



Should the surgical decision be influenced by the diagnostic biopsy in mesothelioma?

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Abstract: Surgical resection is offered to some patients with malignant pleural mesothelioma (MPM), depending on fitness for surgery and apparent technical resectability of the tumor. Due to risk of surgery-related morbidity and mortality in patients with a fatal malignancy, life expectancy is also a primary consideration in the surgical decision. Prognosis is related to the stage and histological subtype of the disease, neither of which can be known with certainty prior to definitive pathological review of the tumor specimen. Therefore, radiology and pleural biopsy, respectively, are used to predict these prognostic factors and to determine potential benefit from surgical intervention. In this review, we discuss the current limitations of histologic subtyping using pleural biopsy as a preoperative predictor. In addition, we explore available and emerging non-histologic analyses of biopsy specimens to evaluate molecular biomarkers, predicted neoantigens and the immune microenvironment. In the context of novel biological and immune-based treatment strategies currently under investigation for mesothelioma, accurate prognostic and predictive information available from biopsy material will likely influence treatment strategy including the surgical decision.

Keywords: Pleural biopsy; biopsy; mesothelioma surgery; surgical decision; diagnosis

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Malignant pleural mesothelioma (MPM) is a fatal malignancy caused by exposure to asbestos that arises in the pleural lining of the lungs. MPM is generally associated with poor prognosis, with median overall survival time from 7 to 19 months after initial diagnosis (1,2).

The diagnosis of MPM is usually made during workup of thoracic symptoms. A chest radiograph and often a contrast-enhanced computed tomography scan are used to visualize hallmark radiographic features such as thickening of pleura, pleural effusion (found in ~70% of patients), loss of hemithoracic volume, irregular fissural thickening and localized mass lesions [for review, see (3)]. However, non-invasive radiographic evaluation cannot usually distinguish benign from malignant disease and only offers

a sensitivity of 40% in detecting malignancy (4). Pleural fluid cytology is commonly non-diagnostic, detecting malignant cells in only 35% of cases (5). Therefore, definitive diagnosis usually requires a pleural biopsy for more definitive histological and immunohistochemical evaluation. Thoracoscopy is frequently used because it is sensitive for malignant disease and allows for direct visualization of biopsy sites, producing large and accurate samples in a disease where specimen size is important. Diagnosis is attained in 75% of specimens greater than 10mm in size compared with only 8% for specimens less than 10 mm (6). Surgical pleural biopsies, typically obtained via thoracoscopy, have become the gold standard diagnostic procedure for MPM with reported sensitivities of 95–98%

with 100% specificity (6,7). Importantly, surgical biopsies are adequate to support immunohistochemical studies critical for differentiating among MPM subtypes and from histologically similar pleural malignancies (8-10).

There is no standard therapy for MPM. Treatment tends to be individualized, ranging from palliation of symptoms to cytotoxic chemotherapy to a variety of surgery-based multimodality regimens. Conservative management is most often indicated, based on considerations commonly encountered at diagnosis including advanced age, comorbidity, poor performance status and disseminated disease. Although MPM is poorly responsive to most classes of cytotoxic agents, treatment with combination platinum-antifolate chemotherapy is commonly applied in the first line based on several positive phase III studies (11,12). More recently, adding bevacizumab has been recommended for appropriate patients (13). Chemotherapy most often can be administered in the community, making it conveniently accessible for most patients.

Mesothelioma is categorized histologically into three subtypes: epithelioid, sarcomatoid, and biphasic (14). The epithelioid subtype is characterized by round or cube-shaped tumor cells. Epithelioid tumors are generally more indolent, less likely to metastasize, and more likely to be surgically resectable and responsive to chemotherapy. Correspondingly, epithelioid MPM is associated with better patient outcome. In contrast, the sarcomatoid subtype of MPM is comprised of spindle-shaped and more aggressively proliferating cells and is associated with rapid progression and short survival (15). For example, after therapeutic surgery, patients with epithelioid, biphasic and sarcomatoid MPM demonstrated respective median survival times of 15.3, 10.1 and 5 months and two-year survival rates of 31.7%, 7.6% and 0% (16).

Biphasic mesothelioma comprises both the epithelioid and sarcomatoid cell types. World Health Organization classification guidelines (17) define this subtype to include tumors ranging from 10% to 90% sarcomatoid component. These cut-points have been published without data-driven justification or update in successive editions of the guidelines (14,17,18). In studies where exhaustive review of final pathology blocks has been undertaken, patient prognosis has been found to depend on which cell type is more dominantly present (19), suggesting that implementing evidence-based subclassification of biphasic MPM may improve prognostic accuracy and allow surgical biopsy to better inform decisions on treatment. Because biphasic tumors are heterogeneous, the relative proportions

of epithelioid and sarcomatoid cells may vary substantially with the pleural location of the biopsy, further reducing the accuracy of biopsy-estimated prognosis for patients diagnosed with this subtype. For example, thoracoscopic biopsy has been reported to misclassify 44% (20), 46% (21) and 58% (22) of biphasic tumors as epithelioid. These findings imply a larger number and distribution of pleural locations where surgical biopsies would need to be obtained to detect biphasic histology with reasonable sensitivity and specificity, particularly if future editions of WHO guidelines were to include subclassification based on a percentage score.

In current practice, prediction of overall tumor subtype and associated prognosis based on the diagnostic biopsy lacks accuracy in most cases to guide the surgical decision. However, the landscape for MPM treatment is changing toward more molecular and immune based approaches, presenting opportunities to use tumor biopsies for novel analyses that may help direct care, while circumventing the limitations of histological interpretation. Specifically, the diagnostic biopsy may be utilized to determine a molecular subtype, derive a molecular prognostic score or predict efficacy of novel targeted biologic or immune modulation therapies emerging as alternatives or adjuncts to surgical intervention.

Surgical biopsies usually provide sufficient tissue to support a range of histologic and molecular testing, including immunohistochemistry, genomic and transcriptomic analyses. Tumor RNA isolated from biopsy specimens can support prognostic testing based on gene expression signatures. For example, a gene ratio test involving expression levels of 4 genes has been rigorously validated in a prospective study (23). The test demonstrates high repeatability and reproducibility, successfully discriminating high and low risk patients based on outcomes following surgery-based therapy. Importantly, the test was further validated using formalin-fixed paraffin-embedded tissue samples, which supports its applicability to routinely collected clinical material (24). In addition, recent RNA-Seq profiling of over two hundred MPM tumors led to identification of distinct molecular clusters that align approximately with tumor histology, reflect gene expression signatures indicative of epithelial to mesenchymal transition and stratify survival (25). Thus, RNA isolated from the diagnostic pleural biopsy specimens can potentially provide a more robust indication of subtype and prognosis than does evaluation of their histology.

Tumor DNA isolated from a biopsy specimen may be

subjected to targeted sequencing to detect known driver mutations indicative of prognosis or predictive of response to certain classes of targeted drugs. Although no targetable oncogenes have yet been identified as drivers of MPM, multiple novel significantly-mutated genes have recently been demonstrated (25) and are currently being investigated for their functional role, prognostic relevance and potential for biologic targeting. Technologies are also under development to use specific detected mutations to predict the availability of neoantigens for directed therapy (26).

Although MPM is characterized by relatively low mutation burden (25), early phase trials of immune checkpoint inhibitor therapy indicate activity in MPM. For example, KEYNOTE-028 (27) demonstrated 20% partial response and 52% stable disease rates using anti-programmed cell death receptor 1 (PD-1) antibody pembrolizumab. Lizotte and colleagues studied the immune profile of fresh MPM tumor biopsies obtained by fine needle aspiration using flow cytometry (28). Lizotte *et al.* found that non-epithelioid tumors demonstrated a more immunosuppressive microenvironment and were more likely to express PD-L1, but patient response in KEYNOTE-028 was unrelated to PD-L1 immunohistochemistry. Ongoing trials of anti-PD1 therapy for MPM include a pre-treatment biopsy to allow discovery of predictive biomarkers relevant to MPM that may ultimately be measurable in biopsy specimens.

Currently, histological analysis of the diagnostic pleural biopsy provides only modest prognostic information, but in the absence of definitive pathological staging and subtyping remains one of few indicators relevant to the surgical decision. In the context of evolving molecular technologies that require diminishing quantities of specimens, and of novel biologic and immune-based therapies, significant potential exists for accurate prognostic and predictive information to be ascertained from molecular analysis of biopsy material prior to determining treatment strategy. As the spectrum of available treatment options continues to expand, surgical intervention might be discouraged where surgical biopsy-based assays predict efficacy for less invasive or morbid alternatives such as targeted biologics or immune modulation. Conversely, prediction of resistance to such therapeutic approaches may shift the risk-benefit analysis in favor of surgical resection.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Merritt N, Blewett CJ, Miller JD, et al. Survival after conservative (palliative) management of pleural malignant mesothelioma. *J Surg Oncol* 2001;78:171-4.
2. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al. Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results in 183 patients. *J Thorac Cardiovasc Surg* 1999;117:54-63; discussion 63-5.
3. Benamore RE, O'Doherty MJ, Entwisle JJ. Use of imaging in the management of malignant pleural mesothelioma. *Clin Radiol* 2005;60:1237-47.
4. Geltner C, Errhalt P, Baumgartner B, et al. Management of malignant pleural mesothelioma - part 1: epidemiology, diagnosis, and staging : Consensus of the Austrian Mesothelioma Interest Group (AMIG). *Wien Klin Wochenschr* 2016;128:611-7.
5. Ruffie P, Feld R, Minkin S, et al. Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: a retrospective study of 332 patients. *J Clin Oncol* 1989;7:1157-68.
6. Attanoos RL, Gibbs AR. The comparative accuracy of different pleural biopsy techniques in the diagnosis of malignant mesothelioma. *Histopathology* 2008;53:340-4.
7. Boutin C, Loddenkemper R, Astoul P. Diagnostic and therapeutic thoracoscopy: techniques and indications in pulmonary medicine. *Tuber Lung Dis* 1993;74:225-39.
8. Brockstedt U, Gulyas M, Dobra K, et al. An optimized battery of eight antibodies that can distinguish most cases of epithelial mesotheliomas from adenocarcinomas. *Am J Clin Pathol* 2000;114:203-9.
9. Cury PM, Butcher DN, Fisher C, et al. Value of the Mesothelium-Associated Antibodies Thrombomodulin, Cytokeratin 5/6, Calretinin, and CD44H in Distinguishing Epithelioid Pleural Mesothelioma from Adenocarcinoma Metastatic to the Pleura. *Mod Pathol* 2000;13(2):107-112.
10. Dejmeek A, Hjerpe A. Reactivity of Six Antibodies in Effusions of Mesothelioma, Adenocarcinoma and Mesothelioidosis: Stepwise Logistic Regression Analysis. *Cytopathology* 2000;11:8-17.
11. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase

- III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636-44.
12. van Meerbeek JP, Gaafar R, Manegold C, et al. Randomized phase III study of cisplatin with or without raltitrexed in patients with malignant pleural mesothelioma: an intergroup study of the European Organisation for Research and Treatment of Cancer Lung Cancer Group and the National Cancer Institute of Canada. *J Clin Oncol* 2005;23:6881-9.
 13. Ettinger DS, Wood DE, Akerley W, et al. NCCN Guidelines Insights: Malignant Pleural Mesothelioma, Version 3.2016. *J Natl Compr Canc Netw* 2016;14:825-36.
 14. Travis WD, Colby TV, Corrin B, et al. World Health Organization International Histological Classification of Tumours: Histological Typing of Lung and Pleural Tumours. 3rd ed. Berlin: Springer, 1999.
 15. Johansson L, Linden C-J. Aspects of histopathologic subtype as a prognostic factor in 85 pleural mesothelioma. *Chest* 1996;109:109-14.
 16. Balduyck B, Trousse D, Nakas A, et al. Therapeutic surgery for nonepithelioid malignant pleural mesothelioma: is it really worthwhile? *Ann Thorac Surg* 2010;89:907-11.
 17. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: International Agency for Research on Cancer, 2015.
 18. Travis WD, Brambilla E, Muller-Hermelink KH, et al. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press, 2004.
 19. Vigneswaran WT, Kircheva DY, Ananthanarayanan V, et al. Amount of Epithelioid Differentiation Is a Predictor of Survival in Malignant Pleural Mesothelioma. *Ann Thorac Surg* 2017;103:962-6.
 20. Bueno R, Reblando J, Glickman J, et al. Pleural biopsy: a reliable method for determining the diagnosis but not subtype in mesothelioma. *Ann Thorac Surg* 2004;78:1774-6.
 21. Greillier L, Cavailles A, Fraticelli A, et al. Accuracy of pleural biopsy using thoracoscopy for the diagnosis of histologic subtype in patients with malignant pleural mesothelioma. *Cancer* 2007;110:2248-52.
 22. Kao SC, Yan TD, Lee K, et al. Accuracy of diagnostic biopsy for the histological subtype of malignant pleural mesothelioma. *J Thorac Oncol* 2011;6:602-5.
 23. Gordon GJ, Dong L, Yeap BY, et al. Four-gene expression ratio test for survival in patients undergoing surgery for mesothelioma. *J Natl Cancer Inst* 2009;101:678-86.
 24. De Rienzo A, Cook RW, Wilkinson J, et al. Validation of a Gene Expression Test for Mesothelioma Prognosis in Formalin-Fixed Paraffin-Embedded Tissues. *J Mol Diagn* 2017;19:65-71.
 25. Bueno R, Stawiski EW, Goldstein LD, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. *Nat Genet* 2016;48:407-16.
 26. Lai J, Zhou Z, Tang XJ, et al. A Tumor-Specific Neo-Antigen Caused by a Frameshift Mutation in BAP1 Is a Potential Personalized Biomarker in Malignant Peritoneal Mesothelioma. *Int J Mol Sci* 2016;17. doi: 10.3390/ijms17050739.
 27. Alley EW, Lopez J, Santoro A, et al. Clinical safety and activity of pembrolizumab in patients with malignant pleural mesothelioma (KEYNOTE-028): preliminary results from a non-randomised, open-label, phase 1b trial. *Lancet Oncol* 2017;18:623-30.
 28. Lizotte PH, Jones RE, Keogh L, et al. Fine needle aspirate flow cytometric phenotyping characterizes immunosuppressive nature of the mesothelioma microenvironment. *Sci Rep* 2016;6:31745.

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