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Reproducibility of histological subtyping of malignant pleural mesothelioma

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Abstract

Malignant pleural mesothelioma (MPM) has a very poor prognosis. Although clinical stage is currently the only reliable prognostic factor, histologic subtyping reportedly also affects prognosis. Some studies propose reclassification of pleomorphic epithelioid as biphasic or sarcomatoid MPM. This study assessed prognostic significance and interobserver agreement in MPM subtyping of small biopsy specimens. We analyzed biopsy specimens, clinical and survival data from records of 108 patients who were diagnosed between 2000 and 2010 at the Institute of Pathology University of Zagreb School of Medicine, of whom 98 had epithelioid MPM, 6 biphasic MPM and 4 sarcomatoid MPM. Among epithelioid subtypes, 44 (44.9%) were solid, 19 (19.4%) tubulopapillary, 18 (18.4%) acinar, 6 (6.1%) adenomatoid, 5 (5.1%) pleomorphic, 4 (4.1%) trabecular and 2 (2.0%) micropapillary subtype. Interobserver reliability for histological diagnosis was found to be $\kappa = 0.72$ ($P < 0.001$). Median overall survival for epithelioid MPM was 10.5 months with an interquartile range (IQR) of 5.8–28.0 months, but significantly shorter for the pleomorphic subtype (3 [IQR 3.0–8.0] months; $P = 0.034$), but not significantly different from biphasic (6.5 [IQR 3.5–15.3] months) and sarcomatoid mesothelioma (4.0 [IQR 1.3–6.8] months; $P = 0.270$). We found strong reproducibility of MPM subtyping with good interobserver agreement. Furthermore, our results indicate that pleomorphic subtype to be a predictor of poor prognosis, and support classifying it with sarcomatoid or biphasic MPM, as patients with the pleomorphic, biphasic or sarcomatoid subtype show similarly poor overall survival.

Key words: malignant pleural mesothelioma subtyping, epithelioid mesothelioma, pleomorphic mesothelioma, survival, prognostic factor.

Introduction

Malignant pleural mesothelioma (MPM) is a rare, aggressive cancer that develops from mesothelial cells. MPM is most commonly caused by exposure to asbestos fibers; because of its long latency period, its increasing incidence is expected to peak in this decade, at least for developed countries [1]. Although MPM is the most common primary pleural malignancy, it is rather difficult to diagnose [2]. It is still incurable, with median survival after symptom onset of up to 12 months, despite advances in multimodality protocols [3–5]. A small number of patients have reportedly survived longer than 5 years [6, 7]. Management of patients with MPM should be based on prognostic factors with more aggressive therapy, for example, applied to patients who are expected to survive longer. Histology and TNM staging show the highest prognostic significance although these classifications are rather robust and not precise [8].

The current 2004 World Health Organization classification of pleural tumors [9] recognizes three main histological types of mesothelioma, epithelioid (accounting for 50–60%), biphasic (25–35%) and sarcomatoid (10–20%) [10]; however, even within single histological types, MPM is very heterogeneous with various histological patterns, especially in the epithelioid type. The importance of histological subtyping lies in their significant bearing on survival, with epithelioid having the best prognosis [11], whereas the pleomorphic subtype and sarcomatoid MPMs both reportedly have similarly poor outcomes [12]. The 2012 Update of the Consensus Statement from the International Mesothelioma Interest Group recommended that MPM diagnoses include subtype if possible, with histological pattern in the description [13]. So far, only Kadota et al have comprehensively subtyped epithelioid mesothelioma and correlated its clinicopathological characteristics and prognosis, mainly using extrapleural pneumectomy and pleurectomy

decortication samples; their study suggested reclassifying pleomorphic epithelioid mesothelioma as a biphasic or sarcomatoid type based on its very poor survival [11], which accords with an earlier study by Ordonez who analyzed 10 pleomorphic mesotheliomas [12].

This study assessed interobserver agreement in subtyping of MPM using small biopsy specimens, and prognostic significance of subtypes.

Materials and Methods

We identified 135 patients who were diagnosed with MPM between 2000 and 2010 at the Institute of Pathology University of Zagreb School of Medicine, using the Institute's records and specimen archives; and extracted each patient's age, sex, asbestos exposure, laterality, presence of pleural effusion, diagnostic procedure, TNM stage, and treatment from the database of the Clinic for Lung Diseases Jordanovac, University Hospital Centre Zagreb, and from the Croatian National Cancer Registry. Patients were restaged according to the seventh AJCC, using mainly computed tomography (CT) and, more recently, positron emission tomography (PET). We ascertained patients' survival data as of 23 August 2013. This study was approved by our institutional review board.

Pathologic diagnosis was based on hematoxylin–eosin (HE)-stained slides and immunohistochemistry, using at least two positive markers of calretinin, CK 5/6, WT-1, and thrombomodulin, and at least two negative markers for adenocarcinoma (carcinoembryonic antigen, thyroid transcription factor-1 and CD15).

All HE-stained slides were reviewed independently by two pathologists (L.B. and S.S.) and classified as epithelioid, sarcomatoid or biphasic type, according to the 2004 WHO classification criteria for pleural tumors [9], and used a median of 3 slides per case (range: 1–16). Epithelioid MPM were further subtyped according to their predominant patterns as

acinar, adenomatoid (microglandular), micropapillary, solid, tubulopapillary, and trabecular as defined previously [11, 13, 14] (Fig. 1 and 2). Slides were reviewed individually by each pathologist but were reviewed together to reach a consensus in cases of disagreement. Myxoid changes in stroma were evaluated in all samples, and regarded as positive if they occupied more than 50% of a tumor sample [15].

Statistical analysis

For all patients, potential prognostic factors were measured at the time of diagnosis and evaluated as categorical variables. Differences in survival time between histology groups were assessed with Kruskal–Wallis test with corresponding Mann–Whitney U test for post-hoc analyses. For OS analysis, Kaplan–Meier curves were compared using log-rank test. All patients still alive at the last follow-up were censored. The Cox proportional hazards regression model was used for multivariate analysis. We calculated hazard ratios and 95% confidence intervals. We analyzed interobserver reliability using the κ statistic to determine consistency between pathologists. $P < 0.05$ was considered significant. All analyses used IBM SPSS Statistics 21.0 (www.spss.com; SPSS Inc., USA).

Results

Patients' demographic and clinicopathological data are summarized in Table 1. Out of the initial 135 patients, we included 108 patients who had microscopically confirmed diagnoses of mesothelioma and complete clinical information. Their median age for all types was 63 (interquartile range; IQR 54–69) years; most patients (65/108, 60.2%) were 65 years or younger. Of the 108 patients, 86.1 % (93/108) were male; 37.9% (41/108) had histories of occupational exposure to asbestos, although this data was not available for all patients; 63.9% (69/108) had tumors in their right lungs; 71.3% (77/108) had pleural effusion; 4.6% (5/108) had stage II disease, 24.1% (26/108) had stage III disease and

71.3% (77/108) had stage IV disease, but none had stage I disease. Some 60.2% (65/108) of patients were diagnosed by video-assisted thoracoscopic surgery; 32.4% (35/108) underwent open biopsy and 7.4% (8/108) had percutaneous pleural biopsy. Only 13% (14/108) underwent palliative surgery, of which 92.9% (13/14) were pleurectomy decortications and one (7.1%; 1/14) was an extrapleural pneumonectomy.

We found 90.7% (98/108) of specimens were epithelioid, 5.6% (6/108) biphasic and 3.7% (4/108) sarcomatoid MPM. Among the 98 epithelioid-type specimens, 44.9% (44/98) were solid, 19.4% (19/98) tubulopapillary, 18.4% (18/98) acinar, 6.1% (6/98) adenomatoid, 5.1% (5/98) pleomorphic, 4.1% (4/98) trabecular and 2.0% (2/98) micropapillary subtypes (Figure 3). Interobserver reliability for the 2 pathologist was found to be κ=0.72 ($P < 0.001$).

Median overall survival (OS) for epithelioid type was 10.5 months (IQR 5.8–28.0 months), whereas the pleomorphic subtype had a significantly shorter OS (median 3 [IQR 3.0–8.0] months, $P = 0.034$), that was not significant different from those of the biphasic (6.5 [IQR 3.5–15.3] months) and sarcomatoid subtypes (4.0 [IQR 1.3–6.8] months; $P = 0.270$). Patients' ages did not significantly differ among the different subtypes of epithelioid MPM or in comparison to the sarcomatoid and biphasic types.

Among epithelioid subtypes, the pleomorphic subtype was associated with significantly shorter OS (median 3 months [IQR 3.0–8.0], $P = 0.034$). The adenomatoid and tubulopapillary subtypes had the longest OS (median 25.5 months each), followed by acinar (median OS 13 [IQR 5.8–29.3] months), trabecular and micropapillary (median OS 11 months each), and solid subtypes (median OS 8.5 months). Cox's proportional hazards regression models proved pleomorphic subtype to be a significant predictor for shorter OS (Table 2). Compared with the pleomorphic subtype, decreased risk of death by subtype was

adenomatoid: 81.5%; tubulopapillary: 80.3%; acinar: 73.2%; solid: 72.9%; trabecular: 61.5%; and micropapillary: 58.9%. Bivariate and multivariate analyses showed age, sex, pleural effusion, laterality, surgery type, myxoid stroma and asbestos exposure had no prognostic significance. Moreover, the log-rank test showed that OS among patients with the pleomorphic subtype did not significantly differ from those with biphasic or sarcomatoid subtypes ($P = 0.270$; Figure 4).

Discussion

We reviewed MPM specimens from the archives of the Institute of Pathology, University of Zagreb School of Medicine to evaluate interobserver agreement in subtyping small biopsy samples, and to evaluate the prognostic significance of subtyping.

Older age, higher clinical stage and non-epithelioid histological type have been associated with shorter survival (review by Pass [16]). The 2012 Update of the Consensus Statement from the International Mesothelioma Interest Group guidelines recognized difficulties with pattern recognition in small biopsies, and recommended using three main histological types (epithelioid, sarcomatoid, biphasic) with pattern descriptions in medical records, if possible [13]. Histological subtyping/patterns in many carcinomas correlate with patients' clinicopathological characteristics [17–22]. A reclassification proposal for resectioned lung adenocarcinoma specimens has even proposed reporting different patterns by 5% increments, based on predominant histology, as these patterns closely correlate to molecular and genetic characteristics and, more importantly, prognosis [23].

The idea of similar correlation in MPM patients is very appealing, especially for centers that do not routinely perform extrapleural pneumonectomies and pleurectomy decortications, and relevant specimens are not abundant. Histopathological typing for

MPM is apparently influenced by the size of tissue sample [24] and those from complete surgical resection may differ from initial diagnostic biopsies [25].

For the purpose of our study we used tubulopapillary, adenomatoid (also called microglandular), solid, acinar, micropapillary, trabecular and pleomorphic subtypes (the latter as defined in the 2004 WHO guidelines) [9]. We found that micropapillary, trabecular and pleomorphic subtypes are relatively few, accounting for only 2%, 4.1% and 5.1% of MPMs, respectively.

This scarcity demonstrates a limitation of our study: the small subject groups for some subtypes. It may also reflect a problem with smaller specimens. Most our samples were obtained using VATS and open biopsy, with a median of 3 slides reviewed per case (range: 1–16). In contrast, almost 90% of samples in the study by Kadota K. et al [11] were diagnosed on much larger extrapleural pneumonectomy and pleurectomy decortication specimens, resulting in significantly more reviewed slides per patient (median: 9 slides, range: 1–43). The very small size of the most of our samples occasionally made subtyping difficult, although interobserver reliability showed substantial agreement.

Because of these small numbers for specific subtypes, some of our statistical results should be viewed cautiously. With that caveat, our results indicate that the very poor OS for the pleomorphic subtype of epithelioid MPM is statistically indistinguishable from biphasic and sarcomatoid types of MPM. The sarcomatoid type has the worst prognosis and is a negative predictive factor for chemotherapy and radiotherapy. To our knowledge, only one large study, by Kadota et al [11] has demonstrated that subtypes within the epithelioid classification had significant prognostic importance; the Kadota study suggested that the pleomorphic subtype be reclassified as biphasic or sarcomatoid, based on their similarly poor outcomes. Ordonez also showed pleomorphic epithelioid MPM to be an adverse

prognostic factor in a 10-patient series [12]. Another study, by Galateau-Salle et al., reported shorter median survival of pleomorphic MPM (7 months) compared with non-pleomorphic MPM (14 months) [26]. However, some authors found no clinical variations among different histological patterns [14].

Our OS hazard ratios should be interpreted only to indicate that the pleomorphic subtype is a negative predictor, whereas the other values indicate tendencies only for each group; for more definitive results, much larger groups of each subtype are needed. Our results might differ from those of Kadota et al [11] for this reason, especially for the micropapillary group which only included 2 patients in our population.

Our findings demonstrate that histological subtyping can be performed even in small samples without abundant tumor tissue, with strong interobserver agreement, and clear prognostic implications. We strongly feel that subtypes such as acinar or adenomatoid should be retained, as we need much more data on each pattern to see their real prognostic significance, which could be obscured by fewer groupings. Although our findings should be interpreted with caution because of the few subjects with certain MPM subtypes, we do support the line that the pleomorphic subtype of epithelioid MPM should be reclassified as a sarcomatoid or biphasic subtype, based on overall survival.

Conflict of interests

The authors declare that they have no conflict of interest.

References:

1. Robinson BWS, Lake RA (2005) Advances in malignant mesothelioma. N Engl J Med 353:1591–1603

2. Oviedo SP, Cagle PT (2012) Diffuse malignant mesothelioma. Arch Pathol Lab Med 136:882–888

3. Sugarbaker DJ, Flores RM, Jaklitsch MT, Richards WG, Strauss GM, Corson JM, DeCamp MM Jr, Swanson SJ, Bueno R, Lukanich JM, Baldini EH, Mentzer SJ (1999) Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: results of 183 patients. J Thorac Cardiovasc Surg 117:54–65

4. Flores RM, Zakowski M, Venkatraman E, Krug L, Rosenzweig K, Dycoco J, Lee C, Yeoh C, Bains M, Rusch V (2007) Prognostic factors in the treatment of malignant pleural mesothelioma at a large tertiary referral center. J Thorac Oncol 2:957–965

5. Bille A, Belcher E, Raubenheimer H et al (2012) Induction chemotherapy, extrapleural pneumonectomy, and adjuvant radiotherapy for malignant pleural mesothelioma: experience of Guy's and St. Thomas' hospitals. Gen. Thorac. Cardiovasc. Surg 60:289–296.

6. Tracey E, Kerr T, Dobrovic A, Currow D (2010) Cancer in NSW: Incidence and Mortality Report 2008. Cancer Institute NSW, Sydney

7. Neumann V, Günthe S, Mülle KM, Fischer M (2001) Malignant mesothelioma-German mesothelioma register 1987–1999. Int Arch Occup Environ Health 74:383–395

8. Rusch VW, Giroux D, Kennedy C, Ruffini E, Cangir AK, Rice D, Pass H, Asamura H, Waller D, Edwards J, Weder W, Hoffmann H, van Meerbeeck JP, IASLC Staging Committee (2012) Initial analysis of the International Association for the Study of Lung Cancer Mesothelioma database. J Thorac Oncol 7:1631–1639

9. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC (2004) Pathology and Genetics of Tumours of the Lung, Pleura Thymus and Heart. ARC Press, Lyon

10. Henderson DW, Reid G, Kao SC, van Zandwijk N, Klebe S (2013) Challenges and controversies in the diagnosis of malignant mesothelioma: Part 2. Malignant mesothelioma subtypes, pleural synovial sarcoma, molecular and prognostic aspects of mesothelioma, BAP1, aquaporin-1 and microRNA. J Clin Pathol 66:854–861

11. Kadota K, Suzuki K, Sima CS, Rusch VW, Adusumilli PS, Travis WD (2011) Pleomorphic epithelioid diffuse malignant pleural mesothelioma: a clinicopathological review and conceptual proposal to reclassify as biphasic or sarcomatoid mesothelioma. J Thora Oncol 6:896–904

12. Ordóñez NG (2012) Pleomorphic mesothelioma: report of 10 cases. Mod Pathol 25:1011–1022

13. Husain AN, Colby T, Ordonez N, Krausz T, Attanoos R, Beasley MB, Borczuk AC, Butnor K, Cagle PT, Chirieac LR, Churg A, Dacic S, Fraire A, Galateau-Salle F, Gibbs A, Gown A, Hammar S, Litzky L, Marchevsky AM, Nicholson AG, Roggli V, Travis WD, Wick M, International Mesothelioma Interest Group (2013) Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 137:647–667

14. Allen TC (2005) Recognition of histopathologic patterns of diffuse malignant mesothelioma in differential diagnosis of pleural biopsies. Arch Pathol Lab Med 129:1415–1420

15. Shia J, Qin J, Erlandson RA, King R, Illei P, Nobrega J, Yao D, Klimstra DS (2005) Malignant mesothelioma with a pronounced myxoid stroma: a clinical and pathological evaluation of 19 cases. Virchows Arch 447:828–834

16. Pass HI (2012) Biomarkers and prognostic factors for mesothelioma. Ann Cardiothorac Surg 1:449–456

17. Orvieto E, Maiorano E, Bottiglieri L, Maisonneuve P, Rotmensz N, Galimberti V, Luini A, Brenelli F, Gatti G, Viale G (2008) Clinicopathologic characteristics of invasive lobular carcinoma of the breast. Cancer 113:1511–1520

18. Motoi N, Szoke J, Riely GJ, Seshan VE, Kris MG, Rusch VW, Gerald WL, Travis WD (2008) Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis. Am J Surg Pathol 32:810–827

19. Solcia E, Klersy C, Mastracci L, Alberizzi P, Candusso ME, Diegoli M, Tava F, Riboni R, Manca R, Luinetti O (2009) A combined histologic and molecular approach identifies three groups of gastric cancer with different prognosis. Virchows Arch 455:197–211

20. Chiaravalli AM, Klersy C, Tava F, Manca R, Fiocca R, Capella C, Solcia E (2009) Lower- and higher-grade subtypes of diffuse gastric cancer. Hum Pathol 40:1591–1599

21. Reeves GK, Pirie K, Green J, Bull D, Beral V, Million Women Study Collaborators (2009) Reproductive factors and specific histological types of breast cancer: prospective study and meta-analysis. Br J Cancer 100:538–544

22. Okudela K, Woo T, Mitsui H, Yazawa T, Shimoyamada H, Tajiri M, Ogawa N, Masuda M, Kitamura H (2010) Morphometric profiling of lung cancers. Its association with clinicopathologic, biologic, and molecular genetic features. Am J Surg Pathol 34:243–255

23. Travis WD, Brambilla E, Noguchi M, et al (2011) International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society: International multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 6:244–285

24. Greillier L, Cavailles A, Fraticelli A, Scherpereel A, Barlesi F, Tassi G, Thomas P, Astoul P (2007) Accuracy of pleural biopsy using thoracoscopy for the diagnosis of histologic subtype in patients with malignant pleural mesothelioma. Cancer 110:2248–2252

25. Arrossi AV, Lin E, Rice D, Moran CA (2008) Histologic assessment and prognostic factors of malignant pleural mesothelioma treated with extrapleural pneumonectomy. Am J Clin Pathol 130:754–764

26. Galateau-Salle F, Le Stang N, Astoul P, Brochard P, Pairon JC, Gilg Soit Ilg A, Imbernon E, Goldberg M (2010) Malignant mesothelioma of the pleura with pleomorphic features: a series of 44 cases. Modern Pathol 23:402A

Figure legends

Fig. 1 Histological presentation of epithelioid malignant pleural mesothelioma subtypes. a: acinar; b: adenomatoid; c: trabecular (hematoxylin–eosin staining; magnification: ×10 [a and b], ×20 [c])

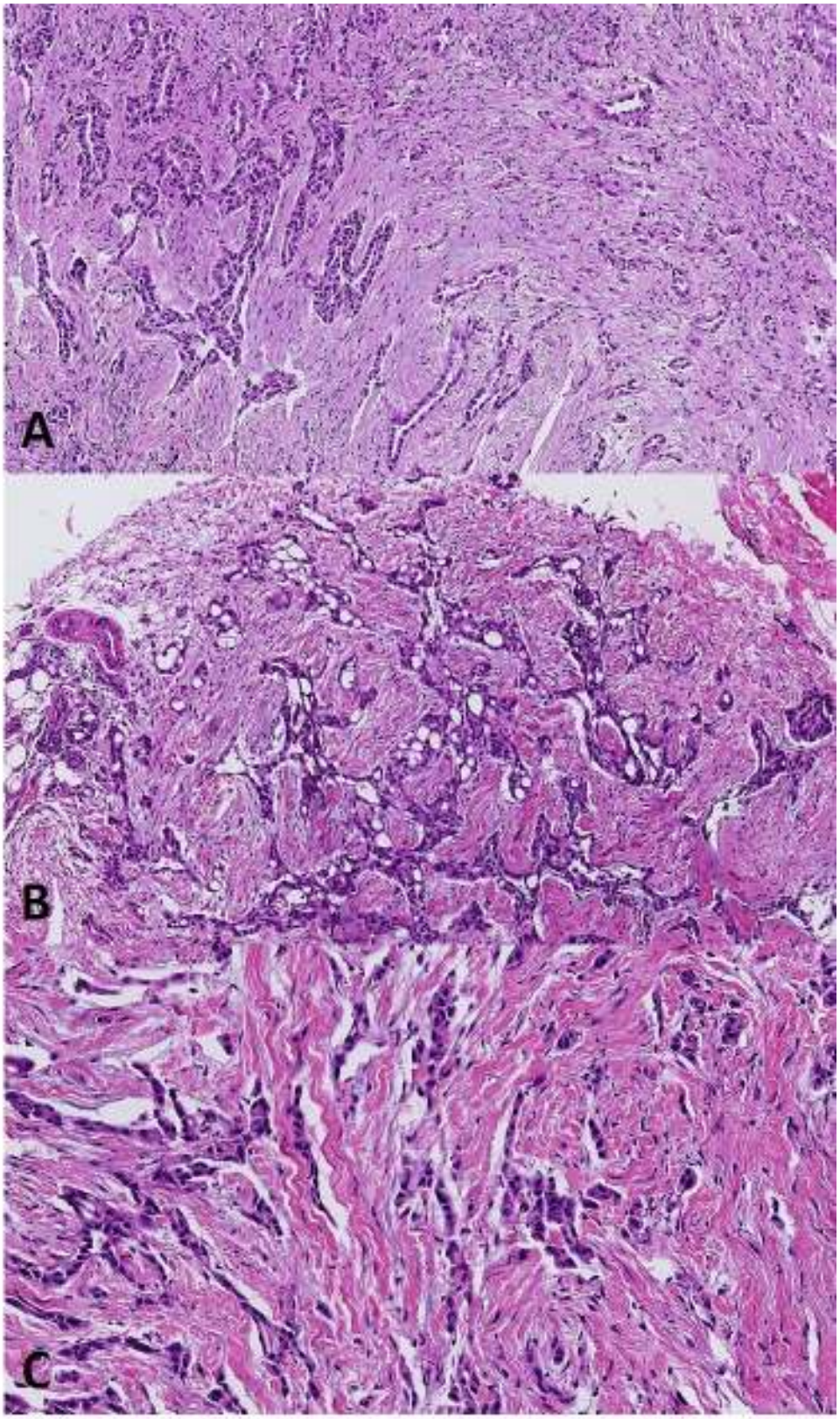
A
B
C

Fig. 2 Histological presentation of epithelioid malignant pleural mesothelioma subtypes. a: micropapillary; b: tubulopapillary; c: solid; d: pleomorphic (hematoxylin–eosin staining; magnification: ×10 [a and b], ×20 [c])

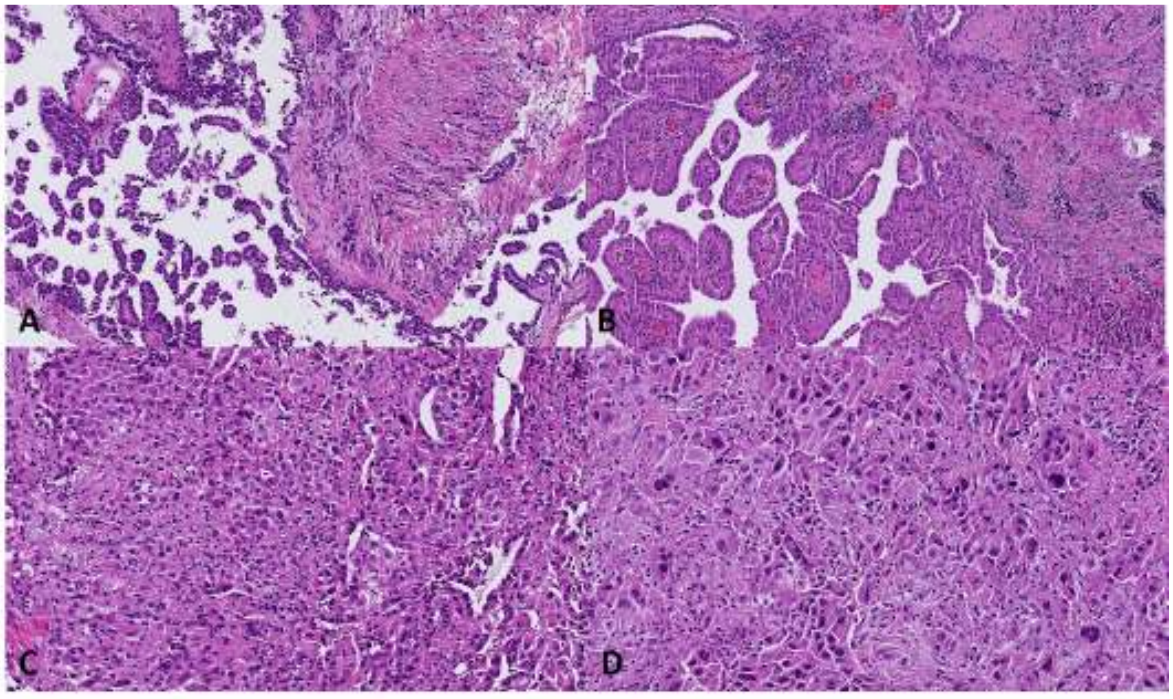

Fig. 3 Distribution of different histological subtypes of malignant pleural mesothelioma in our study group

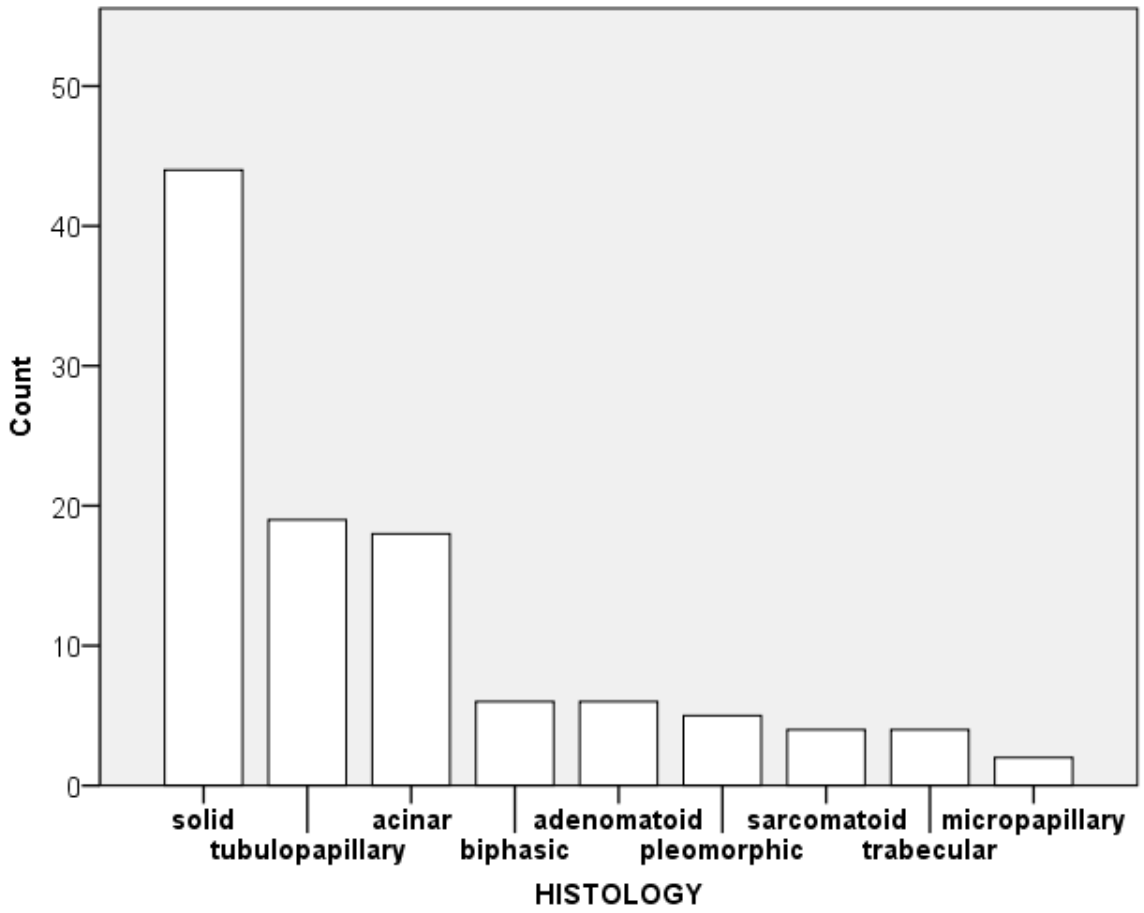

Fig. 4 Overall survival comparison between epithelioid, pleomorphic, biphasic and sarcomatoid MPM using Kaplan–Meier method showed that the latter three types did not significant differ in overall survival, but they each significantly differed from that of the epithelioid type

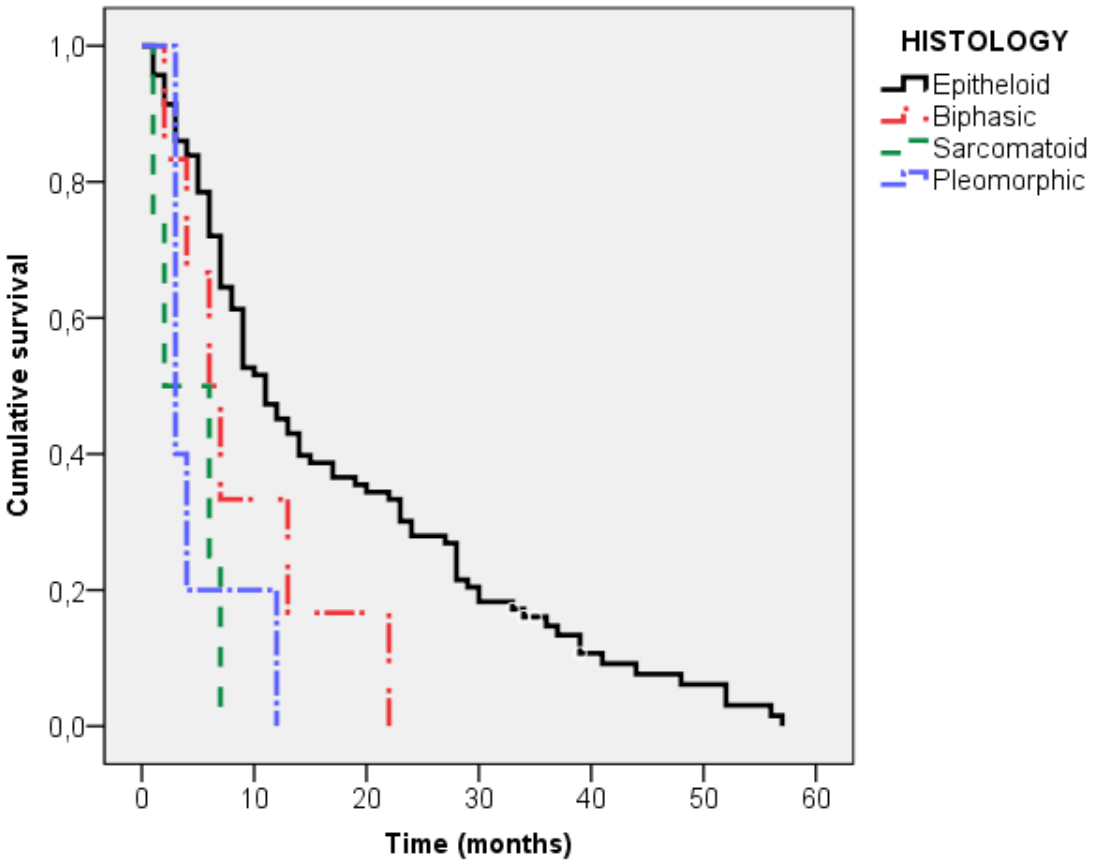

Table 1. Summary of clinical characteristics in 108 patients with MPM

	Number	%
All patients	108	100
Median age, yrs (IQR[a])	63 (54–69)	
Sex		
Female	15	13.9
Male	93	86.1
Side of disease		
Right	69	63.9
Left	39	36.1
Asbestos exposure		
No	19	17.6
Yes	41	38.0
Unknown	48	44.4
Pleural effusion		
No	31	28.7
Yes	77	71.3
Method of diagnosis		
VATS[b]	65	60.2
Open biopsy	35	32.4
Percutaneous pleural biopsy	8	7.4
Clinical stage		
1	0	0
2	5	4.6
3	26	24.1
4	77	71.3
Pleurodesis		
No	57	52.8
Yes	51	47.2
Treatment		
None	34	31.5
Gemcitabine-based	19	17.6
Pemetrexed-based	10	9.3
Others	25	23.1
Unknown	20	18.5

[a]Interquartile range
[b]Video-assisted thoracoscopic surgery

Table 2. Hazard ratios calculated for significant determinants of survival using Cox proportional hazard model

	P	OR	95% CI
Histology			
Pleomorphic [a]	0.006		
Acinar	**0.004**	0.20	0.07–0.59
Adenomatoid	**0.005**	0.16	0.04–0.56
Micropapillary	0.266	0.38	0.07–2.07
Solid	**0.007**	0.25	0.09–0.68
Tubulopapillary	**<0.001**	0.14	0.05–0.41
Trabecular	0.069	0.28	0.07–1.11
Biphasic	0.209	0.45	0.13–1.56
Sarcomatoid	0.949	1.05	0.26–4.15
Age (years)	0.430	1.01	0.99–1.03
Male sex	0.764	0.91	0.50–1.66
Surgical procedure	0.630	1.19	0.58–2.44
Clinical stage	0.327	1.24	0.81–1.90
Right vs. left side	0.167	0.72	0.46–1.14

[a] Reference subtype

Bolded values are statistically significant ($P < 0.05$)