# 89 MALIGNANT MESOTHELIOMA

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## HISTORICAL PERSPECTIVE

The existence of malignant mesothelioma as a primary tumor of the pleura, peritoneum, pericardium, and other organs has long been controversial. As early as 1767, however, Joseph Lieutaud is credited with describing two cases of probable mesothelioma in a study of 3,000 autopsies, and E. Wagner recognized the disease as a pathologic entity in 1870.[238,239,298] Klemperer and Rabin described in detail the histologic features of benign (localized) and malignant (diffuse) mesotheliomas in 1931.[143] A case record of malignant pleural mesothelioma discussed in 1947 led neither to the recognition of the diagnosis nor to the suspicion of asbestos as a causative factor, even though the introductory sentence included the term *asbestos worker*, and later the patient's work was described as "cutting asbestos insulating board."[48] This controversy lasted until 1960, when the major etiologic factor (i.e., asbestos) was established in a seminal report by J. C. Wagner and colleagues in 32 of 33 cases of mesothelioma, largely by environmental exposure in the "Asbestos Hills" of Cape Province in South Africa.[295] Such a singular relationship, confirmed in many other countries including the United States, established the disease as a distinct nosologic entity.[236]

## INCIDENCE AND EPIDEMIOLOGY

Mesothelioma has been such a rare disease, or one recognized so infrequently, that it has not been coded as a separate cause of death and has been seriously underestimated in mortality statistics.[71,236] The age-adjusted incidence of pleural and peritoneal mesothelioma in the United States has been estimated at 14.2 per million per year, with almost a three-fold increase for pleural mesothelioma in Caucasian males between 1973 and 1984.[71] The male-female ratio is about 4:1, and 80% arise from the pleura.[71] Cases tend to be clustered in areas of asbestos product plants and shipbuilding facilities.[94] Similar trends have been reported in other industrialized countries, such as England.[104] In autopsy studies, the frequency of malignant mesothelioma varies from 0.02 to 0.7%, with a rate of 0.2% in the largest series.[127]

In most hospital series, the pleura is more often involved than the peritoneum, with a predominance of the right side over the left (60:40).[127] In some epidemiologic studies monitoring cohorts of asbestos workers, however, the peritoneal form is more common than the pleural.[238]

The mean age of patients is approximately 60 years,[16,93,214,305] but the disease can occur at any age, including in childhood.[116] In a review of 80 children with a diagnosis of malignant mesothelioma, the mean age was 9.7 years, and 59% were male. Only 2 children were noted to have a history of possible asbestos exposure, 1 had received radiotherapy for Wilms' tumor, and 1 had been exposed to isoniazid in utero.[102]

## ETIOLOGY

A unique feature of mesothelioma is its strong relationship with asbestos exposure, which has recently led to great public concern in view of the ubiquitous presence of that mineral.

**Epidemiologic and Clinical Evidence of the Role of Asbestos** Many epidemiologic surveys around the world have revealed prior exposure to asbestos in about 70 to 80% of all cases of mesothelioma when a careful history was taken.[16,63,192,305] Beginning 15 years after onset of exposure, about 6% of asbestos workers over the age of 35 years die of mesothelioma.[238] The death rate from mesothelioma in a cohort of asbestos insulation workers was 344 times higher than in the general population.[236] It is estimated that, from 1940 through 1979, approximately 27.5 million workers were occupationally exposed to asbestos in the United States, with a calculated annual death rate from mesothelioma of about 2,000 in 1980 up to 3,000 in the late 1990s.[190] Exposure can be not only occupational but also environmental, or even familial by household contamination. The latter type of exposure, usually through the work clothes of an asbestos worker, is an important factor for women. It was also found in 5 of 10 young adults (40 years or younger) with mesothelioma who had been exposed in childhood.[134] Insulation, construction, shipyard industries, and automobile brakes are among the many sources of occupational exposure. The delay between first exposure and onset of the disease is extremely long, averaging 30 to 45 years, with a usual range of 10 to 65 years and a standard deviation of 12 years.[63,238,305] Because of such a delay, asbestos exposure can easily be underestimated, since occupational histories are often inadequately documented.[197,280] Moreover, exposure may have been short or minimal,[63,238] although sometimes a very short exposure may have been intense.[306] Pulmonary asbestosis and fibrosis are often absent or are rarely severe and are found at autopsy in about 40% of patients with mesothelioma.[16,63] Due to the long latency and to the vastly increased use of asbestos during and after World War II, the incidence of mesothelioma is expected to continue to increase.[190] Although asbestos exposure and cigarette smoking act synergistically to produce bronchogenic carcinoma, smoking is not a factor for mesothelioma.[183,192,238,291]

The presence of asbestos fibers in sections of lung tissue is another proof of asbestos exposure. Asbestos fibers are more difficult to detect in mesothelioma tissues than in the pulmonary parenchyma. Fibers in tissues can acquire a proteinaceous coating containing iron, leading to the formation of ferruginous bodies.[238] These are not specific and can be called asbestos bodies only if the central core is identified as being asbestos. The asbestos minerals are divided into two major categories: the serpentines (chrysotile) with a general formula $Mg_3Si_2O_5(OH)_4$, forming long hollow tubes, and the amphiboles containing more silica and less magnesium oxide and forming short, straight fibers.[238] Among the various types of asbestos associated with mesothelioma, amphiboles carry the highest risk: crocidolite in South Africa, and amosite in the United States have been most commonly incriminated.[127,183,293] Chrysotile, a long, curly fiber with poor pulmonary penetration which can be dissolved in lung tissue, seems to carry a much lower risk, although it does not appear to be nil.[68,218,293] It has been postulated that mesotheliomas occurring in chrysotile-exposed individuals may be related to contamination by tremolite,[68] another amphibole fiber which has been implicated in cases of mesothelioma in Greece,[150] and which may contaminate other substances, such as talc or vermiculite.[177] On the other hand, another amphibole fiber mined in Finland, anthophyllite, a thick coarse fiber, has been shown to cause calcified pleural plaques but usually not mesothelioma.[127]

These data emphasize the importance of the type of fiber and its physical characteristics and also the fact that most natural asbestos fibers are rarely pure but mixed.[127] Although asbestos fibers can be detected in essentially 100% of the lungs of city dwellers by using special techniques,[151] their number is markedly greater in the lungs of patients with mesothelioma and occupational exposure to asbestos, commonly reaching several million fibers per gram of dry weight.[16] This is particularly true when amphibole fibers are counted.[183] The mean increase of lung fiber burden of mesothelioma patients as compared with controls was seven times higher for pleural and 16 times higher for peritoneal mesothelioma but was lower than for patients with asbestosis (48 times higher than controls) or lung cancer with asbestos exposure (32 times higher than controls).[293] The question of a dose-response relationship between exposure to asbestos and occurrence of mesothelioma has been suggested by indirect methods, such as duration of employment in asbestos factories, or by quantitative measurements of pulmonary asbestos burden,[63] especially if amphibole fibers > 10 microns are considered.[218] No safe threshold has been established for asbestos exposure, however, and the asbestos burden in the lungs of mesothelioma patients forms a continuum that totally overlaps with controls at the lower end.[219,306]

**Experimental Evidence for the Role of Asbestos** Animal experiments have confirmed the oncogenicity of asbestos. A single

intrapleural or intraperitoneal injection of various asbestos fibers (chrysotile or amphibole) produce mesotheliomas in rats, hamsters, and mice, often after a relatively long delay of 7 months or more.[261] Intratracheal instillation or inhalation is less often successful.[25,290] Physical characteristics, rather than chemical properties, are incriminated, since many durable fibers of similar size and shape but of different nature (glass, aluminum oxide, talc, attapulgite) can also produce mesothelioma in animals.[167,251] The most oncogenic fibers are the long, thin ones, with a length > 8 microns and a diameter < 0.25 micron, the so-called Stanton hypothesis, whereas shorter fibers may be inactivated by phagocytosis.[117,251] These long, thin fibers may penetrate deep in the lung parenchyma,[117,221,251] eventually reaching the subpleural and pleural structures and penetrating into cells without killing them, thereby implementing a complex oncogenic process. The effect of gravity on inhaled fibers may explain the predominance of pleural mesothelioma in the lower thorax and on the right side.[138] The pathogenesis of peritoneal mesothelioma is more obscure. Although the disease has not been produced in animals by feeding experiments, ingestion of asbestos fibers is likely to occur through the action of the tracheobronchial mucociliary apparatus, and these fibers may penetrate the gastrointestinal mucosa.[138] Alternatively, retrograde spread to the peritoneal cavity from the pleura may take place.[85] In fact, autopsy studies have revealed that asbestos fibers are found in many organs besides the lungs, including the spleen, thyroid, pancreas, heart, adrenals, kidneys, liver, prostate, and even brain.[17]

The possibility that asbestos exposure increases the risk of other cancers besides mesothelioma and lung cancer has been reviewed.[85] The evidence is strong for laryngeal cancer (relative risk 1.4), suggestive but not conclusive for esophageal cancer, possible for renal cancer, and inconclusive for gastrointestinal, pancreatic, and ovarian cancers (where misdiagnosis of mesothelioma is difficult to exclude). There appears also to be no overall association with lymphomas, except possibly with large cell lymphomas of the oral cavity and gastrointestinal tract (see below).

**Mechanisms of Oncogenesis by Asbestos** The mechanisms of asbestos-induced oncogenesis have not been fully elucidated, but considerable progress has been accomplished in the past few years. There is evidence that depending on the system considered, asbestos can be a complete carcinogen, an initiator, or a promoter.[23] The tumor-promoting model can be best applied to lung cancer, where synergistic interaction between asbestos and cigarette smoke occurs. Compared with nonsmokers not exposed to asbestos, the death rate from lung cancer is multiplied five times in nonsmokers exposed to asbestos, by 11 in smokers not exposed to asbestos, and by 53 in smokers exposed to asbestos.[237] Such an effect has been shown experimentally by exposing tracheal epithelial cells to polycyclic aromatic hydrocarbons and asbestos in various schedules;[23] however, asbestos alone may produce these changes as well,[23] and lung cancer occurs in nonsmokers exposed to asbestos, although to a much lesser degree than in smokers exposed to asbestos. Other changes observed in target tissues compatible with a promoter effect of asbestos include hyperplasia, metaplasia, DNA synthesis, and increased production of oxygen free radicals. Activation of diacylglycerol, protein kinase C, and ornithine decarboxylase also has been reported in a pathway similar to classic tumor promoters, such as phorbol esters.[23,168,183]

Evidence that asbestos can also be a complete oncogen and an initiator lies in the fact that it can produce mesothelioma in humans without interaction with other known carcinogens, such as cigarette smoke, and that a single instillation of asbestos in the celomic cavities or the trachea can produce mesotheliomas in rodents.[23,130,185] Although asbestos is weakly or not at all mutagenic in the classic sense of the word,[23,183] it can induce heritable changes in the growth properties of normal mammalian cells in culture, leading to transformation and immortalization and to chromosomal mutations (aneuploidy and aberrations), which are dependent on fiber size.[23] These changes may occur by physical interference of the mitotic process in the cell by penetrating asbestos fibers,[23,183] or through other mechanisms, such as formation of active oxygen species.[183] The changes provide a rational explanation for the pathogenesis of mesothelioma. Normal human mesothelial cells can phagocytose asbestos fibers and are 10 times more sensitive than normal human bronchial epithelial cells to asbestos cytotoxicity in vitro.[153] Mesothelial cells are 100 times more sensitive than fibroblasts.

Following in vitro exposure to asbestos, mesothelial cells display chromosomal aberrations indicative of clonal origin.[153] Occurrence of DNA strand breaks has been found after exposure of cells to asbestos in vitro.[131,159] Such effects could further lead to activation of oncogenes and/or loss of suppressor genes.[23] Indeed, karyotypic analyses of human mesotheliomas have revealed frequent abnormalities, particularly involving chromosomes 1, 2, 3, 6, 7, 9, 11, 17, and 22.[23,109,183,200] One of the most common nonrandom changes is deletion of the short arm of chromosome 3 between the region of p14 to 21.[200] This finding is of interest, especially since deletions and loss of heterozygosity of the short arm of chromosome 3 have been reported also in lung cancer, particularly the small cell type in the region of p14 to 23,[302] suggesting evidence for a suppressor gene important in respiratory carcinogenesis. A significant correlation exists between chromosomal aberrations and pulmonary asbestos fiber burden in patients with mesothelioma.[268] An inverse correlation between survival and the number of copies of chromosome 7 short arms has been reported.[268] These cytogenetic changes may also be important in explaining the likely constitutional susceptibility to mesothelioma (see below).

Exposure of normal human mesothelial cells to asbestos fibers in vitro has as yet been unsuccessful in producing mesothelioma.[153,183] Malignant transformation was achieved in one experiment by first transfecting cells with a plasmid containing the simian virus SV40, resulting in immortalization, followed by transfection with the EJ-*ras* gene, resulting in tumorigenicity.[208] Exposure to asbestos failed to produce tumorigenicity, however. It may be extremely difficult to realize in vitro all the different conditions and interactions which may operate in vivo.

The existence of transforming genes has been detected in human mesothelioma, but their exact nature remains to be identified.[23,149] They do not seem to be related to the *ras* gene family, which was found activated in 50% of asbestos-induced Syrian hamster tumor cell lines,[23] or to the *myc*, *myb*, *neu*, or *fos* oncogenes.[101] Loss of heterozygosity for the *p53* gene located on the short arm of chromosome 17 has recently been observed in three of four mesothelioma cell lines.[72] In another study of 20 cell lines from 17 patients with malignant mesothelioma, *p53* abnormalities were found in three lines only.[180] Wilms' tumor suppressor gene (*WT-1*) transcripts were found to be expressed in normal human mesothelial cells and in 7 of 7 human mesothelioma cell lines.[297] Recently, changes in another suppressor gene, *p16*, were described, with homozygous deletions in 85% of mesothelioma cell lines and 22% of primary tumor specimens.[65] Asbestos fibers can also transfect cells by binding to exogenous nucleic acids, such as plasmid DNA, which then becomes associated with chromosomal DNA, thereby altering gene expression.[14]

Knowledge of the role of growth factors in the genesis and proliferation of mesothelioma is rapidly expanding. The role of platelet-derived growth factors (PDGF) has been emphasized.[108] Mesothelioma cells express messenger RNAs (mRNAs) for both PDGF-A and -B chains at higher levels than normal human mesothelial cells, whereas the reverse is true for transforming growth factor-β (TGF-β), suggesting that PDGF may be an autocrine growth factor for mesothelioma.[108] The corresponding genes for PDGF-A and PDGF-B (which is almost identical to the c-*sis* gene) are located on chromosomes 7p21 to p22 and 22q13.1, respectively, and although visible abnormalities of these chromosomes are not constant in mesothelioma, alterations at a molecular level cannot be excluded.[108,278] Human mesothelioma cell lines, compared with normal human mesothelial cells, have shown strongly increased expression of the c-*sis* oncogene (PDGF-B) and to a lesser degree of the gene for PDGF-A.[278] Normal mesothelial cell lines seem to express PDGF-α receptor genes, whereas mesothelioma cell lines express predominantly PDGF-β receptor genes.[279] These findings could conceivably provide also a role for the thrombocytosis commonly observed in mesothelioma patients, in view of its negative prognostic influence.[62,63,225] No increased expression of epidermal

growth factor (EGF) was detected in mesothelioma cell lines,[103] whereas in paraffin-embedded human mesothelioma specimens EGF was expressed more commonly in the epithelial cell type.[80] Both normal human mesothelial and human mesothelioma cell lines were shown to express insulin-like growth factor-1 (IGF-1), IGF-binding protein 3, and IGF-1 receptor mRNA, suggesting that IGF-1 may also be an autocrine growth factor.[154] In addition, immunologic factors play a possible role, which is described below.

## OTHER ETIOLOGIC FACTORS

Since about 20% of patients have no demonstrable or anamnestic exposure to asbestos, and some have an asbestos lung burden similar to that of controls, alternative factors are presumably involved. Other etiologic factors are rarely found, however.

The role of various other fibers, such as zeolites (erionite type) from volcanic rocks, has been incriminated in Turkey,[21,22] and a few deposits have been found in Oregon in the United States.[294] The potential of zeolites to produce mesotheliomas has been confirmed experimentally after intraperitoneal injection.[261] After inhalation, the mesothelioma yield from zeolites exceeds that of any other fiber.[294] Workers in the fiberglass industry are being closely monitored, but so far there is no evidence that they have a higher risk for cancer or mesothelioma.[127]

Mesotheliomas have occurred within or in proximity to prior radiotherapy fields. In a cumulative review of 23 cases of possible radiation-induced mesothelioma, including 2 after extravasation of thorium dioxide (Thorotrast), the interval between radiation and mesothelioma ranged from 5 to 41 years (median 13.5 years).[128] Radiation has also been shown to induce mesothelioma in animal experiments.[197]

A few cases of mesothelioma have been described 15 to 33 years following collapsotherapy (the induction of artificial pneumothorax) for tuberculosis, a technique used before effective drugs were available.[66,224] It is speculated that chronic irritation and inflammation may play a role in such cases. A similar mechanism has been postulated in a patient without known asbestos exposure who developed peritoneal mesothelioma associated with severe persistent diverticulitis and peritonitis and showed histologic evidence of benign mesothelial proliferation, atypical mesothelial proliferation, and malignant mesothelioma.[221] A case of peritoneal mesothelioma has also been reported in a patient with familial Mediterranean fever with recurrent peritonitis.[63]

Beryllium has been incriminated in a patient with a mesothelioma of the rectovaginal septum after she repeatedly douched with water containing that element.[110] Beryllium was demonstrated in the tumor itself, but the patient was also environmentally exposed to asbestos.

Two observed associations with mesothelioma are of importance. Various immunoproliferative disorders, particularly of B-cell origin, have been reported, including myeloma, plasmacytoma, lymphocytic lymphoma, and chronic lymphocytic leukemia in patients with asbestosis or mesothelioma.[63,89,106,133] A case-control study showed an association between occupational exposure to asbestos and large cell lymphomas of the gastrointestinal tract and oral cavity.[222] These observations provide further significance to immunologic abnormalities related to asbestos exposure and mesothelioma. Asbestos fibers can disseminate by lymphatic and even hematogeneous routes and can be found in various organs, including lymph nodes and bone marrow.[141] Interestingly, plasmacytomas with frequent C particles have been produced in mice after intraperitoneal injection of asbestos or zeolite fibers.[261] Administration of carrageenan, which depresses lymphocyte and macrophage functions, has tripled the rate of asbestos-induced mesothelioma in rats.[292] It has been shown that asbestos fibers suppress natural killer (NK) cell activity in vitro in a dose-dependent fashion for both human peripheral blood lymphocytes and lung mononuclear cells obtained by bronchoalveolar lavage (BAL).[215] Pre-exposure of cells to interleukin-2 (IL-2) restores NK activity.[215] Human mesothelioma cells in vitro are resistant to NK cell lysis but susceptible to lymphokine-activated killer (LAK) cells, thereby providing a rationale for immunotherapy with IL-2/LAK cells.[164] The absolute number of total peripheral T cells and T helper cells was found to be normal in asbestos workers but reduced in mesothelioma patients, whereas suppressor T cells were elevated in asbestos workers and unchanged in mesothelioma patients.[157] NK activity was depressed in 70% of mesothelioma cases and was partially restored by co-incubation with human interferon-alpha (IFN-α).[157] No clear pattern emerged when histocompatibility antigens (human leukocyte antigens [HLA] A and B) were studied in mesothelioma patients.[296]

Clinical observations also strongly suggest a genetic susceptibility to mesothelioma. Clusters of cases have been reported in some families, often by household exposure to asbestos, and also in identical twins.[7,63,134,171,212,281] The growing knowledge of the genetic changes associated with mesothelioma will better explain these observations and shed more light on the pathogenesis of the disease.

Strain MC 29 avian leukosis virus, an agent which ususally induces myelocytomas in chickens, has also produced mesotheliomas in chickens after injection into the coelomic cavity.[50] Recently, SV40–like DNA sequences were found in 60% (29 of 48) of human mesotheliomas, and the SV large T antigen was expressed in 13 of 16 specimens.[46] SV40 is a DNA tumor virus which can immortalize human mesothelial cells in vitro and also produce mesotheliomas in hamsters when injected intrapleurally. These provocative findings are intriguing and their significance is as yet unknown. It should be noted that the early polio vaccines (both oral and inactivated) were contaminated by SV40 from 1954 until 1960.[46] A number of laboratories have now confirmed that at least 60% of human mesotheliomas contain and express SV40.[195a,265a] In these tumor cells, the SV40 tumor antigen binds and inhibits the cellular tumor suppressors *p53* and *Rb*.[46a,80a] These findings suggest that SV40 may contribute to the development of those human mesotheliomas that occur in people not exposed to asbestos. SV40 may also facilitate asbestos-mediated carcinogenicity. The epidemiologic data available are insufficient to address the role that SV40 may have played in contributing to the increased incidence of mesothelioma in the second half of this century.[254a] The use of vaccination therapy against SV40 tumor antigen is presently under investigation in preclinical studies.[39a,309a] Although many other agents have produced mesothelioma in animal experiments,[197] the disease in humans is overwhelmingly linked to fiber oncogenesis, particularly asbestos, in industrialized countries. Whether cases are due to a genetic susceptibility to background levels of asbestos or to some other etiologic factor(s) in patients with no unusual exposure to asbestos or in those with low asbestos lung burden remains to be determined.

## PATHOLOGY

Mesothelioma tissues have the singular potential of producing tumors of epithelial or mesenchymal type, or both. Such a duality can be explained by embryology. The mesothelium is made of a coelomic epithelium developed from the mesoderm, not the mesenchyme, and is supported by mesenchymal tissue.[143] Tissue culture experiments have confirmed this hypothesis.[254] It is not entirely clear, however, whether the malignant cells arise from the mature mesothelial cells or from undifferentiated mesenchymal cells of the submesothelial tissues.[238] As a result, mesothelioma can be classified under three major histologic types: epithelial or tubulopapillary, the most frequent (50 to 70% of cases); mesenchymal or fibrosarcomatous, the least common (7 to 20% of cases); and mixed or biphasic, intermediate in frequency (20 to 35% of cases). The mixed type is the most characteristic, containing both epithelial and mesenchymal elements (Plate 19, Fig. 89.1); the transition is either abrupt or gradual.[214] Synoviosarcoma is the only other tumor that can produce a pathologic picture similar to that of mixed mesothelioma.[305] This dual appearance of mesothelioma has been shown in tissue culture studies. A change from one morphology to the other may be related to artificial conditions of the media used,[145] since no such conversions have been observed in human mesothelioma growing in nude mice despite repetitive transplantations over >1 year.[258,259] Other subtypes of mesothelioma have been described: desmoplastic with prominent fibrosis[43] and lymphohistiocytoid with intense lymphoplasmacytic infiltration,[122] both most often in sarcomatous mesothelioma. Psammoma bodies can be seen, although rarely, in mesotheliomas.[69,137]

Another remarkable property of the mesothelial cell is the production of hyaluronic acid, a glycosaminoglycan which stains weakly with muci-

carmine and strongly with colloidal iron or Alcian blue and disappears after preincubation with hyaluronidase.[258] The detection of hyaluronic acid is important in the differential diagnosis of mesothelioma, particularly adenocarcinoma, with two reservations: (1) hyaluronic acid may be dissolved in formalin-fixed tissue because it is water soluble, and (2) hyaluronic acid is not specific since it is found also in any rapidly growing tumor containing young connective tissue stroma. Its presence, thus, is of diagnostic importance only for the epithelial type.[69] Its detection in the tumor cell, however, rather than in the stroma is highly suggestive of mesothelioma. On the other hand, mesotheliomas do not usually produce mucin but may contain glycogen. Mucicarmine stain is typically negative. The periodic acid–Schiff reaction, after removal of glycogen by diastase (DPAS), detects neutral mucins and is likely to be positive in adenocarcinoma and negative in mesothelioma.[303] Whereas keratin stains were positive in 86 to 90% of mesotheliomas and 95 to 100% of lung adenocarcinomas,[271,303] vimentin was detected in 86% of the former and none of the latter.[303] A major problem with vimentin, however, is its detection in normal mesenchymal cells.[303] Other useful stains to differentiate epithelial mesothelioma from adenocarcinoma include (1) carcinoembryonic antigen (CEA), usually totally negative or faintly positive in less than 10% of mesotheliomas, compared with 91 to 95% positivity in lung adenocarcinomas; and (2) Leu M1 stain, positive in less than 5% of mesotheliomas but in 80 to 90% of lung adenocarcinomas.[271,303] On the other hand, both human milk fat globulin and epithelial membrane antigen are commonly found in both types of neoplasms and are of little value. In summary, a battery of special stains including alcian blue before and after hyaluronidase, mucicarmine, DPAS, CEA, and Leu M1 are most useful (Table 89.1). These special stains are often necessary to distinguish pleural mesothelioma from adenocarcinoma of the lung, particularly in its "pseudomesotheliomatous" form,[121] or peritoneal mesothelioma from adenocarcinomas of the digestive tract or the ovary. The differential diagnosis of peritoneal mesothelioma from ovarian cancer may be particularly difficult even after special stains; in vitro data suggest that mesothelial cells may also produce the ovarian cancer marker CA 125.[277]

Studies using antimesothelial antibodies, either polyclonal[86] or monoclonal,[191,250,308] are in progress and may prove to be useful, if their specificity is shown to be good. Differentiating mesothelioma from adenocarcinoma is clinically important since it may influence the treatment and help avoid a lengthy, costly, and vain search for another primary lesion. Electron microscopy is helpful in doubtful cases, revealing typical microvilli on epithelial mesothelioma cells (the fibrosarcomatous cells lack them) which are longer and thinner than in adenocarcinomas, as well as tonofilaments and cell junctions.[258]

Cytology has often been disappointing, both in identifying mesothelioma cells and in differentiating them from other tumors or from reactive mesothelial cells.[258] Recent studies have emphasized features such as cellular aggregates (morulae), cannibalism and multinucleation, cytoplasmic vacuolization, and irregular chromatin pattern, which are not constant.[148,304] Electron microscopy can be helpful, if available.[258] The diagnosis of mesothelioma by fluid cytology or needle biopsy often presents a great challenge, as discussed below.

**Table 89.1. Special Stains Useful in Differentiating Malignant Mesothelioma from Metastatic Adenocarcinoma**

| STAIN | Mesothelioma | Adenocarcinoma |
|---|---|---|
| Hyaluronic acid* | + | – |
| Mucicarmine* | – | + |
| PAS | +/– | + |
| D-PAS* | – | + |
| CEA* | – | + |
| Leu M1* | – | + |
| Keratin | + | + |
| Vimentin | + | – |
| HMFG | +/– | + |
| EMA | + | + |

PAS = periodic acid-Schiff (D-PAS: with diastase digestion); CEA = carcinoembryonic antigen; Leu M1 = human myelomonocytic antigen; HMFG = human milk fat globulin; EMA = epithelial membrane antigen.

* Most discriminating stains.

Another difficult task which may lead to considerable clinical problems is the distinction between malignant mesothelioma, particularly of the desmoplastic type, and benign reactive mesothelial hyperplasia, which can appear atypical in a number of conditions, including pulmonary infarction, cirrhosis of the liver, uremia, and metastatic carcinoma.[124] In such cases, even electron microscopy may not be helpful.[260] Suspicion of malignant mesothelioma should arise in case of invasion of surrounding structures, of focally necrotic and avascular areas, and subtle microscopic features, such as piling and aggregation of mesothelial cells, variability in size, nuclear hyperchromasia, mitotic activity, irregular chromatin pattern, and cytoplasmic vacuolization, or in the presence of any florid mesothelial proliferation.[1,144,148,240] Some of these changes have been described several years before the development of mesothelioma; it is not clear whether the tumor is preceded by such preneoplastic mesothelial proliferations,[144] or if it arises directly as a diffuse microscopic neoplasm.[113] A recently described argyrophil stain, the "AgNOR technique" which detects "nucleolar organizer" regions of ribosomal DNA, seems to be effective in differentiating malignant from normal or reactive mesothelial cells.[18] Cytogenetic analysis to detect clonal chromosome aberrations is also of great interest.[100]

Mesotheliomas spread by contiguity over the parietal and visceral serosal surfaces. Pleural mesothelioma extends over the diaphragm, mediastinum, pericardium, and, eventually, the peritoneum. It also extends into the interlobar fissures and into the lung itself by contiguity or by interstitial and alveolar spread.[64] Seeding along the track of needle biopsy channels occurs in 10 to 20% of cases.[63,127] Peritoneal mesothelioma involves mainly the parietal and visceral surfaces, the omentum, and the mesentery with tumor nodules and/or infiltration causing thickening. Involvement of the serosa overlying the small and large bowel, the liver, the spleen, and other organs leads to encasement of these organs in tumor tissue. Lymphatic dissemination is common, and mediastinal nodes are involved in about 50% of cases of pleural mesothelioma.[214,305] Distant blood-borne metastases are more common than was previously thought and are seen at autopsy in 50 to 80% of cases.[214] They can occur in any organ, including the brain.[209] A peculiar pattern of massive hepatic calcifications, attributed to degenerative and necrotic liver metastases, has been described.[42,196]

## CLINICAL FEATURES

The onset of mesothelioma is usually insidious; a common presenting symptom is persistent localized pain.

**Pleural Mesothelioma** Chest pain or dyspnea is almost constant, although of varying degree.[63,214] Pleural effusion is present initially in up to 95% of cases.[63] Later, tumor growth usually results in complete obliteration of the pleural space and encasement of the lung.[93,214,264] Cough, weight loss, and fever are not uncommon. In contrast to benign mesothelioma, clubbing is rare and was seen only in 6% of cases.[51] Mediastinal invasion with dysphagia, phrenic nerve paralysis, pericardial effusion, and superior vena cava syndrome can occur.[225] Spontaneous pneumothorax or hydropneumothorax and Horner's syndrome have been described.[127,206] Progressive invasion of the chest wall often leads to intractable pain.

Chest radiographs reveal a variable amount of fluid, with pleural thickening or pleural nodules, often several centimeters in diameter, imposing a scalloped appearance (Fig. 89.2). Predominance at the base is almost constant. In advanced cases, ipsilateral shift of the mediastinum and retraction of the involved hemithorax are characteristic, unless the tumor volume becomes very large.[63,93] The electrocardiogram (ECG) is abnormal in almost 90% of patients, showing various arrythmias (sinus tachycardia is the single most common change [42% of cases] but also premature atrial or ventricular contractions, atrial fibrillation, or flutter), conduction abnormalities (right-side bundle branch block, left hemiblocks), nonspecific ST-T changes, or left or right hypertrophy.[289] Computed tomography (CT) is most valuable in showing the extent of disease (including chest wall,

mediastinum, pericardium, and diaphragm), relative amount of fluid and tumor, involvement of interlobar fissures, and retraction of the involved hemithorax (Fig. 89.3). In addition, signs of asbestos exposure, such as contralateral pulmonary fibrosis and/or pleural plaques, are seen in 50% of cases and pleural calcifications in 15%.[202] Further studies are needed to evaluate the role of magnetic resonance imaging (MRI). MRI has been better than CT in showing tumor spread into the fissures, diaphragm, and bony structures, whereas both procedures are equally effective to detect invasion into the chest wall, lung, and mediastinum.[145a] Echocardiography is useful to reveal pericardial involvement, especially if cardiac tamponade is suspected.[289] Uptake of gallium $^{67}$GA citrate by mesothelioma tumors has been experimentally demonstrated,[273] and gallium scan was positive in 43 of 49 patients (88%) with pleural mesothelioma.[265] Recently, the role of fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging has been examined in a cohort of 28 patients with suspected mesothelioma (confirmed in 22).[26b] Standardized uptake values (SUVs) were determined from the most active tumor site in each patient. The mean SUV of the deceased patients was 6.6 +/- 2.9, compared with 3.2 +/- 1.6 among the combined survivors. The deceased patients had tumor SUVs that were highly correlated with duration of survival after the PET study. The survival distribution of the high-SUV group showed significantly shorter survivals, compared with the low-SUV group.

Bronchoscopy is usually normal or reveals extrinsic pressure.[206] Thoracocentesis yields a serous to viscous, glutinous fluid, which is occasionally frankly bloody.[206] The fluid is an exudate, and pleural fluid glucose can be low, but this finding is nonspecific.[264] The best positive marker for malignant mesothelioma is the detection of a high level of hyaluronic acid in the fluid,[216,217] but this technique is not yet routinely available. Cytologic studies in large series reveal malignant cells in 16 to 38% of patients, but their exact nature is often undetermined or misclassified, and they are diagnostic in only 3 to 16% of patients with mesothelioma.[1,225] Greater awareness of the disease, increasing expertise, and use of special stains or electron microscopy may improve these disappointing results. Pleural needle biopsy shows malignant disease in 13 to 48% of cases, and a diagnosis of mesothelioma in 10 to 36%.[1,225] Use of Tru-cut needles or CT-guided pleural biopsies need more evaluation.[170] Thoracoscopy is a useful technique in cases where it is technically possible, yielding a diagnosis of mesothelioma in 70 to 80% of cases[170,225] and false-negative results in up to 20% of cases,[179] although it was diagnostic in virtually all patients in another study.[31,33] Otherwise, thoracotomy with open surgical biopsy remains the best diagnostic procedure, yielding the diagnosis in 77 to 100% of patients.[1,225]

There is a lack of positive serum markers currently available for the diagnosis of mesothelioma. Serum CEA and alpha-fetoprotein (AFP) values are usually within normal limits.[52] The detection of an elevated serum level of hyaluronic acid may prove useful in differentiating mesothelioma from other tumors,[76] or to follow the effect of treatment.[77] In an experimental model of human mesothelioma transplanted in nude mice, serum levels of hyaluronic acid became detectable within 4 days after subcutaneous transplantation, before the tumors in mice were palpable.[216] Serum immunoglobulins show no specific pattern.[52]

Median survival is about 10 to 17 months from onset of symptoms and 9 to 13 months from diagnosis.[58,63,127,225] The 3- and 5-year survival probabilities were 10 and 3%, respectively, in one review of 92 cases,[1] and 5.6% for 5-year survival in another review of 123 patients.[39]

**Peritoneal Mesothelioma** Pain and abdominal distention with ascites are almost constant in patients with peritoneal mesothelioma.[63,182] Other clinical findings include nausea and vomiting, bowel obstruction, abdominal and pelvic masses, edema of the lower extremities, fever, hernia, hydrocele, and obstructive uropathy. Coexistent pleural effusion may occur. Direct biopsy by laparotomy or peritoneoscopy is the best diagnostic procedure. Ultrasonography and/or CT are useful techniques to follow the course of the disease and to visualize fluid and tumor masses.[312] Median survival is about 10 months from onset of symptoms and 7 months from diagnosis.[63]

**Paraneoplastic Syndromes** The most frequent paraneoplastic syndromes are hematologic. Among them thrombocytosis (platelet count above 400,000 per microliter) has been first observed by Chahinian and colleagues[63] in about 40% of patients at diagnosis and in up to 90% of patients during the course of the disease, a finding which has been confirmed by others.[187,225] It raises interesting questions about the reported role of platelet-derived growth factors (see above), and thrombocytosis has been linked to a poor prognosis.[62,225,226] It has been suggested in a case of peritoneal mesothelioma that thrombocytosis was secondary to the large amounts of interleukin-6 (IL-6) produced by tumor cells,[125] and this was confirmed in 25 patients with pleural mesothelioma.[188b] A full leukemoid reaction is much less common.[225] Other hematologic manifestations include clotting abnormalities (venous thrombosis, pulmonary emboli) not necessarily associated with thrombocytosis, as well as disseminated intravascular coagulation and autoimmune hemolytic anemias.[13,225] Rare associations include the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypoglycemia, and hypercalcemia.[127,225] Recently, parathyroid hormone–like peptide has been identified in mesothelioma cells, as well as in normal and reactive mesothelial cells.[175]

Human chorionic gonadotropin (hCG) has been detected in ascites fluid and tumor cell lysate but not in the serum of a patient with malignant peritoneal mesothelioma and gynecomastia.[209]

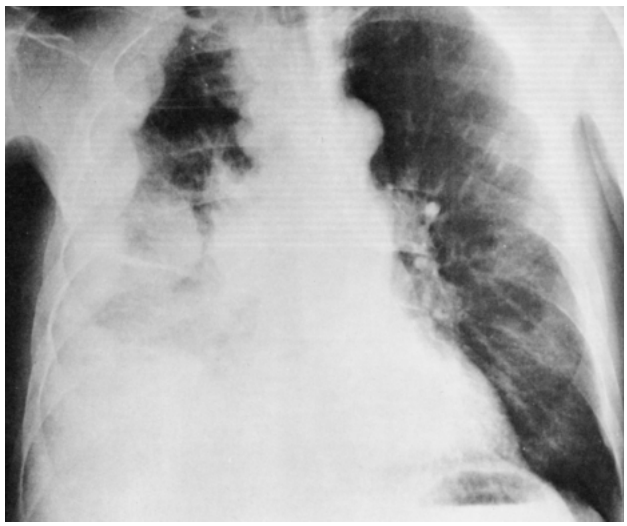

**Figure 89.2.** Malignant pleural mesothelioma, advanced stage. Marked thickening of the right pleura with tumor nodules and retraction of ipsilateral hemithorax. Basal predominance is well shown. No fluid was demonstrable by decubitus films.

## PROGNOSTIC FACTORS

Performance status has been one of the most reliable prognostic factors,[10,63] in addition to the stage, which is discussed below with surgical

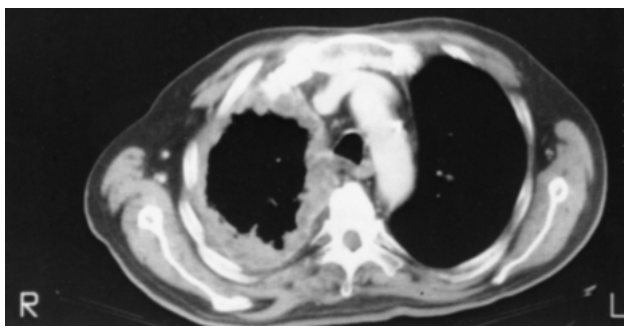


**Figure 89.3.** Malignant pleural mesothelioma, advanced stage. Circumferential thickening of pleura with coalescent nodular tumor masses. Restriction of the right hemithorax is prominent. CT scan at level of aortic arch.

treatment.[33,39,54,225] Epithelial cell type has been associated with a more favorable prognosis in most large series;[1,10,39,63,127,170,225] the fibrosarcomatous type carries the worst prognosis, and the mixed type is intermediate.[10,63,127] Younger age at diagnosis has also been reported as a favorable feature,[10,63] whereas no prognostic differences were found between men and women,[10,63,225] particularly after adjustment for cell type.[1,170] Absence of weight loss, lack of involvement of the visceral pleura, early stage, and epithelial cell type were shown to be favorable prognostic factors in a large group of 188 patients with pleural mesothelioma.[32] The negative prognostic impact of thrombocytosis first reported by Chahinian and colleagues[62] has been confirmed in three other series.[124a,225,226] The prognostic role of other factors (asbestos exposure or not, duration of symptoms, side of pleural disease, and pleural versus peritoneal involvement) is more contradictory at this time.

## OTHER TYPES OF MALIGNANT MESOTHELIOMAS

Mesotheliomas limited to other organs are extremely rare. About 120 cases of pericardial mesothelioma have been reported;[299] this represents the most frequent primary malignant tumor of the pericardium and accounts for half of them.[252] It has been reported at any age; there is a 3:1 male predominance.[275] The tumor produces signs of pericardial effusion, often bloody, leading to cardiac tamponade and/or constriction of the vena cava and great vessels. Local spread as well as metastases involving the pleura, lung, mediastinum, or distant organs occurs in half the cases.[267] Survival time is usually less than 6 months, although 2 patients treated with surgery and radiotherapy survived 1 and 5 years, respectively.[252] The role of asbestos exposure has not been systematically explored, although it was strongly suggested in one report.[24]

Malignant mesothelioma of the tunica vaginalis testis ("adenomatoid tumor") presents as a scrotal mass, often associated with a hydrocele. In a review of 24 cases, median age was 61 (range 21 to 78) years, and asbestos exposure was documented in 6.[8]

## BENIGN MESOTHELIOMAS

Benign mesotheliomas usually are not related to asbestos exposure. Solitary fibrous tumor of pleura is a neoplasm formerly referred to as benign fibrous pleural mesotheliomas. These fibrous tumors of the visceral or parietal pleura are often pedunculated and are unrelated to asbestos exposure. Pleural effusion is exceptional. Most are benign; although a malignant form does rarely occur. Clubbing and osteoarthropathy are common and are present in 20 to 50% of cases versus only 6% in malignant mesothelioma.[51] Hyponatremia attributed to inappropriate secretion of antidiuretic hormone and hypoglycemia have been described.[299] Surgery is curative. Microscopically, these tumors are well circumscribed fibromas with a variable collagenous matrix containing interweaving bundles of ovoid or spindle cells without atypia.[26]

Mesothelioma of the atrioventricular node is very rare (about 50 cases reported), usually minute or even microscopic.[299] Partial or complete nodal heart blocks and/or sudden death are the major consequences of this tumor, which has the distinction of being the "smallest one that can cause death."[299] Two thirds occurred in females, and age ranged from an 8-month-old fetus to an 86-year-old woman.[78]

Adenomatoid tumors are benign mesotheliomas arising in or near the male or female genital tract organs, although occasionally more distantly in the peritoneum.[74]

Benign multi-cystic peritoneal mesothelioma affects mainly young females and produces cysts of variable size and number lined by a single layer of benign mesothelial cells. The major differential diagnoses are lymphangioma and ovarian cancer of low malignant potential. The disease follows a benign course and is compatible with a normal life expectancy, requiring, occasionally, partial excision or decompression for relief of pain or other symptoms. The malignant potential is exceptional.[223,234,301]

## DIFFERENTIAL DIAGNOSIS

Benign asbestos pleurisy occurs in about 3 to 5% of asbestos workers.[49,95] Its latency period from first exposure is usually < 20 years, making it the earliest abnormality, compared with other asbestos-related pleural diseases, such as mesothelioma, pleural plaques, and pleural calcifications.[95] Typically, the effusion resolves spontaneously, but ipsilateral relapses are frequent, and contralateral disease may appear.[25,57] Almost two-thirds may be asymptomatic.[95] Confusion with malignant mesothelioma is common in view of a history of asbestos exposure and a bloody pleural fluid in the majority of cases. Pleural biopsy shows dense fibrosis with scattered nonmalignant cells. Close follow-up is necessary, since some patients have developed malignant mesothelioma 6 to 12 years after such an episode.[57,95]

Mesothelioma is now a common cause of "idiopathic" pleural effusion (Fig. 89.4). At the Mayo Clinic, it accounted for 8% (4 of 51) of all idiopathic pleural effusions and for 22% (4 of 18) of cases for which follow-up allowed a definite diagnosis.[230] Some patients with malignant mesothelioma give a history of recurrent pleural effusion for years before the diagnosis is made. It is often impossible in retrospect to attribute such cases to a slow-growing mesothelioma or a prior benign asbestos effusion. The frequent difficulties of cytologic diagnosis and differentiation from reactive benign mesothelial proliferation, as discussed above, further compound this important clinical problem. Any suspicion added to a history of asbestos exposure warrants an aggressive diagnostic approach, including thoracoscopy or open biopsy, if necessary.

It is difficult to distinguish malignant mesothelioma from other carcinomas and sarcomas. Confusion with a peripheral adenocarcinoma of the lung metastatic to the pleura or with pancreatic, gastrointestinal, or ovarian adenocarcinoma metastatic to the peritoneum or pleura is frequent, not only on frozen sections but also on fixed paraffin sections. Specials stains and analyses of effusions for hyaluronic acid can be particularly useful in these circumstances. Pleural implantation can also occur in invasive thymomas or lymphomas, and desmoid tumors can invade the abdominal or chest walls.

Another difficult problem is to classify the so-called papillary tumors of the peritoneum in women in the absence of an obvious primary tumor such as ovarian serous carcinoma.[137] Special stains for mucin are often negative and of little help. The exact nosologic classification of such tumors is still controversial. Different theories of histogenesis have led to various names, ranging from "papillary carcinoma" arising from embryonic peritoneal nests of Mullerian tissue to "ovarian mesothelioma" arising from the surface of the ovary.[137,193,204] Asbestos exposure is uncommonly found. The course of such tumors appears more protracted than the real diffuse peritoneal mesothelioma, and prolonged survival for years after palliative surgery, and sometimes chemotherapy, is another distinguishing feature which makes recognition of this entity clinically important.[79,204]

## TREATMENT

The lack of uniformity in approach and the small number of patients in most studies at present preclude standardization of the treatment of mesothelioma.

**Surgery** The role of surgery in managing diffuse pleural mesothelioma remains controversial, but there are an increasing number of thoracic oncologic surgeons who are operating for this disease. Nevertheless, overwhelming pessimism for curative surgical options continues in most centers that do not routinely deal with the disease, since the combination of effusive disease and bulky tumor renders surgical eradication virtually impossible. The disappointing long-term overall survival results, the historically high morbidity and mortality rates, as well as the propensity for local recurrences have forced many centers to abandon radical operations, except for the very rare localized situation. The arguments regarding appropriate management of mesothelioma can have geographic differences. This is illustrated in a United Kingdom poll of chest physicians regarding diffuse malignant mesothelioma (DMM). Only 46% of the physicians surveyed would consider referral to a thoracic surgeon for radical resection (Butchart, personal communication). The French approach to the disease has been a concentration on detection of early stage I disease that is treated with intrapleural therapy, including interferon-gamma (IFN-$\gamma$) with or without cisplatin.[36a] Surgery is performed after this therapy only to improve local control, either by pleurectomy or extrapleural pneu-

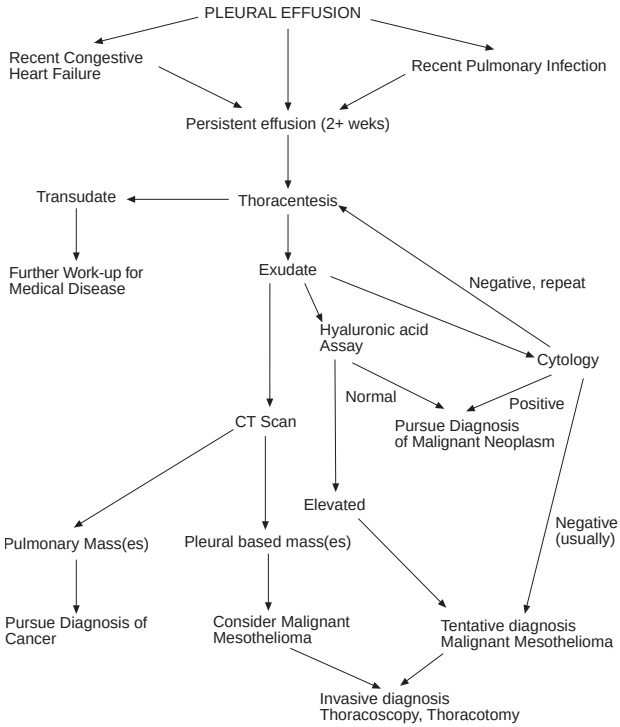


**Figure 89.4.** Pleural effusion algorithm.

monectomy (EPP). In patients with stage II or III mesothelioma, Boutin recommends surgery and postoperative radiation therapy. In the United States, a cohort of specialized cancer centers have evolved that have maintained an interest in the surgical management of the disease. In general, innovative, multi-modality protocols which incorporate surgery as part of the package are being explored in larger numbers of patients.

**Staging for Pleural Mesothelioma.** As described by Rusch,[229a] the staging systems prior to the International Mesothelioma Interest Group (IMIG) Staging System have "(been) to some extent imprecise and incompletely validated." The Butchart classification (Table 89.2) suffers from an absence of TNM descriptors, vague statements regarding lymph node involvement, and degrees of chest wall invasion. Chahinian[54,64a] was the first to devise a TNM-based mesothelioma staging system, with an attempt to qualify the influence of such parameters as loco-regional lymph node involvement and specific sites as well as the extent of invasion (Table 89.3).

The Union Internationale Contre le Cancer (UICC) proposed a TNM staging system that evolved into the presently described IMIG Staging system described by Rusch (Table 89.4). The IMIG staging system has only recently been available, but it has been validated in two large surgical series of mesothelioma.[195b,299] Sugarbaker has proposed the alternative but complementary Brigham Staging System based on tumor, resectability, and nodal status.[257a] In any evaluation for the patient with mesothelioma, careful attention must be paid to the diaphragmatic extent of the tumor with suspicious scans confirmed by laparoscopic evaluation for transdiaphragmatic extension.[71a]

There are now data that suggest that the most important preoperative prognostic indicator may be the T status of the patients. Tumor volumes associated with DMM patients who are found to have no spread to lymph nodes are significantly smaller than in those patients with positive nodes. Moreover, progressively higher IMIG stage is associated with higher median preoperative solid volume of tumor in DMM patients.[195b] Further studies verifying that preresection tumor volume is representative of T status in DMM and can predict overall and progression-free survival as well as postoperative IMIG stage are needed to complement metabolic imaging studies.

**Indications for Surgical Management.** Eiselberg[90a] is credited with the earliest resection of mesothelioma in a 46-year-old man, in whom he removed chest wall and a portion of lung, and much of the original interest in en bloc resection for diffuse malignant mesothelioma originated in Germany between 1920 and 1960. With advances both in surgery and anesthetic management, a more extensive resection that included the lung, pleura, and diaphragm became technically feasible.

Surgery is involved in the management of pleural mesothelioma either for diagnosis, palliative therapy, or as part of a multi-modal therapeutic plan. The operations involved in this management include thoracoscopy, pleurectomy/decortication or EPP. The indications for each of these operations will depend on the extent of disease, performance and functional status of the patient, and the philosophy of the treating institution. Basically, operative intervention in mesothelioma is for primary effusion control, for cytoreduction prior to multi-modal therapy, or to deliver and monitor innovative intrapleural therapies.

In general, the indications for palliative surgery include the control or prevention of effusion that results in disabling dyspnea. The most efficacious, and least invasive of the surgical procedures to accomplish effusion control is thoracoscopy with talc pleurodesis. Success rates in effusion control with talc, used either via thoracoscopy or via slurry, approach 90%. Failure of these techniques are usually associated with mesothelioma with entrapped lung, a large solid tumor mass, a long history of effusion with multiple thoracenteses leading to loculations, or age > 70 years. This technique is widely used, once the diagnosis of mesothelioma is made. Primary-care physicians, however, should carefully deliberate prior to the use of sclerosants and consider the extent of visceral and parietal pleural disease. The use of talc or other sclerosants could impact on the suitability for patients to enter innovative trials that incorporate either pleurectomy or EPP and could jeopardize the ability of the surgeon to spare a lung that may not have visceral pleural implants. The results of videothoracoscopic talc pleurodesis specifically for mesothelioma have shown success rates of 80 to 100% with median survivals ranging from 7 to 9 months, success being defined as no further need for tapping after 1 month.[43a,64b,279a] Patients who were able to have a successful pleurodesis had a significantly longer survival than those who did not, and success depended on the presence of trapped lung or degree of invasion of the pleura.

Effusion control via palliative surgery is occasionally attempted after lesser procedures (including sclerotherapy) have failed due to the inability of the lung to expand. Generally, the procedure of choice for such palliation is a pleurectomy, with or without decortication of the underlying lung. The use of EPP for palliative intent is only rarely described in the literature, and due to its morbidity and mortality, some surgeons state that EPP should never be used for palliative purposes.

The majority of patients seeking treatment for mesothelioma are middle to older aged individuals with a long latency period between asbestos exposure and tumor development. If surgical intervention is to be considered, a detailed physiologic-functional work-up, directed chiefly at the cardiopulmonary axis, must be performed. Poor underlying pulmonary function in patients with malignant mesothelioma usually reflects the burden of asbestos exposure, concomitant smoking history (up to 70% of the patients have had a heavy tobacco intake), and degree of lung trapped by tumor or fluid, and patient age. Cardiac evaluation is important as well. Operations for DMM are

**Table 89.2. Staging Proposed by Butchart et al.[40]**

| | |
|---|---|
| Stage I | Tumor confined within the "capsule" of the parietal pleura, i.e., involving only ipsilateral pleura, lung, pericardium, and diaphragm. |
| Stage II | Tumor invading chest wall or involving mediastinal structures, e.g., esophagus, heart, opposite pleura.<br>Lymph node involvement within the chest |
| Stage III | Tumor penetrating diaphragm to involve peritoneum.<br>Involvement of opposite pleura.<br>Lymph node involvement outside the chest. |
| Stage IV | Distant blood-borne metastases. |

associated with profound blood loss and potentially significant cardiac demands. The patient should be carefully screened for a history of hypertension, angina, previous myocardial infarction, and routine electrocardiograms should reveal no signs of previous injury.

**Rationale of Surgery.** It is difficult to imagine that any diffuse pleural mesotheliomas are amenable to en bloc removal. A small proportion of tumors called mesotheliomas may present as an encapsulated mass, not associated with pleural effusion, and these may be amenable to surgical extirpation with negative margins of resection. The majority of diffuse malignant mesotheliomas, however, cannot be surgically removed en bloc with truly negative histologic margins because many of the patients have had a previous biopsy and there is invasion of the endothoracic fascia and intercostal muscles at that site and/or there is pleural effusion which, although cytologically negative, may be breached, leading to local permeation of tumor cells, either into the residual cavity or into the abdomen. Nevertheless, it is encouraging that in the largest series of EPP performed for mesothelioma from the Boston group, 66 of 183 patients were defined as having negative resection margins after EPP. Patients with this finding who had epithelial mesothelioma were found to have 2- and 5-year survival rates of 68% and 46%, respectively, if the node dissection did not reveal tumor.[257a]

The operation of choice, especially for early pleural mesothelioma, has yet to be defined. There is no doubt that EPP is a more extensive dissection and may serve to remove more bulk disease than a pleurectomy, chiefly in the diaphragmatic and visceral pleural surfaces. Some surgeons, however, will include diaphragmatic resection and pericardial resection with their pleurectomies to accomplish removal of "all gross disease." For EPP, it is almost a necessity to include pericardiotomy, with or without resection, for the maneuver aids in the exposure of the vessels and allows intrapericardial control to prevent a surgical catastrophe. There are no real guidelines preoperatively that one can use to assure the patient which operation will be necessary to accomplish tumor removal. The presence of irregular, bulky disease, on the CT scan, that infiltrates into the fissures probably dictates the necessity for EPP; a large effusion with minimal bulk disease may call for pleurectomy decortication. Moreover, the philosophy of the surgeon regarding the operation may impact on his choice, for some surgeons reserve EPP for those patients with bulky disease that prevents simple pleurectomy, while others feel that the greatest chance for complete gross excision will be via EPP performed in the patient with minimal disease. This important factor—preoperative quantitative bulk of disease—may not only influence the choice or resection but may be an important preoperative prognostic factor in any patient with DMM, as described above.[195b]

**Pleurectomy.** When performed routinely, pleurectomy for mesothelioma can be associated with few major complications. In the series that specify postoperative morbidity, the most common complication was prolonged air leak for > 7 days, occurring in 10% of the patients. On average, the chest tubes can be removed in approximately 5.5 days with > 50% of the patients having the chest tube removed within 4 days. Pneumonia and respiratory insufficiency may occur and is usually related to the burden of disease and preoperative functional status. Empyema is a rare occurrence (2%) and is managed by prolonged chest tube drainage and antibiotics. Hemorrhage requiring reexploration is very rare (< 1%).

Earlier studies in patients requiring pleurectomy (but not having mesothelioma) had an in-hospital or operative mortality of 10 to 18% in the 1960s.[23b,131a] The modern-day mortality from pleurectomy has decreased and is generally considered to be 1.5 to 2%, with death either from respiratory insufficiency or hemorrhage. Most recently,

**Table 89.3. Staging Proposed by Chahinian[53,54]**

| | |
|---|---|
| Stage I | T1, N0, M0 |
| Stage II | T1-2, N1, M0 |
| | T2, N0, M0 |
| Stage III | T3, any N, M0 |
| Stage IV | T4, and N, M0, any M1 |

T = Primary tumor; T1 = Limited to ipsilateral pleura only (parietal pleura, visceral pleura); T2 = Superficial local invasion (diaphragm, endothoracic fascia, ipsilateral lung, fissures); T3 = Deep local invasion (chest wall beyond endothoracic fascia); T4 = Extensive direct invasion (opposite pleura, peritoneum, retroperitoneum); N = Lymph nodes; N0 = No positive lymph node; N1 = Positive ipsilateral hilar nodes; N2 = Positive mediastinal nodes; N3 = Positive contralateral hilar nodes. M = Metastases; M0 = No metastases; M1 = Metastases; blood-borne or lymphatic.

**Table 89.4. New International Staging System for Diffuse Malignant Pleural Mesothelioma**

**T1**

T1a Tumor limited to the ipsilateral parietal +/– mediastinal +/– diaphragmatic pleura
**No involvement of the visceral pleura**

T1b Tumor involving the ipsilateral parietal +/– mediastinal +/– diaphragmatic pleura
**Tumor also involving the visceral pleura**

**T2** Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of diaphragmatic muscle
- extension of tumor from visceral pleura into the underlying pulmonary parenchyma

**T3** Describes locally advanced but **potentially resectable** tumor
Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- involvement of the endothoracic fascia
- extension into the mediastinal fat
- solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall
- nontransmural involvement of the pericardium

**T4** Describes locally advanced **technically unresectable** tumor
Tumor involving all the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features:
- diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction
- direct transdiaphragmatic extension of tumor to the peritoneum
- direct extension of tumor to the contralateral pleura
- direct extension of tumor to mediastinal organs
- direct extension of tumor into the spine
- tumor extending through to the internal surface of the pericardium with or without a pericardial effusion; or tumor involving the myocardium

**N-Lymph nodes**

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Metastases in the ipsilateral bronchopulmonar or hilar lymph nodes
N2 Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes including the ipsilateral internal mammary nodes
N3 Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes

**M-Metastases**

MX Presence of distant metastases cannot be assessed
M0 No distant metastasis
M1 Distant metastasis present

| | |
|---|---|
| **Stage I** | |
| Ia | T1aN0 M0 |
| Ib | T1bN0 M0 |
| **Stage II** | T2 N0 M0 |
| **Stage III** | Any T3 M0 |
| | Any N1 M0 |
| | Any N2 M0 |
| **Stage IV** | Any T4 |
| | Any N3 |
| | Any M1 |

total pleurectomy performed in 50 patients for mesothelioma had a 30-day mortality of 2%. In a recent series of 39 pleurectomies, the hospital mortality was 0%.[195c]

Pleurectomy and decortication are very effective in controlling malignant pleural effusion. Law reports effusion control in 88% of patients having decortication for mesothelioma.[152] In 63 patients having partial decortication and pleurectomy, Ruffie[225] reported 86% control of effusion, and Brancatisano[37a] reported a 98% control of effusion after pleurectomy in 50 cases of pleural mesothelioma.

Many of the published series using pleurectomy for palliative management have added therapies postoperatively in an uncontrolled, institution-related fashion. The majority have had no sampling of the mediastinal nodes, little less a mediastinal dissection. Nevertheless, the overall median survival for patients having pleurectomy alone is approximately 13 months. The patients who receive pleurectomy and decortication alone usually have early effusive disease with minimal bulk tumor. If these patients have epithelial mesothelioma and are not found to have nodal involvement, survival rates can be significantly longer than that quoted above.

**Radical "Curative" Surgery: Extrapleural Pneumonectomy.** Radical EPP classically has been described for pure epithelial tumor, stage I that is technically resectable and encapsulated by the parietal pleura. Due to sampling error, it is impossible to clarify with 100% certainty whether the tumor is a pure epithelial type or mixed tumor on the basis of the preoperative or intraoperative biopsy.

The centers that are able to attract large numbers of mesothelioma patients due to ongoing prospective trials may be relaxing the so-called "classic indications" based on stage, age, and histology. Surgeons at these institutions are chiefly concerned with the patients' functional ability to tolerate the operation and the ability to accomplish maximal tumor debulking. If, indeed, higher-stage patients can undergo the operation with risks equal to pleurectomy-decortication, enthusiasm for its general incorporation in more aggressive adjunctive trials would be justified.

There are few patients who actually qualify for exploration outside the research setting. In Butchart's review, 29 of 46 or 63% of patients were eligible for EPP.[40] The only other series that reveals this percentage is DaValle's, where 33 of 56 patients over a 27-year period had EPP (59%).[96a] Sugarbaker has recently reported 50% of the patients seen at his institution are not eligible for EPP and adjuvant therapy. Unfortunately, these series really do not define why one patient may have a pleurectomy while another would have EPP, and it is obvious, however, that some institutions have simply never adopted the operation as feasible for treatment of the disease.

Probably the most enlightening study on eligibility was the Lung Cancer Study Group (LCSG) malignant mesothelioma pilot study from 1985 to 1988.[226] To be eligible for entry into the study the patient was required to have disease limited to the hemithorax by radiographic evaluation, a residual $FEV_1$ after resection of at least 1L/s and no significant cardiovascular illness—clearly more lenient criteria than those which limited eligibility due to age, histologic type, or presumed stage. Even with these "relaxed" criteria, only 20 of the 83 evaluated patients were resected with an EPP. The reasons that EPP could not be performed were chiefly extent of disease not allowing complete gross resection (54%), inadequate respiratory reserve (33%), stage IV disease (11%), and concurrent medical illness (10%).

Due to its magnitude, EPP has significantly greater morbidity than pleurectomy. The major complication rate ranges from 20 to 40%, and arrhythmia requiring medical management is the most common complication. In Sugarbaker's most recent report, major morbidity occurred in 24% of the patients having EPP and minor morbidity in 41%.[257a] The rate for bronchopleural fistula is greater with right-sided EPPs with an overall fistula rate of 3 to 20%. The bronchopleural fistula can be handled, for the most part, with open thoracostomy drainage with or without muscle flap interposition.

The mortality rates following EPP were unacceptably high in the 1970s with a 31% reported by Butchart.[40] Since then, however, there has been a steady decline in the operative mortality for the operation to consistent rates less than 10% in series of 20 or more patients. Mortality occurs chiefly in older patients from respiratory failure, myocardial infarction, or pulmonary embolus. Rusch[229] reported a perioperative mortality of 6% (3 of 50) after EPP and Sugarbaker reports a perioperative mortality of 3.8% from myocardial infarction and presumed pulmonary emboli.[257a]

Rusch[226] described sites of recurrence after EPP to be distant areas, compared with biopsy only or pleurectomy-decortication, and the local control was superior to that of the other modalities. Pass and colleagues[195c] also found a higher proportion of first sites of local recurrence seen in the pleurectomy population, compared with the patients having EPP. In Sugarbaker's series of patients, Baldini has reported that the sites of first recurrence were local in 35% of patients, abdominal in 26%, the contralateral thorax in 17%, and other distant sites in 8%.[19a]

Long-term survival rates after EPP remain disappointing with the median survivals ranging from 9.3 to 17 months for the majority series (Table 89.5). Rusch[229] reports a median survival of 10 months in her series of 50 EPPs, and the median survival of DMM patients having EPP (all histologies) in the National Cancer Institute (NCI) series is 9.4 months. The majority of patients were pathologic stage II or III in these two series. Most recently, Sugarbaker[257a] has reported a 17-month median survival in a series heavily weighted with stage I, epithelial patients (n = 52 of 183), using a multi-modality approach (see later) whose 2- and 5-year survivals were 68% and 46%, respectively. In the series by Rusch, the 2-year and 5-year survivals of stage I patients (n = 16 of 131) were 65% and 30%, respectively.

**Surgery and Multi-modality Treatment.** The Memorial Sloan-Kettering Cancer Center has been the leading institution for such technique, which includes as complete a parietal pleurectomy as possible to remove the bulk of the tumor followed by permanent (iodine 125, $I^{125}$) or temporary (iridium 192, $Ir^{192}$) implantation to deliver 3,000 cGy in 3 days to a 1-cm distance from the implant plane.[126] Radioactive phosphorus 32 ($P^{32}$) is selectively instilled intrapleurally 5 to 7 days after thoracotomy. This is followed by external beam radiation therapy commencing 4 to 6 weeks postoperatively using electrons and photons to deliver 4,500 cGy in 4.5 weeks. In their series, there was minimum morbidity in the 41 patients discussed and median survival was 21 months at the time of their report. The majority of patients had recurrences at distant sites (54%), with or without local recurrence. Unfortunately, there has been little follow-up information with regard to the ongoing status of these patients, as the median follow-up in 40% of the patients was 12 months or less at the time of the first report in 1984.

Surgery has been part of various multi-modality therapies. There has been interest in combining debulking surgery with intracavitary treatment of pleural mesothelioma (see below). At the Dana Farber Cancer Institute, beginning in 1980, a multi-modality program has evolved consisting of EPP, followed by two cycles of paclitaxel and carboplatin. Concurrent radiation to a dose of 40.5 Gy is given with weekly paclitaxel.[257a] Over a 19-year period, 183 patients were treated with a perioperative mortality of 3.8%. The median survival in this group of patients is approximately 17 months, which is a significant improvement over other trials. Favorable subgroups include those with no mediastinal nodal involvement and epithelial histology.

A large nonrandomized series in Germany[40b] has also shown some prolongation of life expectancy with multi-modal treatment, compared with best supportive care. The treated patients, however, were younger, had a better performance status at presentation, and had no medical contraindications to surgery. These 93 patients chose either best supportive care or multi-modal treatment. Surgery consisted of pleurectomy-decortication or EPP, followed by systemic chemotherapy with Adriamycin, cytoxan, and vindesine. Patients in remission at the end of the chemotherapy (16 of the 57 accrued) received 45 to 60 Gy of radiation therapy to the hemithorax. Median survival was 13 months, compared with 7 months for those receiving best supportive care.

Photodynamic therapy involves the light activated sensitization of malignant cells.[195d] From July 1993 to June 1996, at the NCI, Bethesda, 63 patients with localized DMM were randomized to surgery, with or without intraoperative photodynamic therapy (PDT) directed at the pleural space. All patients received postoperative immunochemotherapy with cisplatin, tamoxifen, and interferon. There

**Table 89.5. Results of Pleuropneumonectomy in Pleural Mesothelioma***

| Authors | Year | No Pts | % Mortality | % Morbidity | % Survival | | | Median Survival (mo) |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1 year | 2 year | 5 year | |
| Worn[307] | 1974 | 62 | NS | NS | NS | 37 | 10 | NS |
| Bamler & Maassen[20] | 1974 | 17 | 23 | NS | NS | 35 | | NS |
| Butchart, et al.[40] | 1976 | 29 | 31 | 43 | NS | 10 | 3.5 | NS |
| Ruffie, et al.[225] | 1989 | 23 | 14 | 24 | NS | 17 | | 9.3 |
| Harvey, et al.[120] | 1990 | 7 | 14 | NS | 28.5 | 28.5 | 28.5 | NS |
| Sugarbaker, et al.[255] | 1991 | 31 | 6 | 19 | 70 | 48 | | NS |
| Rusch, et al.[226] | 1991 | 20 | 15 | 40 | NS | 33 | | 10 |
| Allen, et al.[4] | 1994 | 40 | 7.5 | 30 | 52.5 | 22.5 | 10 | 13.3 |

*Adapted from Allen et al.[4]
NS = not specified.

were no differences in median survival (14.4 versus 14.1 months) or median progression-free time (8.5 versus 7.7 months), and sites of first recurrence were similar. These data revealed that aggressive multimodal therapy incorporating PDT can be delivered for patients with higher-stage DMM, but first-generation PDT does not prolong survival or increase local control for DMM.

Novel multi-modal approaches involving surgery are being developed, using such techniques as pleural perfusion of various chemotherapeutic and biologic agents,[205a] as well as gene therapy, as described below, and further reinforce the importance of surgery in the management of patients with DMM.

**Radiotherapy** Results of radiotherapy for pleural mesothelioma have been generally disappointing (Table 89.6). Conventional doses below 3,000 cGy have produced only temporary relief of symptoms in some cases, and doses in excess of 4,000 cGy are needed to achieve adequate palliation.[112] These doses are difficult to administer in view of the large tumor volume, including the entire hemithorax, diaphragm, and adjacent mediastinum. In one such trial using anterior and posterior portals, 14 patients with pleural mesothelioma were treated with a total of 3,500 to 7,500 cGy (mean 4,500) by three sessions of 330 cGy each per week. Tolerance was reported to be good and pain was controlled. Survival ranged from 1 to 41 months (median 15 months).[96] In another trial, 14 patients were similarly treated with 4,000 to 6,000 cGy. Chest pain disappeared in 10 patients, but survival remained short (mean 10 months).[288] The results of "radical" radiotherapy, however, were almost identical to those of palliative radiotherapy at the Dana Farber Cancer Institute in Boston.[112] Elaborate techniques, such as combined photon and electron beams, use of various blocks, and tissue compensators to shield the lung, have not convincingly yielded superior results.[2] Complex treatment plans using CT scans to include the entire pleura down to the base of the diaphragm have been proposed to deliver up to 4,250 cGy by parallel opposed fields with lung and liver blocks, supplemented with electrons up to 3,600 cGy.[147] The fissures which are commonly involved may not be adequately treated, however. One case treated with fast neutron therapy has remained free of recurrence for over 78 months.[27]

Combining radiotherapy with concomitant chemotherapy using procarbazine, doxorubicin, or cyclophosphamide did not clearly improve response or survival (see Table 89.6), although, again, the lack of randomized trials precludes any firm conclusions. The combined use of surgery (palliative pleurectomy) supplemented by brachytherapy of gross residual disease with $I^{125}$, $Ir^{192}$, or $p^{32}$ followed by external radiation up to 4,500 cGy in 4.5 weeks has been evaluated at the Memorial Sloan-Kettering Cancer Center.[176] Actuarial results in 41 cases, 17 of them still alive, showed an estimated median survival of 21 months and a projected 2-year survival of 40%.[126] The median disease-free survival, however, was only 11 months. The use of local radioactive colloidal gold ($^{198}Au$) in the treatment of pleural effusions has been summarized for a total of 18 cases of mesothelioma, with some long-term control of 3.5 to 11 years in a few of them.[155] It is suitable only in early disease, since its penetration is, at most, 2 to 3 mm only.

In peritoneal mesothelioma, occasional long-term survivors have been described after radiotherapy. In one report, four cases were treated with intraperitoneal instillation of 10 mCi of $^{32}P$ followed by 1,000 to 3,000 cGy to the entire abdomen in 3 to 4 weeks.[220] An additional dose of 1,000 to 2,500 cGy was given to the pelvis in 2 to 3 weeks. Three patients also received chemotherapy (cyclophosphamide, with or without vincristine). Two of these patients survived more than 10 years. The local use of $^{198}Au$ has been reported in 10 cases of peritoneal mesothelioma, with resolution of ascites lasting 2.5 to 51 years in some.[155]

**Chemotherapy** **Single Agents.** Mesothelioma is notorious for its resistance to many chemotherapeutic agents. Possible mechanisms of resistance have implicated overexpression of the multi-drug resistance–associated protein (MRP) and of gamma-glutamylcysteine synthetase rather than P-glycoprotein .[190a]Trials of single agents are summarized in Table 89.7. In large series, response rates to single agents rarely exceed 20%, with few, if any, complete responses. These results are in general agreement with those obtained in a nude mouse model of human mesothelioma.[56,60,61] The most widely tested agents include anthracyclines (doxorubicin, epirubicin) and platinum analogues (cisplatin, carboplatin); response rates are 12 to 15%. Response rates to

**Table 89.6. Radiotherapy (RT) Trials in Malignant Mesothelioma**

| No Cases | RT Total Dose - Gy (range) | Concomitant Therapy | Objective Responses | Survival Median (range) (mo) | Authors (ref.) |
|---|---|---|---|---|---|
| 14 | 45 (35–75 | — | — | 15 (1–41+) | Eschwege et al.[96] |
| 14 | variable (40–60) | — | — | 10* (4–24) | Voss et al.[288] |
| 14 | 25 (17–26) | Doxorubicin | 1 CR, 2 PR | 10 | Chahinian et al.[63] |
| 10 | 40 (10–40) | Doxorubicin | 1 PR, 2 IMP | 11 (5–27) | Sinoff et al.[241] |
| 8 | "radical" (22–56) | — | — | 12 (6–60+) | Gordon et al.[112] |
| 19 | "palliative" (8–57) | — | — | 12 (3–60) | |
| 13 | (40–80) | None | 1 CR, 1 PR | 7.8 | Alberts et al.[2] |
| 10 | 40 | Doxorubicin | 0 | 22.6 | |
| 14 | (40–80) | Procarbazine | 2 PR | 10.9 | |
| 33 | (15–45) | Cyclophosphamide | 3 CR, 24 PR/IMP | 10.8 | |
| 61 | (15–45) | Combinations | 5 CR, 15 PR | 7.9 | |

CR = complete response; PR = partial response; IMP = improvement (< 50% response or regression of evaluable but not measurable disease).

doxorubicin, which ranged from 0 to 100% in various trials at doses of 50 to 75 mg/m$^2$, do not appear to be dose related. The response rate decreases with increasing number of patients, and the value of that agent is now modest, despite early encouraging results.[146,310] A higher dose of doxorubicin (90 mg/m$^2$ divided over 3 consecutive days) with the addition of external radiotherapy combined with half-dose doxorubicin during cycle 2, yielded a 21% response rate (1 complete response [CR] and 2 partial responses [PRs]) in 14 patients with pleural mesothelioma and no response in 2 patients with peritoneal mesothelioma.[63] The high response rate reported for detorubicin, an analogue of doxorubicin, needs confirmation.[70] High doses of cisplatin (80 mg/m$^2$ weekly for six courses, or 40 mg/m$^2$/d for 5 days) appear to produce more partial responses than regular doses of that agent but no complete response. The activity of mitomycin, initially discovered in a nude mouse model,[61] has been confirmed clinically.[19] Paclitaxel (Taxol) has so far shown only modest activity, but these results are preliminary. Dihydro-5-azacytidine was evaluated in mesothelioma because of its selective toxicity for serosal membranes leading to pleuritis and pericarditis. Its activity as a single agent and combined with cisplatin has been low, however (see Tables 89.7 and 89.8). Vinca alkaloids (vinblastine, vincristine, vindesine) and mitoxantrone have virtually no activity, but a recent trial of vinorelbine showed a 21% response rate.[251a] The antifols (methotrexate, edatrexate, trimetrexate) seem to show activity. Results with high-dose methotrexate need confirmation. An apparently active new agent is the novel experimental multi-targeted antifolate (MTA LY231514), which produced 4 responses among 7 patients with mesothelioma and is currently being evaluated in combination with cisplatin.[266a] Results with the taxane drugs as single agents have been disappointing. Onconase is a ribonuclease isolated from the eggs of the leopard frog and has been reported to produce 4 partial responses in 25 patients with mesothelioma.[71b] A randomized trial is currently underway prospectively comparing that agent with doxorubicin.

Some successes have occasionally been observed with the use of 5-fluorouracil (5-FU), oral melphalan,[178] methyl glyoxalbisguanylhydrazone,[58] and prolonged oral etoposide,[243] although a large trial of oral or intravenous etoposide yielded a low response rate of 6%.[230a]

Few complete responses are seen with single agents, and median survival when reported, is usually between 6 to 9 months from treatment. Search for more active agents is needed by using all the available clinical and experimental resources. An in vitro chemosensitivity assay revealed that actinomycin D was the most effective of eight cytotoxic drugs tested, but clinical correlation is lacking at this time.[37]

**Combination Chemotherapy.** Combination chemotherapy is difficult to evaluate, since data on the single agent components are still scarce. Results compiled in Table 89.8 reveal that in most series including more than 10 patients, overall response rates remain below 30%, again with few complete responses. There is no evidence that doxorubicin combinations are superior to doxorubicin alone or to regimens without doxorubicin. Sarcoma-type regimens with doxorubicin combined with dacarbazine (DTIC) or with cyclophosphamide, vincristine, and dacarbazine (Cyvadic) have been disappointing. The combination of mitomycin (M) and cisplatin (C) discovered to be effective in a nude mouse model[61] has been active in a randomized phase II trial by the Cancer and Leukemia Group B (CALGB),[55] where it showed a somewhat higher response rate (26%) than doxorubicin with cisplatin (14%) but no survival advantage. Addition of a third drug to the CM combination included agents such as doxorubicin or vinblastine or interferon-alpha (IFN-α), with no clear-cut benefit. Recently, a four-drug combination, including cisplatin, mitomycin, 5-FU, and (VP16) resulted in 38% partial responses among 45 patients in France, with a median survival of 16 months.[138a] Other doublets using cisplatin combined with a newer agent have yielded results which are remarkable, although still preliminary. In Australia, the combination of gemcitabine and cisplatin yielded a partial response rate of 47.6% in 21 patients, a median survival of 41 weeks, and an estimated 1-year survival of 41%.[40a] Nine of the 10 responses were seen in 13 patients with the epithelial subtype. In Japan, the combination of irinotecan (CPT-11) with cisplatin produced a 40% partial response rate in 15 patients (see Table 89.8).[188a] Pharmacokinetic studies of CPT-11 and of its active metabolite SN-38 in the pleural fluid showed steady state with plasma levels after 6 hours, except in epithelial mesothelioma, where pleural fluid levels of SN-38 were much higher than in plasma. Interestingly, all responses, except one, were seen in the 10 patients with the epithelial type. Some prolonged responses have also been reported with doxorubicin plus 5-azacytidine,[63] methyl CCNU, and actinomycin D[311]; CAP (cyclophosphamide, doxorubicin, cisplatin); and mitomycin plus fluorouracil.[272] A response rate of 53% (9 of 17) was reported with methotrexate and vinblastine.[128a] Eight of the 9 responders also received cisplatin. Preliminary results with a combination of paclitaxel and carboplatin have shown responses.[25a] Thus, despite low overall response rates, therapeutic abstention is not justified. Better still is to include patients in formal clinical trials.

**Intracavitary Chemotherapy.** Intracavitary cisplatin at doses of 90 to 100 mg/m$^2$ with intravenous thiosulfate resulted in 1 response among 8 patients with pleural mesothelioma; among 13 patients with peritoneal mesothelioma, there were 1 CR, 2 PRs, and reduction of ascites in 6 cases.[165,198] In 5 patients with early peritoneal mesothelioma, a combined modality approach, with cytoreductive surgery, intraperitoneal doxorubicin plus cisplatin, and external whole-abdomen radiotherapy up to 30 Gy, resulted in survival of more than 18 months.[9] The intraperitoneal combination of mitomycin and cisplatin was effective in controlling ascites in 6 of 11 patients with peritoneal mesothelioma; 2 patients were without evidence of recurrent disease in the peritoneal cavity for more than 32 and 41 months, respectively.[166] A similar regimen in patients with pleural mesothelioma treated with surgery followed by mitomycin and cisplatin, first intrapleurally, then systemically, resulted in a median survival time of 17 months in 27 patients in one trial[228] and 13 months in 19 patients in another trial.[210] Recently, activity was reported with the use of the liposomal cisplatin L-NDDP.[195f] The exact role of intracavitary chemotherapy and of intracavitary irradiation remains to be defined by prospective trials.

**Biologic and Other Therapies** Human recombinant IFN-α was first shown to potentiate the effect of chemotherapy (cisplatin or mitomycin) in a nude mouse model of mesothelioma.[242] Preliminary results in patients suggest that IFNs may have some activity against mesothelioma. Recombinant human IFN-α given intrapleurally was reported to produce 2 partial responses in 13 patients with pleural mesothelioma.[67] The combination of cisplatin and IFN-α given systemically produced a 32% response rate in 37 patients with pleural mesothelioma.[269] Another trial of weekly systemic administration of cisplatin and IFN-α produced 1 CR and 4 PRs in 13 patients.[201a] Another regimen combining systemic cisplatin and IFN-α with the addition of tamoxifen resulted in a 21% response in 34 patients,[195] while the addition of mitomycin resulted in a 23% response rate in 43 patients.[180a] Intrapleural human recombinant IFN-γ was recently found to be active in early mesothelioma where pleural nodules measure < 5 mm. Four CRs and 1 PR were seen in 9 patients with stage I mesothelioma, versus only 1 PR in 10 patients with stage II disease.[34] A larger trial in 89 patients yielded an overall response rate of 20%, with 45% for stage I disease.[36] IFN-γ has also been active in vitro against human mesothelioma cell lines.[37] On the other hand, IFN-β produced no response in 14 patients with mesothelioma.[287]

Similarly, the effects of IL-2 and LAK cells on immunologic abnormalities secondary to asbestos exposure or mesothelioma, as discussed above, provide a rationale for the clinical trial of such immunotherapy. Preliminary reports of the effect of intrapleural IL-2 showed 4 partial remissions in 17 patients with mesothelioma, with acceptable toxicity,[90,266] and another report in 22 cases showed 1 CR and 11 PRs.[16a]

Further evaluation of these biologic treatments, alone and in combination with chemotherapy, is warranted. Interesting experimental observations in transplanted human mesothelioma in nude mice include "cure" by injecting mice with diphtheria toxin,[205] and decreased tumor growth by photodynamic therapy,[98] which has also been effective in vitro against human mesothelioma cells.[139] Prelimi-

**Table 89.7. Single-Agent Chemotherapy in Malignant Mesothelioma***

| Agent | Dose mg/m2 | No PTS | No CR | No PR | Total Resp | Resp. Rate (%) | Med. Surv. (mo) | Ref. |
|---|---|---|---|---|---|---|---|---|
| Acivicin | 20 × 3 | 19 | 0 | 0 | 0 | 0 | — | 2 |
| | 20 × 3 | 21 | 0 | 0 | 0 | 0 | 7 | 97 |
| | — | 3 | 0 | 0 | 0 | — | — | 249 |
| Total | | 43 | 0 | 0 | 0 | 0 | | |
| Aclacinomycin-A | 85–100 | 10 | 0 | 1 | 1 | 10 | — | 88 |
| Amsacrine | 120 | 17 | 0 | 1 | 1 | 6 | — | 2 |
| 5-Azacytidine | 100–150 | 3 | 0 | 2 | 2 | — | — | 286 |
| | 100–150 | 3 | 0 | 0 | 0 | — | — | 63 |
| Total | | 6 | 0 | 2 | 2 | 33 | | |
| Bleomycin | 20 | 19 | 0 | 2 | 2 | 11 | — | 5 |
| | 15 × 5 | 3 | 0 | 0 | 0 | — | — | 63 |
| Total | | 22 | 0 | 2 | 2 | 9 | | |
| CB3717[†] | 300–400 | 17 | 0 | 1 | 1 | 6 | — | 44 |
| Carboplatin | 400 | 9 | 0 | 2 | 2 | 22 | — | 45 |
| | 300–400 | 17 | 1 | 1 | 2 | 12 | — | 174 |
| | 150 × 3 | 31 | 1 | 4 | 5 | 16 | 8 | 203 |
| | 400 | 40 | 0 | 3 | 3 | 8 | 7 | 282 |
| Total | | 97 | 2 | 10 | 12 | 12 | | |
| Chlorozotocin | 150 | 10 | 0 | 0 | 0 | 0 | — | 5 |
| Cisplatin | 15 × 5 | 6 | 1 | 0 | 1 | 17 | — | 231 |
| | 100 | 9 | 1 | 0 | 1 | 11 | 12[‡] | 75 |
| | 120 | 24 | 0 | 3 | 3 | 13 | 5 | 181 |
| | 100 | 35 | 0 | 5 | 5 | 14 | 7.5 | 314 |
| Total | | 74 | 2 | 8 | 10 | 14 | | |
| Cisplatin high-dose | 40/d × 5 | 12 | 0 | 3 | 3 | 25 | | 207 |
| | 80/wk × 6 | 14 | 0 | 5 | 5 | 36 | | 199 |
| Cyclophosphamide | 1,500 | 21 | 0 | 0 | 0 | 0 | — | 245 |
| | 2,500 | 13 | 0 | 3 | 3 | 23 | 6 | 6 |
| Total | | 34 | 0 | 3 | 3 | 9 | | |
| Cycloleucine | § | 7 | 0 | 2 | 2 | 29 | — | 156 |
| Detorubicin | 40 × 3 | 21 | 2 | 7 | 9 | 43 | 17 | 70 |
| Dihydro-azacytidine | 5,000 | 12 | 0 | 0 | 0 | 0 | 6.2 | 81 |
| | 1,500 × 5d | 41 | 1 | 6 | 7 | 17 | 6.7 | 285a |
| | 1,500 × 5d | 51 | 0 | 2 | 2 | 4 | 4 | 23a |
| Total | | 104 | 1 | 8 | 9 | 9 | | |
| Docetaxel | 100 | 20 | 0 | 1 | 1 | 5 | | 26a |
| Don[#] | 50 × 5 | 7 | 0 | 0 | 0 | 0 | | 88 |
| Doxorubicin | 50 | 5 | 2 | 3 | 5 | 100 | — | 146 |
| | 70 | 5 | — | — | 1 | 20 | — | 235 |
| | 60–75 | 8 | 2 | 0 | 2 | 25 | — | 2829 |
| | — | 11 | 0 | 1 | 1 | 9 | — | 283 |
| | 60 | 21 | 0 | 0 | 0 | 0 | — | 245 |
| | 60–70 | 51 | 2 | 5 | 7 | 14 | 7.5 | 156 |
| Total | | 112 | 6 | 10 | 17 | 15 | | |
| Diaziquone | 25–30 | 20 | 0 | 0 | 0 | 0 | 6 | 87 |
| Docetaxel | 20 | | | | | 5 | | |
| Edatrexate | 80 | 20 | 1 | 4 | 5 | 25 | — | 26 |
| Epirubicin | 110 | 48 | 0 | 7 | 7 | 15 | 10 | 173 |
| | 75 | 21 | 0 | 1 | 1 | 5 | 7.5 | 163 |
| Total | | 69 | 0 | 8 | 8 | 12 | | |
| Etoposide | 150 × 3 IV | 47 | 0 | 2 | 2 | 4 | 7 | 230a |
| | 100/d PO* | 41 | 0 | 3 | 3 | 7 | 9.5 | |
| Total | | | 88 | 0 | 5 | 5 | 6 | |
| Fluorouracil | ‖ | 3 | 2 | 0 | 2 | — | — | 107 |
| | | 2 | 2 | 0 | 2 | — | — | 129 |
| | ** | 20 | 0 | 1 | 1 | 5 | 7 | 120 |
| Total | | 25 | 4 | 1 | 5 | 20 | | |
| Gemcitabine | 1250/wk × 3 | 27 | 0 | 2 | 2 | 7 | 8 | 276a |
| Ifosfamide | 1,200 × 5 | 17 | 0 | 4 | 4 | 24 | 9 | 3 |
| | 2,000 × 4 | 26 | 0 | 2 | 2 | 8 | 6.5 | 315 |
| | 3,000 × 3 | 26 | 0 | 1 | 1 | 4 | 10 | 5a |
| Total | | 69 | 0 | 7 | 7 | 10 | | |
| Methotrexate | †† | 9 | 0 | 4 | 4 | 44 | 13 | 84 |
| | ‡‡ | 60 | 1 | 21 | 22 | 37 | 11 | 244a |
| Mitomycin | 10 | 19 | 0 | 4 | 4 | 21 | — | 19 |
| Mitoxanthrone | 12 | 28 | 1 | 1 | 2 | 7 | — | 92 |
| | Phase 1 | 2 | 0 | 0 | 0 | — | — | 111 |
| | 14 | 34 | 0 | 1 | 1 | 3 | — | 274 |
| Total | | 64 | 1 | 2 | 3 | 5 | | |

continued on next page

**Table 89.7. continued**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Paclitaxel | 250/24h | 35 | 0 | 3 | 3 | 9 | 5 | 285 |
| | 200/3h | 25 | 0 | 0 | 0 | 0 | 10 | 276 |
| Total | | 60 | 0 | 3 | 3 | 5 | | |
| PCNU | 60–90 | 34 | 0 | 0 | 0 | 0 | 3.8 | 300 |
| Pirarubicin | 35–70 | 8 | 1 | 2 | 3 | 38 | 6.5 | 248 |
| | 70 | 35 | 0 | 3 | 3 | 9 | 10.5 | 135 |
| Total | | 43 | 1 | 5 | 6 | 14 | | |
| Topotecan | 1.5/d × 5 | 22 | 0 | 0 | 0 | 0 | 7.5 | 163a |
| Trimetrexate | 6 | 17 | 0 | 2 | 2 | 12 | 5 | 284 |
| | 10 | 34 | 0 | 4 | 4 | 12 | 8.9 | 284 |
| Total | | 51 | 0 | 6 | 6 | 12 | | |
| Vinblastine | 1.4 × 5 | 20 | 0 | 0 | 0 | 0 | 3 | 73 |
| Vincristine | 1.3 | 23 | 0 | 0 | 0 | 0 | 7 | 172 |
| Vindesine | 3 | 17 | 0 | 1 | 1 | 6 | — | 140 |
| | 2 × 2 | 21 | 0 | 0 | 0 | 0 | — | 30 |
| Total | | 38 | 0 | 1 | 1 | 3 | | |
| Vinorelbine | 30 | 19 | 0 | 4 | 4 | 21 | — | 251a |

*Single case reports excluded
† CB3717 = N10-propargyl-5,8 dideazafolic acid
‡ mean (not median)
§ 300mg/kg/d × 8 days
# DON = 6-diazo-5-oxo-L-norleucine
| variable doses (Gerner)
**10–15 mg/kg × 5 days IV bolus
††18–50 g with leucovorin
‡‡ 3 g with leucovorin every 10 days × 4
No PTS = number of patients; CR = complete response; PR = partial response; RESP = response; MED SURV = median survival (mo = months)

nary clinical application of this technique has been reported in mesothelioma patients by administration of a photosensitizer followed by exposure of the tumor to a laser light of appropriate wavelength, either during thoracotomy,[194] or by thoracoscopy.[160] A median survival time of 12 months was observed in 23 patients with pleural mesothelioma treated with surgery and intracavitary photodynamic therapy.[263] Attempts at inhibiting the effects of growth factors, such as PDGF, are being explored with the use of antisense oligonucleotides.[105]

Gene therapy has been successful against human mesothelioma cell lines by transfer of the herpes simplex virus thymidine kinase (hsvtk) with an adenovirus vector, followed by treatment with ganciclovir (GCV).[244] Initial clinical trials with such intrapleural gene therapy in 26 patients at the University of Pennsylvania showed dose-dependent detectable gene transfer in 17 patients, and the maximum tolerated dose was not reached.[252a] One patient with early disease remained without evidence of recurrence in a period of 31 months. One partial response and 3 disease stabilizations were observed.[252a] The median survival was 11 months among the 18 patients who died. A similar approach is under investigation at Louisiana State University. In in vitro mixing experiments, gene-modified ovarian tumor cells killed both mouse and human mesothelioma cells in a dose-dependent manner. Use of the ovarian HSV-TK ovarian cells also prolonged survival of mice with DMM in a dose-dependent fashion. These data have served as the basis for an ongoing phase I clinical gene therapy trial to determine the maximal tolerated dose of an HSV-TK–transduced ovarian cancer cells infused into the pleural cavities of mesothelioma patients followed by systemic administration of GCV.[235a] Another trial of gene therapy in Perth, Australia, has used a vaccinia virus producing Il-2, with no response among the first six patients treated.[252a]

## PROSPECTUS AND PREVENTION

Much research remains to be conducted on mesotheliomas to achieve earlier diagnosis and better treatment of these increasingly frequent neoplasms. The use of a consistent staging system would allow a better evaluation of therapeutic results, particularly for surgery. Further research into the chemotherapy of mesothelioma is warranted, since tumor responses and even complete remissions have already been obtained. Transplanting a rare tumor, such as malignant mesothelioma, into nude mice provides a useful model to evaluate many agents of as yet unknown clinical activity.[56] Correlation between results in that model and clinical experience appears quite good, as shown for agents such as mitomycin, cisplatin, carboplatin, and IFN-α, alone and in various combinations.[61,242] Such correlation has also been shown by direct patient–xenograft comparisons.[60,61] The effects of biologic agents (i.e., IFN, IL-2), alone or with chemotherapy, and of combined modalities, including cytoreductive surgery followed by radiotherapy and/or chemotherapy, deserve further trials.

Meanwhile, preventive measures that attempt to eliminate or at least reduce asbestos pollution are mandatory, with the use of safer and alternative materials for construction, insulation, and other consumer and industrial applications, and by dust control and personal protection. The spraying of asbestos fireproofing was banned in New York in 1972. Dust control has been enforced in the United States by the Occupational Health and Safety Administration.[238] The efficacy of these safety standards has been subject to criticism, since the dose-response relationships of the oncogenic effects of asbestos are not fully established, at least for mesothelioma, for which there appears to be no safe threshold of exposure. Tight encapsulation of friable asbestos in buildings is a necessary measure and often more feasible than costly alternatives, such as total removal.

For individuals who have already been exposed, prophylactic measures could be considered. A synthetic vitamin A analogue, retinyl methyl ether, has been shown to prevent asbestos-induced hyperplasia and squamous metaplasia of hamster tracheal cells in organ culture.[184] Retinoids can reverse these cytologic changes even when administered after their occurrence.[41] Alpha-difluoromethyl ornithine (DFMO), an irreversible inhibitor of ornithine decarboxylase (ODC), has a similar effect, suggesting that this effect is mediated by depletion of polyamines.[41] The role of antioxidant enzymes, such as catalase, has been evaluated for their potential in reducing pulmonary asbestosis or asbestos-stimulated induction of ODC.[169] The prophylactic potential of such compounds may be most useful in asbestos-induced lung cancer rather than in mesothelioma, but clinical trials are necessary to clarify their potential. The increasing knowledge of gene products and growth factors implicated in the genesis of mesothelioma may lead to novel therapeutic and preventive measures, and the study of serum tumor markers such as hyaluronic acid may provide useful tools for screening and early detection in populations at risk.

**Table 89.8. Combination Chemotherapy in Malignant Mesothelioma***

| Regimen | No PTS | CR | PR | OBJ Resp | Resp Rate | Med Surv (mo) | Ref. |
|---|---|---|---|---|---|---|---|
| DOX+DDP | 6 | 1 | 3 | 4 | 67% | 18.5 | 316 |
| DOX+DDP | 19 | 2 | 6 | 8 | 42% | 12 | 123 |
| DOX+DDP | 24 | 0 | 6 | 6 | 25% | 10 | 15 |
| DOX+DDP high dose | 4 | 2 | 1 | 3 | — | | 253 |
| DOX+DDP vs. | 35 | 0 | 5 | 5 | 14% | 8.8 | |
| MITO+DDP | 35 | 2 | 7 | 9 | 26% | 7.7 | 55 |
| MITO+DDP | 12 | 1 | 3 | 4 | 33% | – | 61 |
| GEM+DDP | 21 | 0 | 10 | 10 | 48% | 10 | 40a |
| CPT-11+DDP | 15 | 0 | 6 | 6 | 40% | 7 | 188a |
| DOX+DTIC | 7 | 0 | 3 | 3 | 43% | — | 114 |
| DOX+MeCCNU | 5 | 1 | 0 | 1 | 20% | — | 213 |
| DOX+AZA | 28 | 2 | 5 | 7 | 25% | 13 | 63 |
| DOX+CYC[†] | 11 | 0 | 1 | 1 | 9% | 7 | 12 |
| DOX+IFF | 16 | 0 | 2 | 2 | 13% | 8 | 47 |
| EPI+IFF | 17 | 0 | 1 | 1 | 6% | — | 162 |
| HDMTX+VCR | 9 | 3 | 3 | 6 | 67% | 10 | 82 |
| HDMTX+DDP | 6 | 0 | 4 | 4 | 67% | — | 84 |
| RBZ+DTIC | 23 | 0 | 0 | 0 | 0% | — | 313 |
| VP16+DDP | 26 | 0 | 3 | 3 | 12% | — | 91 |
| VBL+DDP | 20 | 1 | 4 | 5 | 25% | — | 270 |
| 5FU+DDP | 4 | 0 | 0 | 0 | — | — | 63 |
| DHAC+DDP | 29 | 0 | 5 | 5 | 17% | 6.4 | 233 |
| PACLITAXEL+CBDCA | 7 | 0 | 4 | 4 | 57% | — | 127a |
| PACLITAXEL+CBDCA | 7 | 1 | 1 | 0 | 29% | 12 | 25a |
| DOX+DTIC or DOX+CYC+VCR | 24 | 0 | 2 | 2 | 8% | — | 156 |
| DOX+CYC vs DOX+CYC+DTIC[‡] | 76 | 3 | 6 | 9 | 12% | — | 232 |
| DOX+CYC+DTIC | 14 | 0 | 5 | 5 | 36% | — | 11 |
| DOX+CYC+MTX | 11 | — | — | 1 | 9% | — | 201 |
| DOX+CYC+VCR | 8 | 0 | 0 | 0 | 0% | — | 99 |
| DOX+CYC+VCR | 7 | 0 | 0 | 0 | 0% | — | 152 |
| DOX+CYC+VCR vs. | 4 | — | — | 1 | — | — | |
| DOX+CYC+DDP | 23 | 0 | 7 | 7 | 23% | 15 | 240a |
| ACT+CYC+VCR | 2 | 0 | 0 | 0 | — | — | 235 |
| CYC+MTX+DDP | 9 | 0 | 1 | 1 | 11% | — | 63 |
| DOX+DDP+VDS | 11 | 0 | 0 | 0 | 0% | 8 | 188 |
| DOX+MITO+DDP | 23 | 0 | 5 | 5 | 22% | 11 | 195e |
| MITO+VBL+DDP | 39 | 0 | 8 | 8 | 20 | — | 180b |
| CYC+VCR+ACT _ DOX | 29 | 1 | 3 | 4 | 14% | 8.8 | 2 |
| CYC+VCR+MTX+5FU | 4 | 1 | 2 | 3 | — | — | 146 |
| CYVADIC | 4 | 0 | 2 | 2 | — | — | 115 |
| CYVADIC | 8 | — | — | — | [§] | 11 | 246 |
| CAMEO | 12 | 0 | 2 | 2 | 17% | 6.5 | 132 |
| DOX+DDP+MITO+BLEO[#] | 27 | 2 | 10 | 12 | 44% | 15 | 38 |
| MITO+DDP+5FU+VP16 | 45 | 0 | 17 | 17 | 38% | 16 | 138a |

*Single case reports excluded; vs refers to randomized trials, or refers to combined results.

[†] Peritoneal mesothelioma only

[‡] Combined results for both regimens. Response to DOX+CYC=11% and to DOX+CYC+DTIC=13%.

[§] No measurable disease

[|] With hyaluronidase

(see also Table 89-7.)

ACT= actinomycin D; AZA= 5 azacytidine; CYC=cyclophosphamide; DHAC= dihydro-azacytidine; DDP= cisplatin; DOX= doxorubicin; DTIC= 5-aminoimidazole 4-carboxamide (dacarbazine); EPI= epirubicin; 5-FU= 5-fluorouracil; HDMTX= high-dose methotrexate with leucovorin; IFF= ifosfamide; MeCCNU= methyl CCNU; MITO= mitomycin; RBZ= rubidazone; VCR= vincristine; VP16= etoposide; CYVADIC=CYC+VCR+DOX+DTIC; CAMEO= CYC+DOX+MTX+VP16+VCR.

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