Pleural mesothelioma in 2002: Going somewhere very slowly

Harvey I. Pass, MD

See related article on page 1183.

Nothing exasperates a thoracic surgeon more than to be confronted with a mesothelioma. Few such cases are diagnosed per year in the United States, and many of the internists, pulmonologists, and medical oncologists who see these cases refer them to a thoracic surgeon for one purpose: *palliation*. Thoracic surgeons themselves differ remarkably in their approach to this disease, but the good news is that there is a cadre of individuals, including Lee and associates,¹ who actually advocate for novel approaches in the management of this beast.

The most objective method to advocate for change in medical practice is to develop trials that, ideally, will set a new standard of care, and for this disease, the credibility of any trial is strengthened when a multidisciplinary approach is used. In this edition of the *Journal*, Lee and colleagues from the University of California, San Francisco (UCSF), report a multidisciplinary approach to the management of malignant pleural mesothelioma using radical pleurectomy/decortication and radiation in 32 patients. This report, although small, is an enlightening representation of all that is controversial in the care of the patient with the potentially resectable mesothelioma, and many of these issues involve (1) the goals of an operation, (2) patient selection, (3) follow-up methods, and (4) choice of adjuvant therapy. Undoubtedly, there are no standards for these issues that dictate "best practice" for mesothelioma; however, in dissecting the results and recommendations from the UCSF study, the informed reader should be presented with alternative explanations that could be thought provoking.

Goals of the Operation

If mesothelioma is an incurable disease, then what are the goals of an operation in the first place? As Lee's group has pointed out, the operation should be a part of a package of multimodal therapies. The operation performed, however, may depend on whether the patient is entered into a clinical trial (which specifies or does not specify the type of operation to be done) or whether the patient is being treated off-protocol. Once the decision is made that a patient is a candidate for "mesothelioma resection," the surgeon must, in his or her own mind (and ideally written as part of the protocol) define the end points of the operation. Obviously, mesothelioma resections are giant debulkings, cytoreductions, partial resections, or some such designation, and terms such as R0 and R1 are nice but irrelevant. Isn't the ultimate goal of performing an operation for mesothelioma to safely reduce the burden of disease enough so that tumor cannot be seen at the end of the operation? I realize that this sounds incredibly naive. However, if the tumor can be made grossly undetectable and a reproducible way can be found of *documenting* how much residual disease is left after the resection, that will at least provide an objective starting point for each patient so that the degree of cytoreduction is approximately equal. If you want to be "cute," the volume of disease can be measured by means of 3-dimensional reconstructions on the first computed tomographic (CT) scan after resection, and that relative volume can be recorded for each patient.² The most important point, however, is that if the surgeon is confronted with patients of equal cardiopulmonary demographics that permit either pleurectomy/decortication (P/D) or extrapleural pneumonectomy (EPP), it does not matter how this cytoreduction is accomplished: just that it be equal among all individuals and that it be safe. The only

From Harper Hospital, Thoracic Oncology Section, Wayne State University, Detroit, Mich.

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Address for reprints: Harvey I. Pass, MD, Harper Hospital, Thoracic Oncology Section, Wayne State University, 3900 John R. Suite 2101, Detroit, MI 48201 (E-mail: hpass@dmc.org).

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way in which we will be able to interpret and compare surgically based studies in mesothelioma will be to confront and control the heterogeneity of resection results. In fact, the degree of the resection affects the survival of the patients and the progression of the disease.² What is equally important for the surgeon is to recognize early in the course of the dissection that if these goals cannot be accomplished, then the operation should be aborted. Location, degree of invasion, inability to mobilize the tumor safely, or unsuspected extrathoracic spread are but a few reasons for early termination. Nothing is more painfully clear from the Lee article than the fact that the only prognostic variable that correlated with survival was the amount of intraoperative radiation therapy (IORT) ports that were necessary. To summarize, the fewer the number of IORT ports, the greater the survival of the patients, and, in the authors own words, “An increased number of IORT fields reflects a greater extent of residual disease, which might account for the difference in survival.” This agrees with our own data from the National Institutes of Health that if the residual volume of tumor seen on the immediate follow-up CT scan is above a certain threshold, those patients with the higher volumes have shorter times to progression and shorter survival times.² Rusch and Venkatraman³ have also commented on the importance of T status and overall survival in the disease.

Obviously the goal of the cytoreduction harkens back to the ovarian analogy (which, curiously, shares a few unique, overexpressed genes with mesothelioma such as mesothelin⁴) with the hope that the adjuvant therapies can “mop up” the microscopic disease. Whether it is intrapleural radiation therapy with postoperative intensity-modulated radiation therapy (IMRT) as described by Lee, or intrapleural hyperthermic chemoperfusion,⁷ intrapleural chemo-immunotherapy,⁶⁻⁸ intrapleural photodynamic therapy,⁹⁻¹³ intrapleural gene therapy,¹⁴ postoperative chemotherapy, or postoperative radiotherapy,¹⁵ we all want to reset the clock for the mesothelioma patient back to a stage I minimal burden of disease status. This philosophy satisfies the accomplishment gratification of the surgeon and puts the responsibility on adjuvants which, as of yet have, not been able to solve the incredibly complex biology of the disease.

Patient Selection and Type of Operation

All of us can appreciate the difference in homeostatic insults between pleurectomies and extrapleural pneumonectomies, and it is admirable that the authors can be so frank to state, “The decision to perform a lung-preserving procedure in this group of patients was not based solely on their ability to tolerate pneumonectomy but rather based on a bias that P/D is better tolerated in patients with an essentially incurable disease.” This is a fair and accurate statement if one compares two patients with mesothelioma who have identical amounts of tumor, whose tumor can be cytoreduced to equal levels by P/D or by EPP, but one has P/D and the other has

EPP. Without question, the patient who has the P/D will be functionally superior after the operation compared with the patient having the EPP. In fact, having a P/D may open up more experimental protocol options for the patient if the disease progresses. We are not given the luxury as thoracic surgeons, however, to have patients who can have meaningful cytoreductions for mesothelioma by P/D in all cases. If, philosophically, a surgeon believes that an EPP should not be done on an “incurable” patient, that is a different matter, and that stance should be respected. This philosophy will militate that a number of patients with bulky mesotheliomas will not qualify for investigational programs because an EPP would be necessary to accomplish tumor debulking. Frankly, there is no formula for the appropriate operation for mesothelioma, and as a mesothelioma surgeon, one does not have to be wedded to one operation. The surgeon should do what is necessary to accomplish the *goals of the operation* mentioned above while considering the patient’s preoperative functional evaluation.

Certainly, selection must play a role in this decision, and if the patient’s cardiac status is satisfactory, then how does one decide what will be “better tolerated?” In the literature, there seems to be a gray zone between the forced expiratory volume in 1 second of 1.5 L mentioned in the Lee paper and the figure of 2.0 L, which is quoted by Sugarbaker and associates.¹⁶ Sugarbaker and colleagues, however, stress the need for quantitative perfusion scanning in patients with pleural mesothelioma, and others have found that in patients with bulky disease or combination fluid and bulky disease, the affected side may contribute next to nothing to the patients’ pulmonary status. Personally, I am not sure whether there are any preoperative tests at present that will help me with 100% certainty to determine which operation will accomplish these goals short of visual inspection of the pleural war zone.

Comparing Apples . . .

If we can agree that a comparative analysis of therapeutic studies is a useful exercise, then even in incurable diseases, we should agree on some ground rules. In mesothelioma, despite the atrocious staging systems,¹⁷ there is uniform agreement that lymph node involvement is prognostically important. Therefore, is it unreasonable to state that, even if one does not perform an EPP, the disease should be staged with a lymph node sampling or dissection in all of the cases? As reported by Lee and associates in their report, the lack of staging information on 38% of the patients presents problems of potential understaging, which make it extremely difficult to compare their study with established studies. Nevertheless, the authors state that their results are as good as Sugarbaker’s (18.1-month vs 19-month median survival). Closer inspection of the two series reveals that in Sugarbaker’s series, fully 40 (23%) of 176 patients had extrapleural lymph node involvement¹⁶ compared with 12%

in the series reported by Lee and colleagues. In reality, no comparisons can be made because we really do not know what the true stage of 38% of the patients in the Lee study is, and there are no subset data regarding the results of the 18 patients with stage I disease. This is a painful lesson that I have learned, and after having been guilty of inadequate lymph node staging in my first 95 mesothelioma resections,¹⁸ I now perform mediastinal lymph node dissections in all of my P/Ds and EPPs. I believe that more accurate staging in protocols for mesothelioma decreases demographic heterogeneity. Moreover, if it is true that gene or proteomic profiling for this disease will be a more accurate way to define outcomes,^{19,20} it will be absolutely necessary to have accurate staging data.

Follow-up

There are no standards with regard to the radiologic follow-up of patients having surgery for mesothelioma, and this is an issue that is not readily dealt with in the literature. Sugarbaker and associates¹⁶ use 3 to 4-month follow-up schedules with CT documentation of progression. Similar follow-up schedules are used by other investigators.¹⁰ Why is this important? Obviously, if the efficacy of therapy is measured in mesothelioma as a prolongation of time to progression, then it would behoove investigators to be on the same wavelength with regard to follow-up schedules and methods of follow-up (see "Comparing Apples. . ."). In a series of 49 patients with mixed histology, mixed stage pleural mesotheliomas having EPP, Baldini and coworkers²¹ reported a 19-month median time to first recurrence in a series of patients operated on in Boston, 29% of whom had extrapleural lymph node involvement. The median progression-free survival in the Lee series, with 12% documented N2 disease, all of whom had P/D, was 12.2 months. What is even more disturbing about this shorter time to progression in the Lee study is that the follow-up was performed with "chest radiographs every 3 to 4 months with CT investigation of evolving abnormalities." The lack of sensitivity of chest radiographs in the visualization of pleural abnormalities could falsely prolong the time to progression, and it is not unusual to see evolving disease deep in the costophrenic angles in an asymptomatic patient after resection without changes in the chest x-ray film.

Adjuvant Therapies

When surgeons talk about adjuvant therapies that add novelty to surgical resections for mesothelioma, they almost always talk geography . . . New York, Boston, Detroit, Bethesda, Seattle, Los Angeles, San Francisco, and so on. This reflects a commonality of interest as well as commonality of frustration, and it also represents unique technologies that are not commonly available. IORT and IMRT, as described by Lee's group, may actually be more available than other

technologies at a number of institutions, but even the authors of this report are frustrated by the lack of efficacy. We are all flailing and failing with this disease, maybe less than in the past, and we are not organized to combat it as we are in non-small cell lung cancer. In fact, the efforts in mesothelioma are similar to the early efforts in the mid-1980s with phase II trials of induction therapy for lung cancer.

Meaningful, large-scale trials *can* be performed in mesothelioma, and our medical oncologic colleagues have reported a randomized clinical trial comparing pemetrexed (Alimta) and cisplatin to cisplatin alone in more than 446 patients accrued over 20 months.²² Mesothelioma is not going away. More than 250,000 new cases are projected over the next 30 years in Western Europe alone.²³ A collaborative effort, independent of but encompassing all geographies, which combines uniform, objectively documented cytoreduction with a simple, yet promising and available regimen is what is needed to answer therapeutic and biologic questions in this disease.

Surgeons are eternal optimists, and believe me, this disease needs some optimists with good ideas. Got any?

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