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A Histomorphologic Grading System That Predicts Overall Survival in Diffuse Malignant Peritoneal Mesothelioma With Epithelioid Subtype

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Abstract: Diffuse malignant peritoneal mesothelioma (MPeM) is rare and arises from peritoneal serosal surfaces. Although it shares similar histomorphology with its counterpart, malignant pleural mesothelioma, etiologies, clinical courses, and therapies differ. Nuclear grading and level of mitoses have been correlated with prognosis in malignant pleural mesothelioma with epithelioid subtype. Whether nuclear grading and level of mitoses correlate with prognosis in MPeM is still unknown. Our study utilizes a 2 tier system incorporating nuclear features and level of the mitoses to stratify cases of MPeM with epithelioid subtype. Fifty-one cases of MPeM with clinical follow-up underwent retrospective microscopic review. From that subset, 46 cases were of epithelioid subtype, which were then stratified into a low-grade or high-grade tier. Survival times were calculated on the basis of Kaplan-Meier analysis. The low-grade tier had higher overall survival with a median of 11.9 years and 57% at 5 years when compared with the high-grade tier with a median of 3.3 years and 21% at 5 years ($P = 0.002$). Although not statistically significant, the low-grade tier had higher progression-free survival with a median of 4.7 years and 65% at 5 years when compared with the high-grade tier with a median of 1.9 years and 35% at 5 years ($P = 0.089$). Our study is first to specifically evaluate and correlate nuclear features and level of mitoses with overall survival in MPeM with epithelioid subtype.

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Malignant mesothelioma is a rare neoplasm arising from the serosal surfaces of the pleura, peritoneum, tunica vaginalis, and the pericardium. The majority of mesothelioma cases are pleural based, with a strong correlation to prior asbestos exposure.[1,2] Diffuse malignant peritoneal mesothelioma (MPeM) is the second most common site of origin, often with a very poor outcome, as patients are frequently diagnosed at an advanced stage.[3,4] An estimated 10% to 30% of all overall mesothelioma diagnoses per year in the United States occur in the peritoneal cavity.[5] The 3 main subtypes of malignant mesothelioma are epithelioid, sarcomatoid, and biphasic.[4] The most common subtype, the epithelioid subtype, has been further divided into histologic patterns of tubulopapillary, adenomatoid (microglandular), or solid.[6] The 2004 World Health Organization Classification system adds a fourth subtype, desmoplastic[7]; in addition, deciduoid, clear cell, adenoid cystic, small cell, signet-ring cell, oncocytoid, rhabdoid, glomeruloid, and pleomorphic patterns have also been described. Because of the uncommon nature of this neoplasm, few studies have been performed to correlate histologic features and overall outcome, and most pathologic interpretations of cancer rely on specific histologic parameters to provide data on prognosis and staging with some evidence of correlation.[3,8,9] Our group has considerable experience in investigating diffuse MPeM including the cytopathologic aspects of the disease.[10–13] A histomorphologic grading system for pleural mesothelioma has been proposed in 2011 on the basis of nuclear features and level of mitoses by Kadota et al.[1] We used the basis of that study to propose a 2-tier histomorphologic grading system to explore a correlation for nuclear features and level of mitoses with survival in diffuse MPeM of epithelioid morphology.

MATERIALS AND METHODS

Cases of diffuse MPeM (n = 51) from Wake Forest School of Medicine Department of Pathology were collected

spanning the period from 1984 to 2013. All of the patients in our study received standard treatment for disseminated peritoneal mesothelioma, which included cytoreductive surgery, followed by hyperthermic intraperitoneal chemotherapy.[2] The technique for the cytoreductive surgery is described by Levine et al.[14] Clinical information was obtained from a database prospectively maintained by the Surgical Oncology Service at Wake Forest Baptist Health. The clinical information encompassed data elements including sex, age, surgical assessment of resection, and the hyperthermic intraperitoneal chemotherapy regimen at first surgery. Female patients with a history of ovarian carcinoma or where primary serous carcinoma was suspected based on overall clinical assessment were excluded from the cohort. The categories for surgical assessment of resection (R0, R1, R2a, R2b, and R2c) are specifically outlined by Stewart et al.[15] The types of hyperthermic intraperitoneal chemotherapy regimen patients received were divided into those regimens including mitomycin-C versus cisplatin. The evaluation of these specimens along with the associated clinical information was approved by the Wake Forest School of Medicine Institutional Review Board.

Retrospective microscopic examination was performed by 2 experienced surgical pathologists and included review of all available (median: 10, range: 1 to 75 slides/case) hematoxylin and eosin–stained slides for a given patient before hyperthermic intraperitoneal adjuvant chemotherapy. The slides were derived from the initial biopsy and standard cytoreductive large surgical specimen. Confirmation of peritoneal mesothelioma was obtained on the basis of outside institution immunohistochemistry results or clinical impression to support the diagnosis of peritoneal mesothelioma. The cases with nonepithelioid morphology were segmented from those of epithelioid subtype using an Olympus BX41 microscope (Olympus, Tokyo, Japan) with a standard eyepiece of 22 mm diameter. For each case with epithelioid morphology, nuclear atypia and mitoses were examined. Discordance between pathologists in assessment of nuclear atypia and/or mitotic activity was resolved by review of the cases together, and a consensus on grading was reached.

Nuclear atypia was evaluated using a high-power field (HPF) at $\times 400$ magnification (0.237 mm^2 field of view). For nuclear atypia, the area with the highest degree of atypia was recorded and only if it consisted of $> 5\%$ of the entire tumor. The vast majority of tumors exhibited little to no heterogeneity. Tumors consisting of high-grade zones within an overall low-grade tumor were not included in the study, unless consisting of $> 5\%$ of the entire tumor. Considerations in the scoring for nuclear atypia include: nuclear size, nuclear uniformity, shape, membrane outlines and irregularity, nuclear to cytoplasmic (N/C) ratio, chromatin pattern, and prominence of nucleoli. Prominence of nucleoli was evaluated using as reference nearby red blood cells, which measured approximately 7 μm.

After factoring all these considerations, a nuclear atypia score of 1, 2, or 3 was rendered. Mild atypia, or score 1, included nuclei uniform in size and shape, low N/C ratios, a chromatin pattern that was homogenous with a fine granular pattern, and/or indistinct/inconspicuous or very small, distinct nucleoli (< 3 μm). Severe atypia, or score 3, includes marked membrane irregularities, bizarre contours, nuclear enlargement (at least twice as large as others), marked variability in size and shape, high N/C ratios, a coarsely granular chromatin pattern, and/or prominent large nucleoli (>3 μm).

Mitoses were evaluated in 50 HPF areas (11.85 mm^2), with the highest mitotic activity identified after scanning through all tumor slides and counted as an average of mitotic figures per 10 HPF. To distinguish mitotic figures from pyknotic cells, the following were used: absence of a nuclear membrane or a central clear zone, presence of hairy rather than triangular or spiky projections, reflection of a mitotic spindle, and cytoplasmic basophilia rather than eosinophilia. Areas of necrosis and prominent stromal fibrosis or inflammation were avoided, whenever possible. In the cases in which only small areas of viable tumor were available for review, the best attempt was made to assess the equivalent of 10 full HPFs of viable tumor for mitosis counting. A mitotic score was rendered using the following cutoff values: mitotic score 1 for 0 to 1/10 HPF, mitotic score 2 for 2 to 4/10 HPF, and mitotic score 3 for $> 5/10$ HPF.

The summation of the nuclear atypia score and the mitotic score resulted in the implementation of a 2-tier system. The low-grade tier included cases with a total sum of 3 or less. The high-grade tier included cases with a total sum of 4 to 6, 6 being the maximum sum.

The Kaplan-Meier method was used to estimate overall survival (OS) and progression-free survival (PFS) times for the low-grade and high-grade groups from the epithelioid subtype. If a patient died without a known date of recurrence/progression, the patient's length of progression-free time was calculated as being half of their survival time; this midpoint approach avoids being potentially too conservative (placing progression at date of surgery) or too liberal (placing progression date at time of death). This choice of progression-free time is routinely used when the date of progression is unknown; using the midpoint of the survival length prevents overestimation of PFS that would likely occur by using date of death. Patients with R0, R1, and R2a defined groups (ranging from no gross disease with negative microscopic margins up to 5 mm of residual tumor) were used in the PFS calculations. The aggregate of the R0, R1, and R2a defined groups were deemed complete resections. Those patients as defined as R2b and R2c (6 mm or greater in gross residual disease) were not considered to be disease free. The aggregate of the R2b and R2c defined groups were deemed incomplete resections. To assess differences in the study groups, the log-rank test of the χ^2 approximation was used, and a P-value < 0.05 was deemed to be significant.

RESULTS

Of the 51 cases of diffuse MPeM, 46 cases were of epithelioid subtype and 5 cases of nonepithelioid

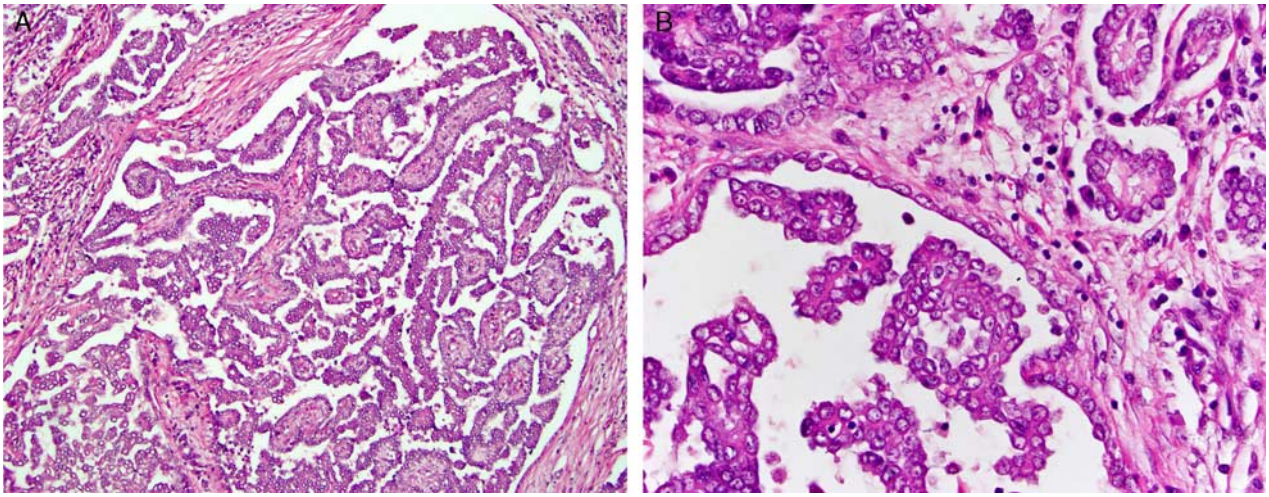

FIGURE 1. A and B, Representative images of the low-grade tier (hematoxylin and eosin). The tumor cells show mild atypia (score 1) with nuclei that are uniform in size and shape with a finely granular chromatin pattern. Mitoses are <1/10 HPF (score 1). 863 × 677 mm (72 × 72 DPI).

morphology. Of the 46 cases of epithelioid subtype, 18 cases were classified in the low-grade tier, and 28 cases were classified in the high-grade tier. Figures 1A and B are representative images of cases in the low-grade tier and Figures 2A and B are representative images of cases in the high-grade tier. In the 5 cases of nonepithelioid morphology, 4 cases were of biphasic subtype and 1 case of undifferentiated sarcomatoid subtype.

Table 1 outlines OS times, with Figure 3 displaying the corresponding OS Kaplan-Meier curves. The low-grade tier had the higher OS with a median of 11.9 years and 57% at 5 years when compared with the high-grade tier with a median of 3.3 years and 21% at 5 years ($P = 0.002$). Table 2 outlines PFS times with, Figure 4 displaying the corresponding PFS Kaplan-Meier curves. The low-grade tier had the higher PFS with a median of 4.7 years and 65% at 5 years when compared with the high-grade tier with a median of 1.9 years and 35% at 5 years. PFS was of borderline statistical significance ($P = 0.089$).

The proportion of cases within each category for surgical assessment of resection between the 2 tiers is outlined in Supplemental Digital Content Table 1 (Supplemental Digital Content 1, http://links.lww.com/PAS/A390). Additional information of OS and PFS times for the cases of nonepithelioid morphology is outlined in Supplemental Digital Content Table 2 (Supplemental Digital Content 2, http://links.lww.com/PAS/A391). Comparisons of OS and PFS level of statistical significance overall for the study cohort and individually between the study groups (ie, low-grade tier, high-grade tier, and nonepithelioid morphology) are outlined

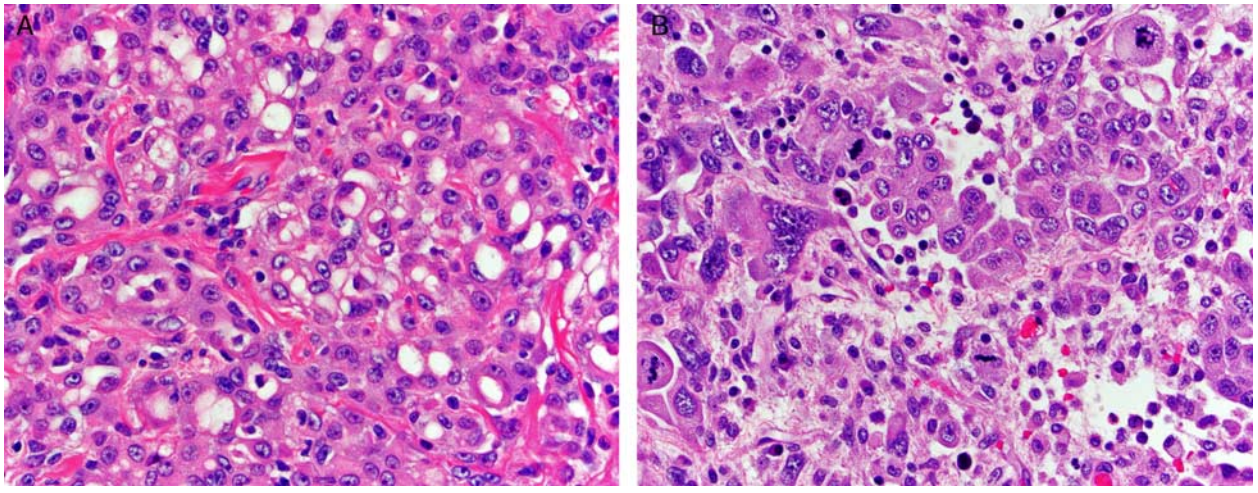

FIGURE 2. A and B, Representative image of the high-grade tier (hematoxylin and eosin). The tumor cells show severe atypia (score 3) with nuclei that have marked membrane irregularities, bizarre contours, nuclear enlargement, marked variability in size and shape, coarsely granular chromatin pattern, and prominent large nucleoli (> 3 μm). Mitoses are >5/10 HPF (score 3). 863 × 677 mm (72 × 72 DPI).

TABLE 1. OS Times

		%						
Time	**Group**	**6 mo**	**1 y**	**2 y**	**3 y**	**5 y**	**Median**	**N**
Survival	Low grade	1	94 (6)	87 (9)	87 (9)	57 (13)	11.9 y	18
Survival	High grade	71 (9)	68 (9)	68 (9)	52 (10)	21 (9)	3.3 y	28

in Supplemental Digital Content Table 3 (Supplemental Digital Content 3, http://links.lww.com/PAS/A392).

Assessment for confounding factors was compared between the 2 tiers. All 51 cases showed invasion, eliminating that variable as a confounding factor. No statistically significant difference between the 2 tiers was seen with sex (17/28 [61%] female vs. 10/18 [56%] male; $P = 0.77$). No statistically significant difference between the 2 tiers was seen with age (mean 48 y [SD ± 15 y] in low-grade vs. mean 52 y [SD ± 15 y] in high grade; $P = 0.39$).

With surgical assessment of resection, no statistically significant difference between the 2 tiers was seen when evaluating the proportion of each defined group within each tier (2/18 [11%] R0, 3/18 [17%] R1, 8/18 [44%] R2a, 2/18 [11%] R2B, 3/18 [17%] R2C in low grade; 5/28 [18%] R0, 0/28 [0%] R1, 14/28 [50%] R2a, 3/28 [11%] R2b, 6/28 [21%] R2c in high grade; $P = 0.32$). No statistically significant difference between the 2 tiers (5/18 [28%] in low grade vs. 5/28 [18%] in high grade; $P = 0.48$) was seen in the subset of complete resections without any gross disease (R0 and R1 aggregated). Furthermore, between the 2 tiers, the proportion of incomplete resections (R2b and R2c aggregated) that encompassed cases excluded from the PFS analysis showed no statistically significant difference (5/18 [28%] in low grade vs. 9/28 [32%] in high grade; $P > 0.99$).

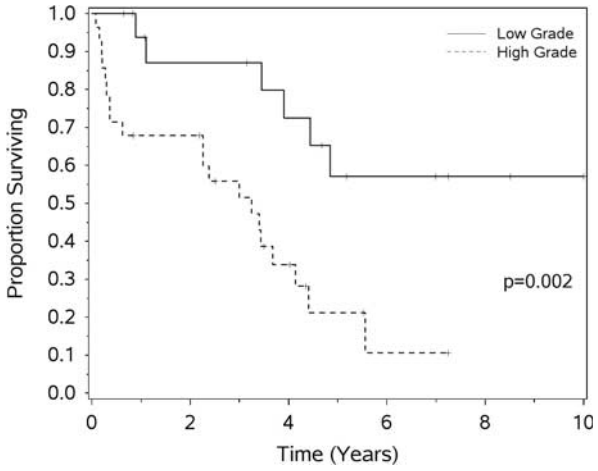

FIGURE 3. Kaplan-Meier analysis of OS for groups in the low-grade tier and high-grade tier for MPeM with epithelioid subtype. The low-grade tier had the higher OS with a median of 11.9 years and 57% at 5 years when compared with the high-grade tier with a median of 3.3 years and 21% at 5 years. The results did achieve statistical significance ($P = 0.002$). 396 × 317 mm (96 × 96 DPI).

Finally, with types of received hyperthermic intraperitoneal chemotherapy regimen, no statistically significant difference between the 2 tiers was seen with regard to variations of mitomycin-C (4/18 [22%] low grade vs. 12/28 [43%] high grade; $P = 0.21$) or cisplatin (8/18 [44%] low grade vs. 9/28 [32%] high grade; $P = 0.53$).

DISCUSSION

Albeit sparse with malignant mesothelioma, several studies have attempted to explore histomorphologic features in correlation with prognostic significance. Moreover, most of those studies have focused on malignant pleural mesothelioma as opposed to diffuse MPeM. Even fewer are studies that have tangentially addressed the effect of histomorphologic features on diffuse MPeM in correlation with prognostic significance.[16–19] This is probably attributable to rarity of diffuse MPeM and experience in managing and collecting large study cohorts.

Our group has extensively investigated both the clinical and pathologic features of diffuse MPeM, including the investigational biomarker aspects of the disease.[10–13] With this experience, we have been able to accrue a very large cohort for such a rare disease and, in addition, be the first study to focus specifically rather than tangentially on the correlation between histomorphologic features and prognostic significance.

The study by Kadota et al[1] was a landmark because it was able to associate prognosis of malignant pleural mesothelioma based specifically on nuclear features and the level of mitoses. That study showed a histomorphologic grading system that correlated with OS and PFS times. Taking a similar approach, our study used a 2-tier system of low grade versus high grade to explore OS and PFS times with diffuse MPeM.

In our study cohort, for those cases with epithelioid morphology there was clear delineation with statistical significance between the low-grade tier versus the high-grade tier group (median of 11.9 y and 57% at 5 y vs. a median of 3.3 y and 21% at5 y). This clear delineation between the low-grade tier and high-grade tier of diffuse MPeM supports use of such a 2-tier grading system in the reporting of diffuse MPeM.

In our study cohort, for those cases with epithelioid morphology, correlation was evident in PFS times between the low-grade tier versus the high-grade tier group (median of 4.7 y and 65% at 5 y vs. a median of 1.9 y and 35% at 5 y). These PFS results came close but did not reach statistical significance ($P = 0.089$), and there is a potential reason for this.

The number of cases used in the statistics for PFS were lower in both the low-grade and high-grade tiers, due to the nature of calculating PFS, as the cases excluded in both tiers had incomplete resections (R2B/C) and therefore were never considered recurrence free. In the low-grade tier, this corresponded to 5 of 18 (27.7%) cases. In the high-grade tier, this corresponded to 9 of 28 cases (32.1%). Although the completeness of surgical cytoreduction is a major prognostic factor, no statistically significant difference

TABLE 2. PFS Time

		%						
Time	**Group**	**6 mo**	**1 y**	**2 y**	**3 y**	**5 y**	**Median**	**N**
Progression-free	Low grade	1	84 (10)	65 (14)	65 (14)	65 (14)	4.7+ y*	13
Progression-free†	High grade	68 (11)	58 (11)	47 (11)	41 (11)	35 (11)	1.9 y	19

*Median not yet reached (survival still > 50% at last subject).
†No resection of R2B/C.

was found between the low-grade and high-grade tiers in terms of complete or incomplete resections. Furthermore, it is conceivable that with more accrued cases, statistical significance for PFS could be achieved.

The low number of available cases (n = 5) did preclude generating statistically significant correlations comparing diffuse MPeM of epithelioid morphology versus nonepithelioid morphology. This was not surprising, as biphasic, undifferentiated, and sarcomatoid morphologies are rare manifestations of diffuse peritoneal mesothelioma, an already rare disease. Several studies have shown that biphasic and undifferentiated/sarcomatoid subtypes have a worsened prognosis and refractory response to chemotherapy compared with the epithelioid morphology.[18–21] That stated, despite the relatively low number of available cases, it was surprising to see that OS times were remarkably better than the high-grade tier of epithelioid morphology (21% and 75% at 5 y, respectively, for OS).

Over the last decade, aggressive regional therapy using cytoreductive surgery and hyperthermic intraperitoneal chemotherapy has been increasingly applied to patients with diffuse MPeM. There are 2 rationales behind this therapeutic approach.

The first rationale is that complete or near-complete cytoreduction in generally over one half of all patients undergoing exploration is achievable. Theoretically this is due to diffuse MPeM remaining confined to the peritoneal cavity in the majority of cases and because the peritoneal implants are superficial and do not invade the underlying tissues deeply until the late stages.

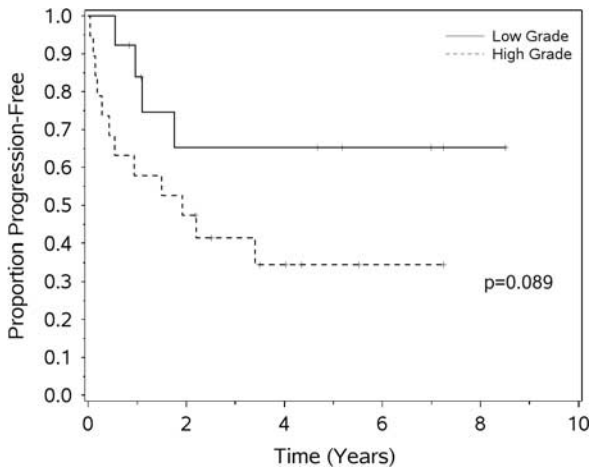

FIGURE 4. Kaplan-Meier analysis of PFS for groups in the low-grade tier and high-grade tier for MPeM with epithelioid subtype. The low-grade tier had the higher PFS with a median of 4.7 years and 65% at 5 years when compared with the high-grade tier with a median of 1.9 years and 35% at 5 years. The results came close but did not achieve statistical significance ($P = 0.089$). 396 × 317 mm (96 × 96 DPI).

The second rationale is that direct intraperitoneal administration of chemotherapy permits a several-fold increase in drug concentration in the peritoneum compared with systemic administration.[22] Despite this regional advantage, direct penetration into tumor tissue is limited to a few millimeters and, hence, the theoretical enhancement through heating the perfusate containing chemotherapy.

With cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, OS in recent studies ranges from a median of 10.8 to 63 months and 17% to 53% 5-year survival rates.[3,23–29] Despite efficacy, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy has considerable reported preoperative morbidity and mortality ranging in recent studies from 30% to 39% preoperative morbidity and up to 6% preoperative mortality.[3,23–25,28]

As all cases in our study cohort, regardless of grade tier, received cytoreductive surgery, followed by hyperthermic intraperitoneal chemotherapy, the separation of malignant mesothelioma of epithelioid subtype into 2 tiers should be considered, at this juncture, as prognostic, as opposed to predictive, for hyperthermic intraperitoneal chemotherapy.

Potential areas of future investigation include aggregating experiences from multiple institutions to see whether our results are validated and to look further into investigational predictive biomarkers for those cases in the high-grade tier.

In conclusion, our study shows that using a 2-tier histomorphologic grading system for epithelioid diffuse MPeM is prognostically effective at determining OS. Of our cases in the low-grade tier, epithelioid MPeM has a longer survival time when compared with our cases of epithelioid MPeM in the high-grade tier.

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