumor is left behind in almost 80 percent of these cases. For this reason, 80 to 90 percent of patients experience recurrence after the surgery. This procedure is also associated with a number of postoperative complications, including air leak, bleeding, and pus formation. Another disadvantage of this surgical technique is the difficulty in performing postoperative radiation therapy, which risks lung-related side effects because the involved lung is preserved. Conflicting evidence exists regarding the impact of P/D on the life expectancy of patients with mesothelioma, with some studies suggesting it prolongs life and others indicating it does not. Despite its questionable effect on survival, P/D may be a reasonable surgical option for some patients.

EPP

This procedure is the most aggressive surgical treatment of malignant mesothelioma, as reflected by its high morbidity (illness/disease) rate of 60 percent and its mortality (death) rate of 4 to 9 percent. This procedure involves the removal of both layers of the pleura along with the involved lung, some of the lymph nodes, the diaphragm, and the pericardium, the last two sites of which are then reconstructed with synthetic materials.

Although this procedure has inherent dangers, it does permit the use of radiation therapy following surgery since the involved lung has been removed. Evidence suggests that the combination of these two therapies may be able to both reduce recurrence at the original tumor site and prolong survival in patients with early-stage disease. Chemotherapy is now often incorporated into the treatment plan as well, either before or after surgery.

However, because of the morbidity and mortality associated with this procedure, EPP has strict patient-selection criteria, including early-stage disease, good cardiac health, no history of certain cardiac or lung surgeries, no significant kidney or liver disease, and little, if any, chest pain. Furthermore, this procedure should only be done by surgeons experienced in performing this operation. Because most patients are diagnosed with advanced, or late-stage, disease, few people can be considered for this type of treatment, and even fewer are eligible once all the other selection criteria are taken into account. A recent study reported a six-month survival advantage for patients who underwent either EPP or P/D for mesothelioma compared to those patients who were eligible for but did not undergo surgery.

Radiation Therapy ›

Unlike most tumors, which grow as a sphere or ball of tumor cells, mesothelioma typically grows as a sheet of tumor cells, blanketing the lung. This characteristic makes it difficult to treat mesothelioma with radiation therapy, which works best when it is targeted to a defined area. With mesothelioma, the challenge is to deliver enough radioactivity to the sheet of tumor to destroy it without damaging underlying structures, such as the lungs, heart, liver, and spinal cord. For this reason, radiation therapy is generally used to treat

localized patches of tumor recurrence or small areas of tumor left behind after surgery. There is no evidence to suggest that radiation therapy alone improves survival in mesothelioma patients, but it does alleviate pain for approximately half of the patients receiving it. Radiation therapy may also be used to treat chest wall wounds caused by a biopsy or drainage procedure.

When radiation therapy is administered after EPP, patients do appear to have improved outcomes; however, because mesothelioma is so rare, it is difficult to conduct large enough studies to prove that the addition of radiation therapy improves survival. Nonetheless, this combination of radiation and surgery does appear to offer patients good outcomes, particularly in a subset of patients with a specific set of circumstances (i.e., no evidence of residual disease after surgery, no spread of tumor to lymph nodes outside of the pleura, and a type of tumor called epithelioid).

Chemotherapy >

Since a cure is rarely possible, the goals of current chemotherapy regimens are to prolong the survival of mesothelioma patients and improve their quality of life by relieving some of their disease-related symptoms. Ideally, a chemotherapy regimen will be able to achieve both goals simultaneously.

Approval by the U.S. Food and Drug Administration (FDA) of a new chemotherapy drug, Alimta (pemetrexed), in 2004 has led to the largest improvement ever in the outcomes of mesothelioma patients. Alimta acts as an antifolate drug, that is, it disrupts the metabolism of folic acid in cancer cells. When added to another chemotherapy drug called Platinol (cisplatin) in a clinical trial, Alimta prolonged the average survival of mesothelioma patients by almost three months. In addition, Alimta also relieved pain, relieved shortness of breath, and improved lung function in some patients. Because of these encouraging results, the combined administration of Alimta and Platinol given intravenously once every three weeks has become standard therapy for the treatment of newly diagnosed mesothelioma. Also, results were seen in a recent phase III trial with a similar design combining Platinol with another antifolate drug called Tomudex (raltitrexed). This further confirms the benefit of antifolates for treating mesothelioma, although Tomudex is not currently available.

Premedication with folic acid and vitamin B12 is necessary when taking Alimta in order to reduce the frequency of side effects, which can include fatigue, nausea, vomiting, anorexia (loss of appetite), constipation, mouth sores, and myelosuppression (low blood cell counts). More severe side effects, including renal failure and hearing loss, can also occur in rare instances. To reduce the risk of these toxicities, some physicians combine Alimta with Paraplatin (carboplatin), an agent similar to Platinol. Paraplatin has a reduced risk of renal dysfunction, hearing loss, vomiting, and peripheral neuropathy (tingling, numbness, or pain in the arms and/or legs), although it does more commonly lower blood counts.

Mesothelioma patients tend to remain on a chemotherapy regimen until the cancer worsens or

Mesothelioma is a disease triggered by asbestos, a toxic substance many thought was banned in the United States long ago. It is diagnosed in approximately 3,000 Americans every year.

Written for families, patients, and professionals, *Understanding Mesothelioma* is an essential guide to comprehending and combating mesothelioma. In these pages, the editors of *CURE* magazine explore mesothelioma in depth and review current surgeries, drug therapies, research, and clinical trials.

People who have mesothelioma will benefit from an abundance of practical information, including a list of common side effects and how to combat them, how to find a medical specialist, and what patient's rights are under the law.

This book also offers details useful to family members and loved ones caring for people with mesothelioma, listing valuable resources, such as support groups and nonprofit organizations.

The editors of *CURE* magazine are the authors of this book and responsible for its content.
This book is made possible by generous support from Baron & Budd, P.C.

CURE is a quarterly magazine that combines science with humanity to empower cancer patients and their caregivers with the latest information on every aspect of cancer—from the technical and the scientific, to the social and emotional.

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ISBN 978-0-980130829