Malignant Pleural Mesothelioma
A Proposed New Staging System

Malignant pleural mesothelioma (MPM) is a disease that is infrequently encountered in the usual pulmonary practice. There are estimated to be 2,000 to 3,000 cases per year in the United States. Based on past exposures to asbestos, it has been projected that the annual deaths from mesothelioma will peak at 3,060 cases in the year 2002 and start to taper off. An estimated 1,495 mesothelioma deaths will occur in 2022. Thus, we can be assured that this disease will be around for the rest of our professional lives.

Asbestos, especially amphiboles, has been touted as the causative agent. However, in a number of reported series, 50% or less of mesothelioma patients have a history of occupational exposure. Is this a problem with inadequate occupational histories or inadequate data in the retrospective chart review? Perhaps, or as has been proposed by others, it may be that there is no threshold level of exposure that is safe in certain genetically predisposed individuals. In a classic article by Roggli et al., they quantitated the number of asbestos bodies in the lung tissue of patients who died with asbestosis without mesothelioma, with MPM, and 50 patients who died from other causes. Patients with asbestosis without mesothelioma had the highest fiber count. Those with MPM had an intermediate number of fibers, although some of the mesothelioma cases had fiber counts that overlapped with the general population. Are some people predisposed to this disease? The answer is unknown, but there may be inherited or acquired genetic mutations that predispose certain individuals.

The diagnosis of MPM can be difficult. Most patients present with a pleural effusion. Cytology of the pleural fluid has been diagnostic in one third of cases or less in most reports. Many patients have undergone thoracotomy or, more recently, thoracoscopy with pleural biopsy for the definite diagnosis. Even then, there can be difficulties with the pathologic diagnosis. Expert panels have been set up to review cases when MPM is the suspected diagnosis.

MPM has been histologically divided into epithelioid, fibrosarcomatous, and mixed cell types. Epithelial histology has been associated with somewhat better survival. Cell type, patient performance score, and weight loss are the most important prognostic factors for survival. The median survival time in large series varies from 8 to 12 months with less than 20% of patients alive at 2 years. The majority of those who survive for 2 years have the epithelial histology.

The beneficial effects of treatment for MPM are moot. While there has been the occasional promising

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report in carefully selected patients, others have not shown any substantial effect of therapy on survival. In their extensive review of the literature on chemotherapy for MPM, Hansen and Hansen concluded that there is no standard therapy and that combination chemotherapy regimens are of marginal benefit over some single agent therapies. They recommended further prospective phase II trials to identify new active agents/therapies for this recalcitrant disease.

Perhaps, the major area of debate in treatment of MPM is the role of surgery. While some authors have concluded that radical surgery does not influence survival, other reports have suggested that surgery may be beneficial. To date, there have been no randomized prospective trials to evaluate the role of surgery (or any other form of therapy) in patients with MPM because of limited numbers of patients with the diagnosis. The promising results by Rusch et al and Sugarbaker et al may well reflect the treating physicians' ability to select the best patients for operation (good performance score, no weight loss, and epithelial histology). The skeptic might suggest that the good survival in their series has little or nothing to do with the treatment. These patients may have done as well as if they were treated with shark cartilage (another unproven therapy).

In this issue of CHEST (see page 1122), Rusch and colleagues have proposed a new staging system for MPM. As they outlined, there have been five previously proposed staging systems but none have been universally adopted. There is very little prospective data available from carefully staged patients based on surgical-pathologic data. In 1986, Mountain proposed a new international staging system for lung cancer based on the tumor, node, metastasis (TNM) system. That staging system has been universally accepted for the staging of non-small cell lung cancer. It has been accepted by the international community primarily because it is based on a large body of surgical-pathologic data that has confirmed the different survival time of patients in each of the designated stages. We do not have the luxury of this kind of data in patients with MPM. The proposed staging system for MPM is similarly based on the TNM classification. The number of patients that have been extracted from the literature to serve as the basis for the T1a, T1b, and T2 categories are limited and generally constitute less than 50 patients each. Similarly, the number of patients with N1 or N2 disease are small. The number of cases with adequate information about T and N status do not allow us to determine the utility and accuracy of the proposed new staging system.

What are the merits of this proposed new classification? I think that it serves as an excellent starting point. What is clear from the literature is that there is very little surgical-pathologic data that is available in these patients, especially in those with less than bulky disease. I would agree with Dr. Rusch that our fund of knowledge about this disease is rudimentary and many years behind our knowledge of lung cancer. I strongly support the proposed classification and believe that we need to collect prospectively accurate surgical-pathologic data.

There are several risks associated with the publication of this proposed new staging system. One is that some physicians will use this as a justification for attempts at surgical resection when, in fact, no data is presented that would necessarily justify a surgical approach. I am not categorically opposed to surgical resection but believe that any surgery should be part of a prospective trial of therapy against this disease. We do not need 100 additional extrapulmonary pneumonectomies done haphazardly at 50 different institutions added to an already confusing literature. The second risk is that 5 years from now, we will be no better off than we are today, unless careful attention is paid to prospective collection of data. Ideally, there should be a central registry for data that is collected on standardized forms, much like the ones used in the current national intergroup trials that are evaluating the role of adjuvant and neoadjuvant therapies in patients with non-small cell lung cancer. I would challenge the International Mesothelioma Interest Group to develop such a system and registry. Additionally, there is a need for careful pathologic review by a panel of pundits of all cases entered into this registry to guarantee the accuracy of diagnosis. Obviously, all of this will require time and money. Funding for such a project should be sought from the National Cancer Institute, Union Internationale Centre Cancer, or other organizations with a vested interest such as the American Cancer Society.

Finally, Dr. Rusch and the International Mesothelioma Interest Group are to be congratulated on their initial efforts with this new staging system for MPM and are challenged to present prospectively collected data to us in 5 years, based on this classification. By then, they hopefully will have collected a large amount of information that can be used to substantiate or revise their proposed staging system.

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References
Age and Reversible Lung Disease

Let’s Grow Old, But Not Be Forgotten or Ignored!

Recently, Paoletti and coworkers showed that there is a definite increase in the degree of bronchial responsiveness to methacoline, which occurs in the later stages of life, particularly among men. Chang et al. showed that clearly reversible obstructive lung disease (as defined by accepted spirometric criteria) occurs with very significant frequency among the elderly. In their discussion, the authors correctly point out that routinely investigating this possibility in elderly patients labeled as having COPD, particularly in those without a clear history of smoking, may result in better therapy for a significant proportion of them. Within this context, it would be reasonable to assume that careful management should result in a much better quality of life for those patients. Moreover, the resulting increase in patient well-being, and the likely decrease in emergency room visits or hospitalizations or both, could result in a substantial decrease in the health-care costs associated to their long-term care. That this is a highly desirable outcome is self-evident and hardly deserving of an editorial comment. However, while reading this paper an obvious but nonetheless worrisome thought occurred to me: Would Chang and colleagues have embarked upon such a study if they had not had an a priori suspicion that the elderly may not be as aggressively studied or treated, or both, as younger patients are? The potential for “benign neglect” (probably largely unintentional, to be sure) has always been a reality for the elderly in our health-care system. How many times does a physician dismiss a symptom off hand just because the patient is old? Do we really pay the same attention to the 80-year-old woman complaining of stomach pain or dizziness for the first time as we do to the 40-year-old executive with the same symptoms?

The potential for even more serious age-based bias is present in the new health-care systems currently evolving throughout this country. As the prospect of ever-increasing managed-care looms very large in the medical horizon, widespread interest in cost-management strategies has grown among physicians and the health-care industry in general. Paramount among those concerns are issues related to the appropriate use of screening and diagnostic tests, or of specific therapies, in terms of their cost-effectiveness when applied to well-defined patient population groups. Of course, using age as a (even if not necessarily the) criterion to allocate health resources is not a novel idea, nor is it necessarily wrong or unfair. For example, advancing age can indicate the need for close monitoring of certain conditions, like breast, prostate, or colon cancer, in persons with the appropriate risk factors. There is little debate over the appropriateness of most of these positive interventions. If any disagreement exists, for the most part it is limited to deciding which age threshold is best to use in a given scenario. However, there are a large number of myths and misconceptions surrounding the issue of age, health, and health-care costs in the United States. This is a valid source of concern because age has long been used, or at least proposed, as a (or even the) major determinant of whether certain diagnostic or therapeutic interventions should be offered or withheld from a given patient. Well-known examples include, among others,