Recurrence of Malignant Pleural Mesothelioma at the Resection Borders—Local or Distant Recurrence?

We congratulate Gomez et al for their very important contribution on the patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy, for malignant pleural mesothelioma. Studies about patterns of failure are of great importance because patterns of local and distant failure might be the most important test of adequate treatment planning and treatment success.2

After extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy, only 16% of the patients experienced local recurrence, whereas, distant recurrence was observed in 59% of the patients. If we go into details, the predominant site of distant recurrence was contralateral hemithorax in the majority of the patients (41%, n = 35) followed by abdomen and pelvis, including liver in 28% of the patients (n = 24). In general, distant recurrence is defined as tumor that has spread to organs or tissues distant from the primary tumor site. It is questionable whether these kind of recurrences might be hematogenous spread. Thus, the question arises whether recurrence at the resection borders in terms of contralateral hemithorax or abdomen and pelvis should be (still) considered as local recurrence or distant recurrence for malignant pleural mesothelioma?

Servet Bölükbas, MD, PhD
Department of Thoracic Surgery
Dr Horst-Schmidt-Klinik Teaching Hospital of Johannes Gutenberg University, Mainz Wiesbaden, Germany

Michael Eberlein, MD, PhD
Division of Pulmonary, Critical Care and Occupational Medicine Carver College of Medicine University of Iowa Iowa City, Iowa

Joachim Schirren, MD, PhD
Department of Thoracic Surgery
Dr Horst-Schmidt-Klinik Teaching Hospital of Johannes Gutenberg University, Mainz Wiesbaden, Germany

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In Response:
We thank Drs. Bölükbas, Eberlein, and Schirren for their letter and their inquiry regarding patterns of recurrence for malignant pleural mesothelioma at the resection borders. We do concur that the classification of recurrence in this setting requires special consideration, because of the unique components of an extrapleural pneumonectomy. And indeed, it can be difficult to distinguish between microscopic residual disease that has occurred at the surgical/radiation field margin versus tumor spread hematogenously to the contralateral hemithorax or abdomen. Unfortunately, there is no way to determine with absolute certainty the process underlying these recurrences, particularly with the additional concern that has been previously published of tumor seeding through biopsy or surgery.1,2 Therefore, much of the categorization for reporting purposes relies on clinical judgment.

In the vast majority of cases that we have classified as being distant recurrences, the tumors have been located at sites not in direct continuity with the postpneumonectomy space. Most contralateral lung recurrences in this series were intraparenchymal tumor nodules, not pleural-based recurrences and are most probably related to hematogenous spread. Similarly, liver recurrences were exclusively intraparenchymal. One certainly could argue (as has been done in the past by others) that intra-abdominal recurrences are secondary to seeding at the time of surgery and should be classified as “local” recurrences. However, a significant number of patients will have occult carcinomatosis before surgery, so transdiaphragmatic spread to the abdominal cavity (either by direct invasion or, more likely by lymphogogenous spread) is a common feature of this disease even without violation of the diaphragm during extrapleural pneumonectomy. It is therefore not surprising that abdominal recurrences are observed after cytoreductive surgery.

At our institution, we classify recurrence of disease that occurs in a region that is clearly in the resection bed or at the resection margin above the diaphragm, or in the mediastinal lymph nodes, as local–regional recurrence. In contrast, disease that is evidently removed from the ipsilateral hemithorax or is below the diaphragm, including contralateral lung nodules,
abdominopelvic or peritoneal disease, and contralateral pleural disease, is classified as a distant recurrence. The aims of this classification are not only to convey the mechanism of progression but also to clarify options for salvage therapy. Further studies comparing outcomes in patients with marginal recurrences versus removed distant metastases will provide further enlightenment regarding the optimal manner in which to allocate and treat this distinct group of patients.

Daniel Gomez, MD
Anne Tsao, MD
David Rice, MD
Departments of Radiation Oncology
Division of Radiation Oncology, Thoracic/Head and Neck Medical Oncology
Division of Cancer Medicine, and Thoracic and Cardiovascular Surgery
Division of Surgery
MD Anderson Cancer Center
Houston, TX

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Are Prognostic Factors for Leptomeningeal Metastases Defined Sufficiently to Permit Tailored Treatment?

Lee et al. are to be congratulated for their analysis of patients with non–small-cell lung cancer (NSCLC) and leptomeningeal metastases (LM). Several aspects regarding the study warrant commentary.

First, this was a single-institution retrospective study, in which all patients with LM defined by positive cerebrospinal fluid (CSF) cytology were included. Consequently, the study cohort was heterogenous with respect to identified LM-prognostic features (the presence or absence of radiographic bulky disease, carcinomatous encephalopathy, performance status, CSF flow disruption, and burden of systemic disease), and therefore, it was unclear how many patients could be considered as favorable risk and LM-treatment appropriate. Strikingly different than the literature, the current study had a high incidence of LM at diagnosis of NSCLC (17%), a near-uniform concordance of positive CSF cytology (100%) and magnetic resonance imaging findings consistent with LM (94%), a high incidence of hydrocephalus (17%), lack of spine LM-related disease, and a high incidence of brain metastasis (66%).

Because of the retrospective nature of the study, there were no a priori determinants of treatment such that treatment was defined individually, without apparent standardization making cross-comparisons between treatment groups problematic. There was no characterization before intra-CSF chemotherapy of whether patients underwent radioisotope CSF flow studies, to determine CSF compartmentalization because of LM that would compromise intra-CSF drug distribution. Although 66% of all the patients manifested brain metastasis, only 32% received whole-brain radiotherapy (WBRT). Furthermore, there was no mention of administering spine radiotherapy for symptomatic or radiographically bulky disease in spine. Table 3 suggests that 13% of patients received supportive care (no explanation as to why), 12% were not treated with intra-CSF chemotherapy (again no explanation as to why), and only 12% received all three modalities of therapy (WBRT, systemic, and intra-CSF chemotherapy), a therapeutic strategy, which the authors conclude, results in best outcomes.

The study was unclear as to how determinations of CSF abnormalities were made (dichotomous or continuous variable), which according to the authors contention, impact survival independent of treatment. Nonspecific CSF abnormalities likely reflect CNS tumor burden more closely correlated with magnetic resonance imaging–defined disease. The authors posit that ventriculo-peritoneal shunting is associated with improved survival, which seems counterintuitive because such patients by definition are poor candidates for intra-CSF chemotherapy because of CSF compartmentalization. WBRT in isolation has been shown to be of limited benefit in patients with NSCLC and LM. LM is a neuroaxis disease, with CSF dynamically circulating through brain and spine compartments. Consequently, it is not surprising that treatment of only a single CSF compartment with WBRT does not impact survival.

The statement that intra-CSF chemotherapy, WBRT, and epidermal growth factor receptor inhibitors, but not cytotoxic chemotherapy, with recognized limited CNS penetration improves survival in patients with NSCLC and LM seems overreaching, given the challenges of a retrospective study and lack of appropriate controls, which necessarily results in treatment-selection bias. As the authors indicate, management of solid tumor-related LM remains challenging because of a paucity of prospective trials and consequently the lack of standardization in LM-related treatment that is evidenced based.

Marc C. Chamberlain, MD
Department of Neurology and Neurosurgery
University of Washington
Fred Hutchinson Cancer Center
Seattle Cancer Care Alliance
Seattle, Washington
Bernardo H.L. Goulart, MD
Department of Medicine
University of Washington
Fred Hutchinson Cancer Center
Seattle Cancer Care Alliance
Seattle, Washington

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Address for correspondence: Marc C. Chamberlain, MD, University of Washington, Fred Hutchinson Cancer Center, Seattle Cancer Care Alliance, 825 Eastlake Avenue E, Mailstop: G4-940, Seattle, WA 98109. E-mail: chamberla@u.washington.edu

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