Patients generally die of respiratory failure after a median survival of 6-18 months in various series (range: weeks to 16 years). Anition and small bowel obstruction from direct extension through the diaphragm develop in about one third. Cardiac complications of pericardial or myocardial involvement result in a smaller percentage of deaths. Younger age, 0-1 performance status, epithelial histology, lack of chest pain at diagnosis, and therapy with pleuropneumonectomy and chemotherapy are associated with a significantly longer survival (Tables 1 and 2).

**STAGING**

While multiple staging systems for malignant mesothelioma have been published (Table 3), none reproducibly predicts survival with statistical significance. Obstructive spirometric changes are unrelated to mesothelioma or asbestosis. Pulmonary function tests may document restrictive lung disease resulting from encasement of the lung and assess the feasibility of pneumonectomy. A CT scan of the primary to assess the extent of disease is indicated if treatment is contemplated. The role of magnetic resonance imaging has not yet been evaluated. While bone, brain, and liver metastases, or extension into other serosal surfaces are found at autopsy in more than half of patients, in the absence of symptoms or laboratory abnormalities, clinically relevant metastases are sufficiently uncommon at presentation to render extensive baseline evaluation unproductive. If the initial diagnostic biopsy is equivocal, additional diagnostic studies may be useful to locate an occult primary adenocarcinoma or to document tumor in locations rarely involved by mesothelioma. A markedly elevated serum CEA suggests a diagnosis other than mesothelioma.

**REFERENCES**

1. Antman KH. Clinical presentation and natural history of benign and malignant mesothelioma. Semin Oncol 1981; 8:313
12. Antman K, Shemin R, Ryan L, et al. Malignant mesothelioma: prognostic variables in a registry of 180 patients, the Dana-Farber Cancer Institute and Brigham and Women's Hospital experience over two decades, 1965-1985

**Therapeutic Approach to Malignant Mesothelioma**

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Malignant mesothelioma is a relatively rare tumor which has received considerable interest because of its association with asbestos exposure in the workplace and in the environment. There is a sharply rising incidence of this tumor due, in part, to the increased use of asbestos beginning during WWII. There has thus been a considerable population exposed to asbestos who are at increased risk of developing malignant mesothelioma and other asbestos-related diseases. Nevertheless, clinical data defining the optimal management of this disease are only beginning to develop. There remains considerable disagreement about the appropriate application of individual or combined modality treatments.

In the past because of the difficulties in establishing the diagnosis, mesotheliomas presented late with obliteraton of the pleura and considerable deterioration of patient characteristics so that therapies had little or no impact upon survival. As a result of public and medical awareness, patients present with earlier disease, allowing for many treatment opportunities. Review of patient demographics, treatment, and outcome using multivariate analysis showed that before 1980, the significant prognostic factors for outcome included: female sex, early stage, and long duration of symptoms. Treatment could not be shown to be an

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important variable. A more recent analysis of these factors showed that the favorable prognostic factors include: performance status, absence of chest pain, and chemotherapy or pleuroneumonectomy (pleural disease). That treatment was found to be a significant favorable prognostic factor for survival and is an important recognition of our increasing ability to deal with this disease.

In the past, surgery had a very limited role in the treatment of mesothelioma. Surgery was necessary to obtain adequate tissues to provide the histologic diagnosis. More aggressive procedures yielded relatively high morbidities with 2-year survivals of 10–37% and 5-year survivals of 10% or less. This led many authors to suggest that an aggressive surgical approach was not warranted in mesothelioma. With the refinement of surgical techniques, a corresponding decrease in operative morbidity, and the earlier presentation of mesothelioma, pleurectomies and pleuroneumonectomies can now be and are being performed with increasing frequency, alone and as part of combined modality treatments.

Radiotherapy for malignant mesothelioma has also been applied with diverse opinions about its potential utility. In some instances, authors suggested that there is little benefit from radiation treatment of malignant pleural mesothelioma. The patient characteristics in these series are, however, not well defined. Several large scale reviews have clearly demonstrated that multiple prognostic factors impact on treatment including histology, stage, site of disease, performance status, presence or absence of weight loss, and other comorbid diseases. Thus, patients in some of these series may have had very diverse pretreatment characteristics. For example, patients with large volume disease, ie, dense infiltration of the pleura are unlikely to have significant benefit from irradiation to the entire pleura because of the limitations of dose. Nevertheless, radiation therapy has been applied to relieve pain, indicating that there is at least some antitumor activity. The application of radiotherapy alone, however, cannot be demonstrated to improve the survival in this disease, where the median duration of survival is about 10 months. Technical innovations in radiotherapy including computerized port planning, custom-made blocks, and megavoltage equipment now allow chest irradiation to be given safely to areas of disease using up to 60 Gy. This radiation dose has the potential for being tumoricidal and, in combination with other treatments, may add significantly to local control and survival. Other forms of radiotherapy have also been tried. Intracavitary P and coloidal Au have each been reported to produce some long-term survivals in anecdotal reports. This approach, however, requires the pleural space to be intact. As mesothelioma progresses, it obliterates the pleural space, so that this approach is limited to early disease. This technique also has the problems of dealing with a radioactive patient. Another approach, brachytherapy, has been used as part of combined modalities, usually pleurectomy and external beam irradiation.

The application of chemotherapy for malignant mesothelioma has been confused by the anecdotal nature of most of the reported treatment series. For example, in the past, patients with malignant mesothelioma were often included in treatment series of soft tissue sarcomas. Thus, reviews of chemotherapeutic activity tend to be summations of small series. Such summations of necessity do not take into account dose or schedule of drugs. Nevertheless, such reviews have suggested that there are several agents which can produce antitumor regressions. None of the studies in large volume disease have been shown to have a measurable impact on survival of the entire group, but some individuals can have dramatic responses with prolongation of survival. Recently, experimental models have been developed for testing drugs in animal xenografts offering a new method for identifying potentially active treatments. In addition, studies of novel approaches for the delivery of chemotherapy have indicated that intracavitary treatment, particularly intraperitoneal chemotherapy, can produce favorable situations for optimizing the pharmacodynamics of drugs such as cisplatin and doxorubicin, ie, there is a high local concentration for prolonged periods. This approach has produced dramatic antitumor responses in peritoneal disease. The response in pleural disease has been less striking.

The public awareness of the health risks of asbestos exposure has led to an increased screening for asbestos-related disease in exposed individuals. This, in the past decade, resulted in patients presenting with earlier disease. The earlier disease in turn provides the opportunity of studying this disease with more aggressive combined modality approaches including surgery, radiotherapy, and chemotherapy. Preliminary studies have suggested that the use of combined modality treatments in this earlier disease population can shift both the overall survival and long-term survival.

One such approach that has shown initial promise has been the application of combined modality treatment in peritoneal mesothelioma. In this circumstance, surgery is utilized for both diagnosis and debulking of all visible tumor. Intracavitary chemotherapy utilizing alternating courses of cisplatin and doxorubicin are instilled through an indwelling catheter. Following 10 cycles of chemotherapy, whole abdominal irradiation is added. This approach has produced very promising results, with some patients alive and free of disease for 4+ years. A similar approach in pleural disease has also been initiated. In this circumstance pleuroneumonectomy is performed with excision of the diaphragm and the installation of a graft. Postoperative IV chemotherapy is administered utilizing multiagent chemotherapy such as cyclophosphamide, doxorubicin, and cisplatin. After the completion of six cycles of chemotherapy, the patient receives chest and mediastinal irradiation.

These aggressive multimodality approaches require a carefully screened population with adequate pretreatment prognostic factors including performance status, weight loss and absence of significant comorbid disease. For the patient whose disease is beyond this combined modality approach or in whom such aggressive surgical procedures are not feasible, phase II studies of new agents or new combinations are clearly warranted.

Since many of the patients exposed to asbestos can now be identified, careful observation with the high index of suspicion for mesothelioma is critical to identify early stage disease. Considering that the median duration of survival for all patients in the past has been less than a year, aggressive combined modality treatment studies are clearly appropriate. To develop the best data regarding optimal
clinical treatment, patients with malignant mesothelioma should be referred to centers where there is specific interest and expertise in the treatment of this disease. This will permit uniform treatment for larger groups and a better understanding of treatment outcome. It will also allow for the acquisition of tumor tissue to be studied in vitro for a better understanding of the biology of this disease. Furthermore, referral of patients to such treatment centers will allow for the development of the technical expertise necessary for the aggressive surgical and irradiation treatments as well as the supportive care necessary to conduct the chemotherapy. The ongoing systematic use of clinical trials for these patients is likely to continue to yield important information in our understanding and treatment of this disease.

REFERENCES
1 Selikoff IJ. Cancer risk of asbestos exposure: origins of human cancer. Cold Spring Harbor Laboratory, 1977; 1765-84

Clinical Trials for Clinicians

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Clinical trials are widely used to gain information about the effectiveness of therapies for patients with cancer. Prognostic information and data required for cost-benefit analysis are also obtained. The modern theory of clinical trials has evolved as a joint discipline involving both medical and statistical science. Many new statistical techniques have been developed to meet the special circumstances of planning and analyzing clinical trials. The critical role of prospective data collection, management, and quality control as integral parts of the study conduct has also been recognized.

We define a clinical trial as an experiment conducted with human subjects in which treatments are initiated for the purpose of evaluating one or more therapies. Our definition implies the existence of a prospective plan of action to be undertaken for the treatment of patients. The application of the ideas of statistical inference to clinical trials is illustrated in Figure 1.

The recognition that observed results from a clinical trial are estimates of population characteristics and of outcomes is fundamental to an appreciation of the objectives, the rationale, and the limitations for statistical methods in clinical research. One must bear in mind that observed treatment effects are composed of the average true effect (which is typically the component of interest), plus the random error (variability), plus the systematic error (bias). Thus:

Observed True Systematic Random Treatment = Treatment + Error + Error Effect Effect (Bias) (Variability)

Systematic error refers to any feature that may cause the observed effect to be nonrepresentative of the true effect that the trial is designed to estimate. Random error refers to the fact that a different sample of patients, even if selected in an identical manner from the same population, could yield a different observed result by chance alone. As the goal for clinical trials is to obtain information about the true treatment effect, the objectives of clinical trial methodology are, therefore, to minimize biases and to minimize variability of trial estimates.

MINIMIZING BIAS

The Role of Randomization

One of the major mechanisms to control biases in treatment comparisons is represented by randomization. The term randomization refers to the use of a chance mechanism as a means for allocating treatments to patients so that neither the patient nor the physician knows in advance which therapy will be used. By giving each patient the same opportunity to receive any of the therapies under investigation, the characteristics of the patients assigned to the different treatment groups will be "alike on the average" with respect to all factors likely to effect outcome. In this way, any observed differences in results between groups will tend to be due to the treatments. Additional control of bias might also be achieved if the treatments are blinded so that follow-up and assessment of effectiveness is not influenced.

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