Review

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Comparative genetics of diffuse malignant mesothelioma tumors of the peritoneum and pleura, with focus on BAP1 expression

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Abstract: Malignant mesothelioma (MM) is a malignancy arising from the mesothelial cells lining the thoracic and abdominal serosal cavities. The pleural space is the most commonly affected site, accounting for about 80% of cases, while peritoneum makes up the majority of the remaining 20%. The different types of mesotheliomas are generally considered as distinct diseases with specific risk factors, therapeutic strategies and prognoses. Epidemiological and clinical differences between pleural and peritoneal MM raise questions about the involvement of different molecular mechanisms. Since the *BAP1* gene is involved in the BAP1 cancer syndrome and seems to be a prognostic factor in MM, this review presents an overview of BAP1 alterations in mesothelioma comparing pleural and peritoneal localizations.

Keywords: BAP1, hereditary syndrome, mesothelioma, molecular alteration, prognostic factors

Introduction

Malignant mesothelioma (MM) is a rare disease that results from unregulated proliferation of the mesothelial cells lining the pleural, peritoneal and pericardial cavities. Localized MMs are rare and appear as solitary circumscribed nodular tumors, attached either in a sessile or pedunculated manner to the surface of the pleura or peritoneum. In opposition, diffuse MMs are characterized by diffuse spread over the serosal surface. By definition, localized and diffuse MMs are histologically and immunohistochemically identical [1]. Most MMs are related to exposure to mineral fibers, especially asbestos and erionite. The percentage of asbestos exposure differs depending on the cavity involved: from 70% in pleural MM to only 30% in peritoneal MM [2]. Other clinical differences include younger age of incidence in peritoneal MM and sex ratio [3].

Histologically, according to the 2015 WHO classification [4], MM can be categorized into epithelioid, sarcomatoid and biphasic subtypes. Localized malignant mesotheliomas, well-differentiated papillary mesothelioma and adenomatoid tumors have mainly been observed in the pleura, which is why they were excluded from this review. Differences of incidence have been observed for each histological subtype depending on MM location. Sarcomatoid and biphasic mesotheliomas are very rare in peritoneal MMs, while they represent 20–25% of pleural MMs [4].

The biochemical mechanisms responsible for the genesis of MM are not completely understood and most data come from pleural MM analyses. As a result of asbestos exposure, the inflammatory response generates resistance to apoptosis and accumulation of DNA damage [5]. In parallel, various cellular pathways such as receptor tyrosine kinase (RTK), Hippo signaling or PI3K/AKT pathways are altered [6, 7]. Promoter methylation of known tumor suppressor genes has also been observed, suggesting that epigenetic inactivation may be involved in the development and progression of MM tumors [8]. Finally, the main genetic alterations described in MM include cyclin-dependent kinase inhibitor 2A (CDKN2A)/alternative reading frame (ARF), neurofibromatosis type 2 (NF2) and BRCA1-associated protein-1 (BAP1) gene alterations [9–11]. Interestingly, the *BAP1* gene, located on chromosome 3p21.1, has been shown to be an important tumor suppressor gene in MM. Altered BAP1 was found in 42% of mesothelioma tumors through combining array CGH analysis and sequencing data [10]. Initially identified as a BRCA1-binding protein, BAP1 is a deubiquitinating enzyme with a C-terminal

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active hydrolase domain (UCH) and N-terminal nuclear localization signals (NLS1, NLS2). It has been postulated that BAP1 functions as a tumor suppressor through different mechanisms that all require nuclear localization of the BAP1 protein. Somatic *BAP1* mutations have been reported in other malignancies including uveal melanoma and renal cell carcinoma. The most exciting discoveries of the past years were the description of germline *BAP1* mutations and the existence of family cases of mesothelioma tumors [12, 13].

In the scientific literature on mesothelioma carcinogenesis, most papers include pleural mesothelioma tumors, while only few papers focus on the peritoneal localization of the disease. The molecular pathogenesis of peritoneal mesothelioma has mainly been described through the extrapolation of findings from pleural mesothelioma. The main objective of the present review is to provide an overview of BAP1 alterations in mesothelioma. We will compare DNA loss, *BAP1* mutation and BAP1 protein expression in both pleural and peritoneal MMs.

BAP1 DNA loss in malignant mesothelioma

DNA copy number or DNA rearrangement can be investigated through different techniques including array-comparative genomic hybridization (CGH), multiplex ligation-dependent probe amplification assay (MLPA), next generation sequencing (NGS) or conventional cytogenetic analysis. Using these methods, 3p21 rearrangement has been reported in 30 to 65% of mesotheliomas [10, 14–20]. Until recently, the biological differences between pleural and peritoneal mesothelioma had not been investigated in relation to DNA copy number, since most CNA studies focused on pleural disease. In 2015, Alakus et al. published an analysis on 12 peritoneal mesotheliomas and identified loss of BAP1 DNA in five cases (42%) through targeted sequencing [17]. A recent paper published by Columbia University compared genomic imbalances between 48 peritoneal epithelioid mesotheliomas and 41 pleural epithelioid mesotheliomas [21]. The authors described similar recurrent genomic imbalances between pleural and peritoneal mesotheliomas although their frequencies differed depending on the site of tumor origin. DNA loss on the 3p chromosome arm including the *BAP1* gene was observed for both localizations, but with higher frequency in pleural mesothelioma (the difference was not statistically significant). Based on these results, peritoneal and pleural MMs show a similar genomic profile through array-CGH analysis. DNA loss in 3p21 occurred in both pleural and peritoneal mesotheliomas without statistically significant differences (Table 1).

BAP1 mutations in malignant mesothelioma

Since the discovery of BAP1 alterations in mesotheliomas and uveal melanomas, the number of articles describing *BAP1* mutations has increased (Table 2). In 2011, Bott et al. described somatic mutations in 23% of pleural mesotheliomas, and Testa et al. described germline mutations in two families with multiples MMs and/or uveal melanomas [10, 12]. Since 2011, somatic *BAP1* mutations have been described in 20 to 61% of pleural mesotheliomas [10, 15, 16, 22–25] (Table 2) whereas

Table 1: Frequency of 3p21 DNA loss in pleural and peritoneal malignant mesothelioma.

Source	Pleural MM, n (%)	Peritoneal MM, n (%)	Total number of MMs, n (%)	Method
Taguchi et al. [14]	13/23 (57)	0	13/23 (57)	Cytogenetic analyzis
Bott et al. [10]	16/53 (30)	0	16/53 (30)	CGH
Yoshikawa et al. [15][a]	11/18 (61)	NA	11/18 (61)	CGH
Nasu et al. [16][a]	9/22 (41)	NA	9/22 (41)	MLPA
Alakus et al. [17]	0	5/12 (42)	5/12 (42)	NGS
Cigognetti et al. [18][b]	36/51 (71)	NA	36/51 (71)	Cytogenetic analyzis
Taylor et al. [19]	0	1/1 (100)	1/1 (100)	Cytogenetic analyzis
Emi et al. [20][a]	11/17 (65)	NA	11/17 (65)	MLPA

CGH, array comparative genomic hybridizitation; MLPA, multiplex ligation-dependent probe amplification assay; NA, not available. [a]The exact localization of the disease was not specified. By default, the data are completed in the "pleural MM" part of the Table. [b]The study included MM peritoneal cases but results on these specific cases were not specified. By default, the data are completed in the "pleural MM" part of the Table.

Table 2: Frequency of somatic *BAP1* mutations in pleural and peritoneal malignant mesothelioma.

Source	Pleural MM, n (%)	Peritoneal MM, n (%)	Total number MMs, n (%)
Bott et al. [10]	24/121 (20)	0	24/121 (20)
Yoshikawa et al. [15][a]	11/18 (61)	NA	11/18 (61)
Zauderer et al. [25]	24/121 (20)	0	24/121 (20)
Nasu et al. [16][a]	6/22 (27)	NA	6/22 (27)
Lo Iacono et al. [22]	78/123 (63)	0	78/123 (63)
Alakus et al. [17]	0	5/12 (42)	5/12 (42)
Guo et al. [23]	8/22 (36%)	0	8/22 (36)
Sheffield et al. [26]	0	0/2	0/2
De Rienzo et al. [24]	31/147 (21)	0	31/147 (21)
Bueno et al. [27]	46/202 (23)	0	46/202 (23)

NA, not available. [a]The exact localization of the disease was not specified. By default, the data are completed in the "pleural MM" part of the Table. [b]The study included MM cases but results on these specific cases were not specified. By default, the data are completed in the "pleural MM" part of the Table.

27.3% of peritoneal mesotheliomas included somatic *BAP1* mutations [17, 26]. Such mutations have been found in a substantial proportion of epithelioid mesotheliomas (71%) and to a lesser extent in sarcomatoid mesotheliomas (< 5%) [25]. A recent publication by Bueno et al. [27] described *BAP1* as the most frequently mutated gene in malignant pleural mesothelioma before *NF2* and *TP53*. *BAP1* mutations include base substitution leading to nonsense and missense mutations, frameshift insertions or deletions, splice-site mutations, truncations or rearrangements. Truncating mutations frequently result in the loss of the NLS and/or C-terminal protein-binding domain. Missense mutations affect the ubiquitin hydrolase function of BAP1.

Germline *BAP1* mutations are considered as a predisposing factor for mesothelioma and uveal melanoma, as well as basal cell carcinoma, cutaneous melanoma or renal cell carcinoma [12, 28–31]. Germline mutations in *BAP1* increase patient susceptibility to asbestos-induced malignant mesothelioma [32] and may contribute to MM development through the same mechanisms as somatic mutations, regulating cell cycle progression, chromatin modulation and DNA double-strand break repair via the BRCA1/BARD1 complex [33]. Nevertheless, germline *BAP1* mutations are not frequent in sporadic MM, with a prevalence of about 1–2% [12, 15, 34–36]. Ohar et al. identified germline *BAP1* mutations in nine out of 150 MM cases (6%) with personal or family history of cancer [37]. Out of these nine indexed MM cases, five (55.6%) were peritoneal and four (44.4%) were thoracic, while 116 MM cases without germline *BAP1* mutation (82.3%) were thoracic and 25 (17.7%) were peritoneal. All nine MM cases had histories of asbestos exposure. In accordance with the hypothesis, the authors did not find any germline *BAP1* mutations in the 153 individuals with significant exposure to asbestos without mesothelioma. Battaglia et al. made an exhaustive description of every published germline *BAP1* mutation depending on tumor origin. Like somatic mutations, germline mutations included missense, nonsense or deleterious frameshift mutations, truncations or rearrangements. In some cases, one *BAP1* allele was lost via monosomy 3 and the other was non-functional due to an inactivating BAP1 mutation, in accordance with Knudson's two-hit model [33]. Finally, Cheung et al. reported an asbestos-exposed family with high incidence of cancer, including eight cases of pleural MM. BAP1 tumor sequencing of four cases in this family did not show any *BAP1* mutation nor DNA loss in 3p21 (n = 2). This suggests that another susceptibility locus may contribute to high MM incidence in this family [38].

To summarize, both pleural and peritoneal mesotheliomas include germline and somatic *BAP1* mutations. Such mutations result in loss of protein function, confirming the role of *BAP1* as a tumor suppressor gene.

BAP1 protein expression in malignant mesothelioma

A large number of immunohistochemical markers have been proposed to support the diagnosis of mesothelioma. In addition to two positive (i.e. calretinin, cytokeratin 5/6 or HBME1) and two negative markers (i.e. TTF-1, BerEP4, Napsin A) [4], auxiliary markers such as epithelial membrane antigen, p53 or GLUT1 are also useful tools. Although these markers may be helpful in borderline cases, they do not show enough sensitivity or specificity

Table 3: Frequency of BAP1 protein loss by immunohistochemistry in pleural and peritoneal malignant mesothelioma.

Source	Pleural MM, n (%)	Peritoneal MM, n (%)	Total number of MMs, n (%)
Bott et al. [10]	27/47 (57)	0	27/47 (57)
Yoshikawa et al. [15][a]	NA	NA	11/17 (65)
Arzt et al. [41][a]	74/123 (60)	NA	74/123 (60)
Nasu et al. [16][a]	61/91 (67)	NA	61/91 (67)
Farzin et al. [39]	106/229 (46)	0	106/229 (46)
Sheffield et al. [40][b]	7/26 (27)	NA	7/26 (27)
Cigognetti et al. [18][b]	139/212 (66)	NA	139/212 (66)
Singhi et al. [42]	0	49/86 (57)	49/86 (57)
McGregor et al. [43]	65/111 (59)	0	65/111 (59)
Sheffield et al. [26]	0	0/2 (0)	0/2
Lo Iacono et al. [22]	56/116 (48)	0	56/116 (48)
Jaouen et al. [44]	12/25 (48)	0	12/25 (48)
Hwang et al. [47]	8/13 (62)	2/2 (100)	10/15 (67)

NA, not available. [a]The exact localization of the disease was not specified. By default, the data are completed in the "pleural MM" part of the Table. [b]The study included peritoneal MM cases but results on these specific cases were not specified. By default, the data are completed in the "pleural MM" part of the Table.

for widespread ordinary clinical use. Loss of BAP1 protein nuclear expression has been described in 27 to 67% of mesothelioma cases regardless of their primary localization [15, 16, 18, 22, 26, 39–44] (Table 3). Genetic results are correlated to BAP1 immunohistochemistry (IHC), since all mutated samples showed loss of BAP1 protein expression [10, 15, 16, 22]. Cytoplasmic BAP1 tumor cell staining may be expected when mutations result in truncated BAP1 with no NLS, or bearing mutations in the catalytic subunit that prevent BAP1 autodeubiquitination, which is required for nuclear localization. Most mutated forms fall into this category. These results suggest that IHC may be the most reliable and accessible method to identify MM biopsies that include *BAP1* genetic alterations. Consequently, BAP1 IHC is an important tool to separate benign from malignant mesothelial proliferations. In case of mesothelial proliferation, the specificity of IHC BAP1 staining loss for the diagnosis of malignant mesothelioma in tissue biopsy and effusion cytology specimens is very high [18, 40, 44–47]. Nevertheless, we have to keep in mind that loss of BAP1 staining is not specific to mesothelioma and may occur in various malignancies including lung cancer [44, 45].

BAP1 as a prognostic factor in malignant mesothelioma

Malignant mesothelioma is difficult to diagnose at an early stage, lacks effective treatment and is associated with poor prognosis. MM prognosis depends on the histological type, from worst to best: sarcomatoid, non-epithelioid and epithelioid MM [4]. Recently, better knowledge of the molecular biology of MM has led to the identification of promising biomarkers, which may contribute to the individualization of therapeutic approaches. BAP1 loss associated with improved survival in pleural MM [39, 41, 43] has been reported. In some reports however, the analysis did not reach significance in multivariate analysis accounting for histological subtype [43]. Baumann et al. reported that MM arising from germline *BAP1* mutations was clinically less aggressive and frequently associated with prolonged survival [48]. This information should be taken into account to provide appropriate genetic counseling and clinical management to MM patients with germline *BAP1* mutations. Zauderer et al. did not find any correlation between somatic *BAP1* mutations and survival in 121 cases of pleural MM [25]. No data have been reported for peritoneal MM.

Discussion

The pleura is the most common MM localization before the peritoneum. Consequently, the molecular pathogenesis of MM is mostly derived from descriptions of pleural MM. While these tumors arising from different sites have similar morphologies, peritoneal MM presents with unique characteristics such as younger median age and higher frequency in female patients [49]. In this review, we would like to compare molecular pathogenesis in pleural and peritoneal MM with focus on the *BAP1* gene.

The discovery of an inherited cancer syndrome caused by germline *BAP1* mutations, the correlation between genetic alterations and BAP1 expression, the availability of a specific antibody that could be used in histopathological examination and the specificity of BAP1 loss for the diagnosis of malignant mesothelioma may explain the dramatic increase in the number of articles that have reported analyses of BAP1 expression in mesothelioma since 2011. Although most articles deal with pleural mesothelioma, some focus on peritoneal MM. The published data suggest similar molecular pathogenesis of pleural and peritoneal MM, including DNA loss in 3p21, 9p21 and 22q12 [21]. Somatic and germline *BAP1* mutations have been described in both sites and systematically led to BAP1 inactivation.

The discovery of the BAP1 cancer predisposition syndrome has had a number of clinical implications. If *BAP1* mutations are identified in the tumors, testing for germline *BAP1* mutations should be preferably considered within the framework of a family cancer genetic screening unit. Patients with confirmed germline *BAP1* mutations will need appropriate genetic counseling for themselves and their families. As a consequence, these patients will require close monitoring for the early detection and curative resection of uveal and cutaneous melanoma, and should be informed of the risk for MM and other malignancies.

BAP1 IHC is a cheap and quick way to screen tumors with *BAP1* mutations, since paraffin-embedded tumor tissue is readily available. Tumors that present with loss of nuclear BAP1 expression may then undergo subsequent confirmatory sequencing. The correlation between immunohistochemical and sequencing data in MM and other tumors is strong. Therefore, the immunohistochemical screening for BAP1 should become a standard histopathological test for MM or melanocytic tumors [10, 15, 16, 22, 50]. More specifically, BAP1 IHC is a highly specific marker to differentiate mesothelioma from reactive mesothelial proliferations. In case of noninvasive mesothelial proliferation, loss of BAP1 expression is highly suggestive of a malignant disease [18, 40, 45, 47].

The role of *BAP1* mutations and BAP1 expression as prognostic biomarkers is still emerging. It should be noted that results differ depending on tumor origin. Multivariate analysis demonstrated that BAP1 expression was an independent prognostic factor for colorectal cancer (CRC) [51]. The clinicopathological significance and oncologic outcomes of BAP1 loss in renal cell carcinoma (RCC) have been investigated. IHC for BAP1 loss was performed in 559 non-metastatic RCC using tissue micro-array. Cox regression indicated significantly worse disease-free and overall survival for patients with BAP1-negative (82/559, 14.7%) than patients with BAP1-positive tumors [52]. Different results have been observed in pleural MM, and BAP1 protein loss is paradoxically associated with improved survival [39, 41, 43]. No data are available for peritoneal mesothelioma, although it is known to be associated with longer survival than pleural MM. To date, the way to consider this prognostic histopathological marker in ordinary clinical practice is still unclear.

Currently, the therapeutic strategy in pleural and peritoneal MM is to provide specific standard protocol for each MM localization. Patients with pleural MM are mostly treated with systemic chemotherapy recently added with anti-VEGF drug [53]; patients with peritoneal MM undergo surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) [54, 55]. If future studies are able to define a therapeutically accessible synthetic lethal target in the setting of BAP1 loss, it could eventually benefit patients with *BAP1*-negative or mutation tumors, regardless of the site of tumor origin.

To conclude, the latest reports on peritoneal mesothelioma confirmed the data observed in pleural mesothelioma, which suggests that both localizations have similar genetic background. BAP1 IHC should be used in ordinary diagnosis to help the pathologist separate MM from reactive mesothelial proliferations in the pleural and peritoneal cavities, in tissue samples and effusion cytology specimens. For clinical practice and in case of family cancer history, the absence of BAP1 staining in tumor cells may suggest the presence of germline *BAP1* mutations. These patients should be considered for *BAP1* genetic testing to identify those who may undergo further screening. Indeed, early diagnosis and treatment may be partly responsible for significantly improved mesothelioma prognosis in germline *BAP1* mutation carriers.

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References

1. Allen TC, Cagle PT, Churg AM, Colby TV, Gibbs AR, Hammar SP, et al. Localized malignant mesothelioma. Am J Surg Pathol 2005;29:866–73.
2. Spirtas R, Heineman EF, Bernstein L, Beebe GW, Keehn RJ, Stark A, et al. Malignant mesothelioma: attributable risk of asbestos exposure. Occup Environ Med 1994;51:804–11.
3. Gallot C, Bonnet N, Chérié-Challine L. Mandatory notification of mesotheliomas in France: main results, 2012–2013 [Déclaration obligatoire des mésothéliomes en France : principaux résultats, 2012–2013). Bull Epidémiol Hebd 2015;3–4:47–54.
4. Travis WD, Brambilla E, Burke AP, Marx A, Nicholson AG. WHO classification of tumours of the lung, pleura, Thymus and heart. Fourth Edition. In IARC; (WHO classification; vol. 7).
5. Sekido Y. Molecular pathogenesis of malignant mesothelioma. Carcinogenesis 2013;34:1413–19.
6. Brevet M, Shimizu S, Bott MJ, Shukla N, Zhou Q, Olshen AB, et al. Coactivation of receptor tyrosine kinases in malignant mesothelioma as a rationale for combination targeted therapy. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer 2011;6:864–74.
7. Sekido Y. Inactivation of Merlin in malignant mesothelioma cells and the Hippo signaling cascade dysregulation. Pathol Int 2011;61:331–44.
8. Zhang X, Tang N, Rishi AK, Pass HI, Wali A. Methylation profile landscape in mesothelioma: possible implications in early detection, disease progression, and therapeutic options. Methods Mol Biol Clifton NJ 2015;1238:235–47.
9. Sekido Y, Pass HI, Bader S, Mew DJ, Christman MF, Gazdar AF, et al. Neurofibromatosis type 2 (NF2) gene is somatically mutated in mesothelioma but not in lung cancer. Cancer Res 1995;55:1227–31.
10. Bott M, Brevet M, Taylor BS, Shimizu S, Ito T, Wang L, et al. The nuclear deubiquitinase BAP1 is commonly inactivated by somatic mutations and 3p21. 1 losses in malignant pleural mesothelioma. Nat Genet 2011;43:668–72.
11. Cheng JQ, Jhanwar SC, Klein WM, Bell DW, Lee WC, Altomare DA, et al. p16 alterations and deletion mapping of 9p21-p22 in malignant mesothelioma. Cancer Res 1994;54:5547–51.
12. Testa JR, Cheung M, Pei J, Below JE, Tan Y, Sementino E, et al. Germline BAP1 mutations predispose to malignant mesothelioma. Nat Genet 2011;43:1022–5.
13. Wiesner T, Fried I, Ulz P, Stacher E, Popper H, Murali R, et al. Toward an improved definition of the tumor spectrum associated with BAP1 germline mutations. J Clin Oncol Off J Am Soc Clin Oncol 2012;30:e337–40.
14. Taguchi T, Jhanwar SC, Siegfried JM, Keller SM, Testa JR. Recurrent deletions of specific chromosomal sites in 1p, 3p, 6q, and 9p in human malignant mesothelioma. Cancer Res 1993;53:4349–55.
15. Yoshikawa Y, Sato A, Tsujimura T, Emi M, Morinaga T, Fukuoka K, et al. Frequent inactivation of the BAP1 gene in epithelioid-type malignant mesothelioma. Cancer Sci 2012;103:868–74.
16. Nasu M, Emi M, Pastorino S, Tanji M, Powers A, Luk H, et al. High Incidence of Somatic BAP1 alterations in sporadic malignant mesothelioma. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer 2015;10:565–76.
17. Alakus H, Yost SE, Woo B, French R, Lin GY, Jepsen K, et al. BAP1 mutation is a frequent somatic event in peritoneal malignant mesothelioma. J Transl Med 2015;13:122.
18. Cigognetti M, Lonardi S, Fisogni S, Balzarini P, Pellegrini V, Tironi A, et al. BAP1 (BRCA1-associated protein 1) is a highly specific marker for differentiating mesothelioma from reactive mesothelial proliferations. Mod Pathol Off J U S Can Acad Pathol Inc 2015;28:1043–57.
19. Taylor S, Carpentieri D, Williams J, Acosta J, Malignant Peritoneal SR. Mesothelioma in an Adolescent Male With BAP1 Deletion. J Pediatr Hematol Oncol 2015;37:e323–7.
20. Emi M, Yoshikawa Y, Sato C, Sato A, Sato H, Kato T, et al. Frequent genomic rearrangements of BRCA1 associated protein-1 (BAP1) gene in Japanese malignant mesothelioma-characterization of deletions at exon level. J Hum Genet 2015;60:647–9.
21. Borczuk AC, Pei J, Taub RN, Levy B, Nahum O, Chen J, et al. Genome-wide analysis of abdominal and pleural malignant mesothelioma with DNA arrays reveals both common and distinct regions of copy number alteration. Cancer Biol Ther 2016;17:228–35.
22. Lo Iacono M, Monica V, Righi L, Grosso F, Libener R, Vatrano S, et al. Targeted next-generation sequencing of cancer genes in advanced stage malignant pleural mesothelioma: a retrospective study. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer 2015;10:492–9.
23. Guo G, Chmielecki J, Goparaju C, Heguy A, Dolgalev I, Carbone M, et al. Whole-exome sequencing reveals frequent genetic alterations in BAP1, NF2, CDKN2A, and CUL1 in malignant pleural mesothelioma. Cancer Res 2015;75:264–9.
24. De Rienzo A, Archer MA, Yeap BY, Dao N, Sciaranghella D, Sideris AC, et al. Gender-specific molecular and clinical features underlie malignant pleural mesothelioma. Cancer Res 2016;76:319–28.
25. Zauderer MG, Bott M, McMillan R, Sima CS, Rusch V, Krug LM, et al. Clinical characteristics of patients with malignant pleural mesothelioma harboring somatic BAP1 mutations. J Thorac Oncol 2013;8:1430–3.
26. Sheffield BS, Tinker AV, Shen Y, Hwang H, Li-Chang HH, Pleasance E, et al. Personalized oncogenomics: clinical experience with malignant peritoneal mesothelioma using whole genome sequencing. PloS One 2015;10:e0119689.
27. Bueno R, Stawiski EW, Goldstein LD, Durinck S, De Rienzo A, Modrusan Z, et al. Comprehensive genomic analysis of malignant pleural mesothelioma identifies recurrent mutations, gene fusions and splicing alterations. Nat Genet 2016;48:407–16.
28. de la Fouchardière A, Cabaret O, Savin L, Combemale P, Schvartz H, Penet C, et al. Germline BAP1 mutations predispose also to multiple basal cell carcinomas. Clin Genet 2015;88:273–7.
29. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, Gaudino G. BAP1 and cancer. Nat Rev Cancer 2013;13:153–9.

30. Popova T, Hebert L, Jacquemin V, Gad S, Caux-Moncoutier V, Dubois-d'Enghien C, et al. Germline BAP1 mutations predispose to renal cell carcinomas. Am J Hum Genet 2013;92:974–80.
31. Klebe S, Driml J, Nasu M, Pastorino S, Zangiabadi A, Henderson D, et al. BAP1 hereditary cancer predisposition syndrome: a case report and review of literature. Biomark Res 2015;3:14.
32. Xu J, Kadariya Y, Cheung M, Pei J, Talarchek J, Sementino E, et al. Germline mutation of BAP1 accelerates development of asbestos-induced malignant mesothelioma. Cancer Res 2014;74:4388–97.
33. Battaglia A. The importance of multidisciplinary approach in early detection of BAP1 tumor predisposition syndrome: clinical management and risk assessment. Clin Med Insights Oncol 2014;8:37–47.
34. Betti M, Casalone E, Ferrante D, Romanelli A, Grosso F, Guarrera S, et al. Inference on germline BAP1 mutations and asbestos exposure from the analysis of familial and sporadic mesothelioma in a high-risk area. Genes Chromosomes Cancer 2015;54:51–62.
35. Rusch A, Ziltener G, Nackaerts K, Weder W, Stahel RA, Felley-Bosco E. Prevalence of BRCA-1 associated protein 1 germline mutation in sporadic malignant pleural mesothelioma cases. Lung Cancer Amst Neth 2015;87:77–9.
36. Sneddon S, Leon JS, Dick IM, Cadby G, Olsen N, Brims F, et al. Absence of germline mutations in BAP1 in sporadic cases of malignant mesothelioma. Gene 2015;563:103–5.
37. Ohar JA, Cheung M, Talarchek J, Howard SE, Howard TD, Hesdorffer M, et al. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. Cancer Res 2016;76:206–15.
38. Cheung M, Kadariya Y, Pei J, Talarchek J, Facciolo F, Visca P, et al. An asbestos-exposed family with multiple cases of pleural malignant mesothelioma without inheritance of a predisposing BAP1 mutation. Cancer Genet 2015;208:502–7.
39. Farzin M, Toon CW, Clarkson A, Sioson L, Watson N, Andrici J, et al. Loss of expression of BAP1 predicts longer survival in mesothelioma. Pathology 2015;47:302–7.
40. Sheffield BS, Hwang HC, Lee AF, Thompson K, Rodriguez S, Tse CH, et al. BAP1 immunohistochemistry and p16 FISH to separate benign from malignant mesothelial proliferations. Am J Surg Pathol 2015;39:977–82.
41. Arzt L, Quehenberger F, Halbwedl I, Mairinger T, Popper HH. BAP1 protein is a progression factor in malignant pleural mesothelioma. Pathol Oncol Res 2014;20:145–51.
42. Singhi AD, Krasinskas AM, Choudry HA, Bartlett DL, Pingpank JF, Zeh HJ, et al. The prognostic significance of BAP1, NF2, and CDKN2A in malignant peritoneal mesothelioma. Mod Pathol 2016;29:14–24.
43. McGregor SM, Dunning R, Hyjek E, Vigneswaran W, Husain AN, Krausz T. BAP1 facilitates diagnostic objectivity, classification, and prognostication in malignant pleural mesothelioma. Hum Pathol 2015;46:1670–8.
44. Jaouen A, Thivolet-bejui F, Chalabreysse L, Piaton E, Traverse-glehen A, Isaac S, et al. BRCA1 associated protein 1 (BAP1) expression in pleural diffuse malignant mesothelioma: a comparative cytological and histological analyses on 50 patients. Ann Pathol 2016;36:111–19.
45. Churg A, Sheffield BS, New G-SF. Markers for separating benign from malignant mesothelial proliferations: are we there yet? Arch Pathol Lab Med 2015;140:318–21.
46. Andrici J, Sheen A, Sioson L, Wardell K, Clarkson A, Watson N, et al. Loss of expression of BAP1 is a useful adjunct, which strongly supports the diagnosis of mesothelioma in effusion cytology. Mod Pathol 2015;28:1360–8.
47. Hwang HC, Sheffield BS, Rodriguez S, Thompson K, Tse CH, Gown AM, et al. Utility of BAP1 immunohistochemistry and p16 (CDKN2A) FISH in the diagnosis of malignant mesothelioma in effusion cytology specimens. Am J Surg Pathol 2016;40:120–6.
48. Baumann F, Flores E, Napolitano A, Kanodia S, Taioli E, Pass H, et al. Mesothelioma patients with germline BAP1 mutations have 7-fold improved long-term survival. Carcinogenesis 2015;36:76–81.
49. Baratti D, Kusamura S, Deraco M. Diffuse malignant peritoneal mesothelioma: systematic review of clinical management and biological research. J Surg Oncol 2011;103:822–31.
50. Shah AA, Bourne TD, Murali R. BAP1 protein loss by immunohistochemistry: a potentially useful tool for prognostic prediction in patients with uveal melanoma. Pathology 2013;45:651–6.
51. Tang J, Xi S, Wang G, Wang B, Yan S, Wu Y, et al. Prognostic significance of BRCA1-associated protein 1 in colorectal cancer. Med Oncol 2013;30:541.
52. Kapur P, Christie A, Raman JD, Then MT, Nuhn P, Buchner A, et al. BAP1 immunohistochemistry predicts outcomes in a multi-institutional cohort with clear cell renal cell carcinoma. J Urol 2014;191:603–10.
53. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the mesothelioma avastin cisplatin pemetrexed study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet 2015;347:1405–14.
54. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol 2009;27:6237–42.
55. Baratti D, Kusamura S, Cabras AD, Deraco M. Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperthermic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. Ann Surg Oncol 2012;19:1416–24.