Clinicopathologic Indices Can Improve Patient Selection in Malignant Mesothelioma

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The clinical management of malignant mesothelioma may ultimately be transformed by the elucidation of novel biomarkers that can predict the evolution of disease and guide the development of targeted therapies. However, despite relevant advances, more basic research is urgently required to support the development of therapies applicable to the patients for whom surgical resection is not an option.

The authors should be congratulated for their comprehensive review of prognostic factors in malignant pleural mesothelioma. Although the paper emphasizes the emergence of molecular and genetic biomarkers, which hold great promise for transforming the management of malignant mesothelioma, the authors also cite numerous studies of hard clinical indices that have prognostic significance in mesothelioma. These include basic epidemiologic variables, clinical characteristics, common blood assays, findings on various imaging modalities, gross features of the tumor, and anatomic extent of disease. Perhaps most critical from a surgical perspective is the association between tumor volume and outcome, which was first documented in a prospective study by Pass et al.[1] This study heralded the central role of cytoreductive surgery in the multimodality treatment of malignant mesothelioma.

The overall approach to treating any solid tumor is macroscopic complete resection,[2] followed by adjuvant therapy for micro-metastatic control. In our experience with mesothelioma, dating back to the 1980s, aggressive treatment with extrapleural pneumonectomy (EPP) followed by adjuvant therapy for micro-metastatic control has been the best approach for achieving long-term survival in select patients.[3,4] While the technique of EPP may have reached a theoretical plateau in terms of safety, morbidity management, and mortality, there remains ample room for improvement in patient selection and in the development of innovative new therapies.

In an effort to improve patient selection at our institution, we conducted several retrospective studies on our own patient database to identify the clinical and pathologic characteristics of patients who experience long disease-free survival after EPP followed by adjuvant therapy.[3,5] On the basis of these findings, we identified a constellation of factors associated with low risk for the development of recurrent disease. We used these factors to develop a low-risk profile and a risk stratification system for patient selection, recently presented at the 92nd Annual Meeting of the American Association for Thoracic Surgery, and submitted for publication to the Journal of Thoracic and Cardiovascular Surgery.[6] Features associated with low risk in this system include epithelial histological subtype by biopsy, low computed tomography (CT)-derived tumor volume, female gender, and normal hemoglobin level.

Critical to this work was the development of new methods that allow practical and accurate preoperative quantification of tumor volume by CT. The study, cited in this review, established 500 cm$^3$ as the reference cutoff value for tumor volume.[7] The median estimated tumor volume was 319 cm$^3$. By univariate analysis, tumor volume, hemoglobin concentration, platelet count, pathologic TNM category, and administration of adjuvant chemotherapy or radiation therapy met the criteria for inclusion in the reverse stepwise regression analysis. In the final model, tumor volume, hemoglobin concentration, and administration of adjuvant chemotherapy or radiotherapy were identified as independently associated with overall survival.

The value of aggressive surgery for malignant mesothelioma, a topic of controversy for many years, was recently affirmed in an initial study of the new International Association for the Study of Lung Cancer Mesothelioma database, currently the largest international database examining outcomes in surgically managed MPM patients.[4] The conclusion of this paper summarizes the case for aggressive cytoreduction in malignant mesothelioma: “For the stage I patients in our data set, those treated with EPP survived longer than other patients did. Why the EPP patients survived longer—because of superior intervention, better overall risk profile, or other considerations specific...
to the institution or region—cannot be determined without some understanding of how treatment was selected for these patients. Within the individual centers that contributed to this database, stage I disease was generally managed exclusively by EPP to the exclusion of P/D [pleurectomy/decortication], or vice versa. As with lung cancer, different surgical procedures may be appropriate for different groups of patients having MPM. It is perhaps time to study this question prospectively with more restricted-stage and prognostic-factor eligibility than has been done in the past.” Our experience supports this view.

The clinical management of malignant mesothelioma may ultimately be transformed by the elucidation of novel biomarkers that can predict the evolution of disease and guide the development of targeted therapies. However, despite relevant advances, more basic research in molecular biology, genetics, immunology, pharmacology, and oncology is urgently required to support the development of therapies applicable to the patients for whom surgical resection is not an option, which comprise the majority in malignant mesothelioma. In the meantime, surgeons should be encouraged to examine their own clinical data and to incorporate existing clinical indices into their patient selection practices, since these are inexpensive, readily available, and can be easily obtained and analyzed preoperatively.

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