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Despite multiple diagnostic toolkits, the diagnosis of diffuse malignant pleural mesothelioma relies primarily on proper histologic assessment. The definitive diagnosis of diffuse malignant pleural mesothelioma is based on the pathologic assessment of tumor tissue, which can be obtained from core biopsy sampling, pleurectomy, or other more extensive resections, such as extrapleural pneumonectomy. Given its rarity and overlapping microscopic features with other conditions, the histologic diagnosis of diffuse malignant pleural mesothelioma is challenging. This review discusses the pathologic features and the differential diagnosis of diffuse malignant pleural mesothelioma, including select diagnostic pitfalls.

**The Molecular Basis of Malignant Pleural Mesothelioma** **383**

Benjamin Wadowski, Assunta De Rienzo, and Raphael Bueno

Malignant pleural mesothelioma (MPM) is a rare, aggressive malignancy of the pleural lining associated with asbestos exposure in greater than 80% of cases. It is characterized by molecular heterogeneity both between patients and within individual tumors. Next-generation sequencing technology and novel computational techniques have resulted in a greater understanding of the epigenetic, genetic, and transcriptomic hallmarks of MPM. This article reviews these features and discusses the implications of advances in MPM molecular biology in clinical practice.

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Harvey I. Pass, Marjan Alimi, Michele Carbone, Haining Yang, and Chandra M. Goparaju

Malignant pleural mesothelioma (MPM) is an asbestos-related neoplasm that can only be treated successfully when correctly diagnosed and treated early. The asbestos-exposed population is a high-risk group that could benefit from sensitive and specific blood- or tissue-based biomarkers. We review recent work with biomarker development in MPM and literature of the last 20 years on the most promising blood- and tissue-based biomarkers. Proteomic, genomic, and epigenomic platforms are covered. SMRP is the only validated blood-based biomarker with diagnostic, monitoring and prognostic value. To strengthen development and testing of MPM biomarkers, cohorts for validation must be established by enlisting worldwide collaborations.

**The Staging of Malignant Pleural Mesothelioma 425**

Caleb J. Euhus and R. Taylor Ripley

Staging of malignant pleural mesothelioma has been challenging because of a paucity of cases and poor survival. At least 5 staging systems were proposed before 1990 until the first consensus system was published in 1995. This system used tumor, node, metastasis designations and borrowed heavily from parenchymal lung cancer descriptors. With the establishment of a database to collect cases from 1995 to 2013, evidence-based revisions to the 1995 staging classification were published in 2016. With improving imaging technology, clinical staging will become more refined and, it is hoped, more useful for prognostication even without operative resection.

**Preoperative Identification of Benefit from Surgery for Malignant Pleural Mesothelioma 435**

Isabelle Opitz and Katarzyna Furrer

In the absence of standardized treatment algorithms for patients with malignant pleural mesothelioma, one of the main difficulties remains patient allocation to therapies with potential benefit. This article discusses clinical, radiologic, pathologic, and molecular prognostic factors as well as genetic background leading to preoperative identification of benefit from surgery, which have been investigated over the past years to simplify and at the same time specify patient selection for surgical treatment.

**Extended Pleurectomy and Decortication for Malignant Pleural Mesothelioma 451**

R. Taylor Ripley

Extended pleurectomy and decortication (ePD) is a difficult operation performed for the surgical resection of malignant pleural mesothelioma that can achieve a macroscopic complete resection with preservation of the lung. With lower perioperative mortality, similar long-term survival, and better tolerance in patients with lower performance status, ePD has become the preferred operation rather than extrapleural pneumonectomy despite lack of a direct comparison. As ePD has become more popular, international collaboration is underway to create surgical guidelines based on collection of operative data. These efforts will improve the safety and standardization of this operation.

**The Role of Extrapleural Pneumonectomy in Malignant Pleural Mesothelioma 461**

Laura L. Donahoe and Marc de Perrot

Extrapleural pneumonectomy (EPP) is the most extensive form of surgery for mesothelioma, involving en bloc resection of visceral and parietal pleura, lung, diaphragm and pericardium, with reconstruction of the pericardium and diaphragm. It can be performed safely in carefully selected patients. It should be performed in experienced centers as part of a multimodality treatment plan. The SMART approach, with a short course of induction hemithoracic radiation followed by EPP has demonstrated safety and value of hypofractionated hemithoracic radiation combined with complete macroscopic resection. We are conducting a clinical trial with oligofractionated hemithoracic radiation in early-stage mesothelioma.

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Kenneth E. Rosenzweig

The treatment of malignant pleural mesothelioma with radiation therapy has always been a technical challenge. For many years, radiation therapy was delivered after extrapleural pneumonectomy with acceptable results. As the utilization of pleurectomy/decortication increased, techniques, such as pleural intensity-modulated radiation therapy (IMRT) have been introduced. The experience with these techniques have grown and multiple trials using IMRT, both in the setting of extrapleural pneumonectomy or pleurectomy, are being conducted to assess its effectiveness.

**Taken Together: Effective Multimodal Approaches for Malignant Pleural Mesothelioma 481**

Kimberly J. Song, Raja M. Flores, and Andrea S. Wolf

Malignant pleural mesothelioma is an aggressive, deadly cancer often requiring input from multiple medical disciplines. Treatment has evolved over the last several decades with increasing evidence and ongoing advances in chemotherapy, radiation, and immunotherapy; however, no standard treatment regimen has yet been defined. Regardless of the overall strategy, surgery remains the foundation of treatment to remove macroscopic disease, and preservation of lung parenchyma via extended pleurectomy/decortication may be preferable to extrapleural pneumonectomy.