

2018 Update on Mesothelioma Diagnosis, Staging and Treatment Guidelines

Dr. Marcelo Luiz Balancin^{1*}, Dr. Alexandre Muxfeldt Ab'Saber^{2,3}, Dr. Vanessa Martins¹ & Dr. Vera Luiza Capelozzi¹

¹*Department of Pathology, Faculty of Medicine, University of São Paulo, Brazil*

²*Pathology Division, Clinics Hospital, Faculty of Medicine, University of São Paulo, Brazil*

³*Oncocentro Foundation, São Paulo, Brazil*

***Correspondence to:** Dr. Marcelo Luiz Balancin, Department of Pathology, Faculty of Medicine, University of São Paulo, Brazil.

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Abstract

Malignant Mesothelioma (MM) is a low incidence, highly fatal neoplastic conditions, that affects serous membranes, mainly associated with asbestos exposure. As an occupational disease, it does not spare neither workforce nor near mining areas inhabitants, as a consequence of direct exposure to asbestos-fibers. Symptoms develop late after exposure, from a twenty to forty years' latency interval, usually diagnosed at a late stage, and can be considered a Global Health issue, as incidence is increasing worldwide due to increased industrial demand of asbestos fibers. In the last two years, new guidelines on diagnostics, treatment, follow-up and staging have been issued and will be addressed in this review, including the latest concepts, histopathologic diagnostic criteria and guidelines, molecular aspects, treatment updates and new potential drug targets, including immunotherapy.

Introduction

Malignant mesothelioma has historically been reported from the foundations of anatomic pathology as a discipline in Medicine. From as early as 1767, in autopsy studies, Joseph Lieutaud reported cases of fleshy epithelioid masses of “pleural tumors”, the first possible reports of mesothelioma [1].

The term primary mesothelioma of the pleura was proposed in 1920 [2] by Du Bray and Rosson in response to a controversial entity, endothelioma of the pleura, which was described as a predominately epithelioid tumor, sometimes with a spindled cell component, believed to arise from pleural lymphatic endothelia. In this paper, the authors discussed the origin of these tumors from pleural lining epithelia, the mesothelium. They were based on cell culture experiments, reported some years earlier [3], that had demonstrated the transition of epithelioid to spindled cell phenotype from mesothelial to fibroblastic cells, allowing the assumption of a mixed epithelioid and sarcomatoid component to be present in this tumor.

Klemperer and Rabin [4], in 1931, started diffusing the term mesothelioma for these pleural based tumors, grossly beholding a uniform appearance, although microscopically composed by various histologic forms, some appearing either epithelioid, sarcomatoid or as mixed phenotype neoplasms [5].

The next thirty years were paved with controversies and misuses of the terms, although progress was made in epidemiological research. In 1960, the seminal paper “Diffuse Pleural Mesothelioma and Asbestos Exposure in the Northwestern Cape Providence” was published [6], reporting the prevalence of mesothelioma in workers and inhabitants by a crocidolite mining area (the so-called “Cape Blue asbestos”, found in the hills west of Kimberly, in the northwest Cape Providence of South Africa). Since then, effort has not been spared to investigate the link between exposure to asbestos fibers and mesothelioma, including longer (amphibole) and shorter fibers (chrysotile). In the latest IARC monograph series, from 2012, it has been reinforced as a Class I carcinogen [7], denoting its strong role played as a cancer causing agent.

Actually, asbestos-related cancer burden is estimated around 20 000 asbestos-related lung cancers and 10 000 mesotheliomas annually across western Europe, Scandinavia, North America, Japan and Australia [8], representing about 107 000 deaths and 1 523 000 disability-adjusted life years, as estimated in 2004 [9]. Unfortunately, epidemiological data is not strongly reliable for public health measures, as sub notification is an issue in many countries, as Brazil, a large producer [10], with around 2000 death related cases notified in the last 20 years [10]. In an epidemiologic review from the late 1990s, Peto [8] alerts the risk of a worldwide mesothelioma epidemics in the first decades of the 21st century, as a consequence of its peak demand from industry in the 1970s and its forty-year latency interval to symptoms development. Although banned by some countries in the 1970s and by the European Union in 2005, it is not universally banned and we might be facing a worldwide epidemic, specially from countries that still mine or employ it, as China, India, Russia, Zambia, Colombia and Kazakhstan [9].

Asbestos exposition is estimated to account for around 70-80% of cases of MM [9]. The remaining cases have been associated with diverse factors, some bearing questionable evidence, as Polio vaccine. SV40 virus, previous exposure to radiation therapy for Hodgkin Lymphoma treatment are two other oncogenic candidates, although current evidence is weak [9]. BAP1 familial cancer syndrome has been accountable for

around 10-20% of cases, and might be associated to a greater number, if its behavior is of a “tumor initiator”, as proposed by some [11].

World Health Organization (WHO) Classification

The 2015 WHO Classification of Tumors of the Pleura [12] defines MM as a malignant tumor originated from mesothelial cells. Pleural MMs can be distinguished in three histologic subtypes: epithelioid, sarcomatoid and biphasic; other entities, benign, with much better prognosis, have been defined as localized malignant mesothelioma (LMMs) and well-differentiated papillary mesotheliomas (WDPMs), which are discussed elsewhere [11].

Epithelioid mesothelioma is the most common histologic subtype of MM, followed by sarcomatoid and biphasic [11]. A variety of subtypes have been identified in epithelioid pleural MM: tubulopapillary, papillary, acinar, micropapillary (without a fibrovascular core), trabecular solid, acinar, adenomatoid, pleomorphic, as well as other subclassification from anecdotal case series reported, as deciduoid [13] and “with signet ring features” [14]. Although these subtypes have been reported by many authors, some interchangeably and in a not clear way, WHO recognizes them under the type of epithelioid tumors. Reproducibility has been attained for the most common subtypes, as well as some prognostic features have been commonly reported, as more common lymphovascular invasion in micropapillary tumors and worse prognosis for epithelioid tumors with pleomorphic features [11]. Stronger evidence and more data is needed for an assertive subclassification, as emerging data shows promising results for a prognostic subclassification of the epithelioid subtype [15], regarding nuclear features [15,16], especially if coupled with predictive information on target biomarkers.

Sarcomatoid mesothelioma is the second most common histologic type within WHO classification, and associated with worse prognosis, comprising also the desmoplastic and biphasic subtypes. Morphologically, it is expected to be composed of a malignant mesenchymal spindled cell proliferation, in a diffuse and infiltrative fashion over the pleural surface, mimicking sarcomas. In the deciduoid type, a dense collagenized tissue separates a storiform (or “patternless pattern”), sometimes hypocellular malignant mesothelial cell proliferation, present in at least 50% of the tumor. The biphasic pattern is expected to show at least 10% of each major component (epithelioid and sarcomatoid). An important remark is about the description of heterologous elements diagnosed within these tumors, as, for example, cartilaginous or bone tissue [17], reinforcing the caution of a sarcomatous neoplasm as differential diagnosis.

In Figures 1 and 2 are exemplified morphological aspects of the different subtypes, from epithelioid mesothelioma, with subconjunctival adipose layer infiltration (Fig1.A) of a hypercellular malignant epithelioid proliferation, mainly in a solid and diffuse, layer-like, fashion, dissecting and promoting pleural collagenesis (Fig1.B), of well-delimited neoplastic cells, hepatoid-like, with prominent nucleoli (Fig1.C). Figure 2 illustrates the most important morphologic differences between Sarcomatoid (Fig2.A), Desmoplastic (Fig2.B) and Epithelioid Pleomorphic (Fig2.C) types. These morphological features should be regarded with attention in order to elect MM as a differential diagnosis in epithelioid and/or sarcomatoid pleural neoplasm.

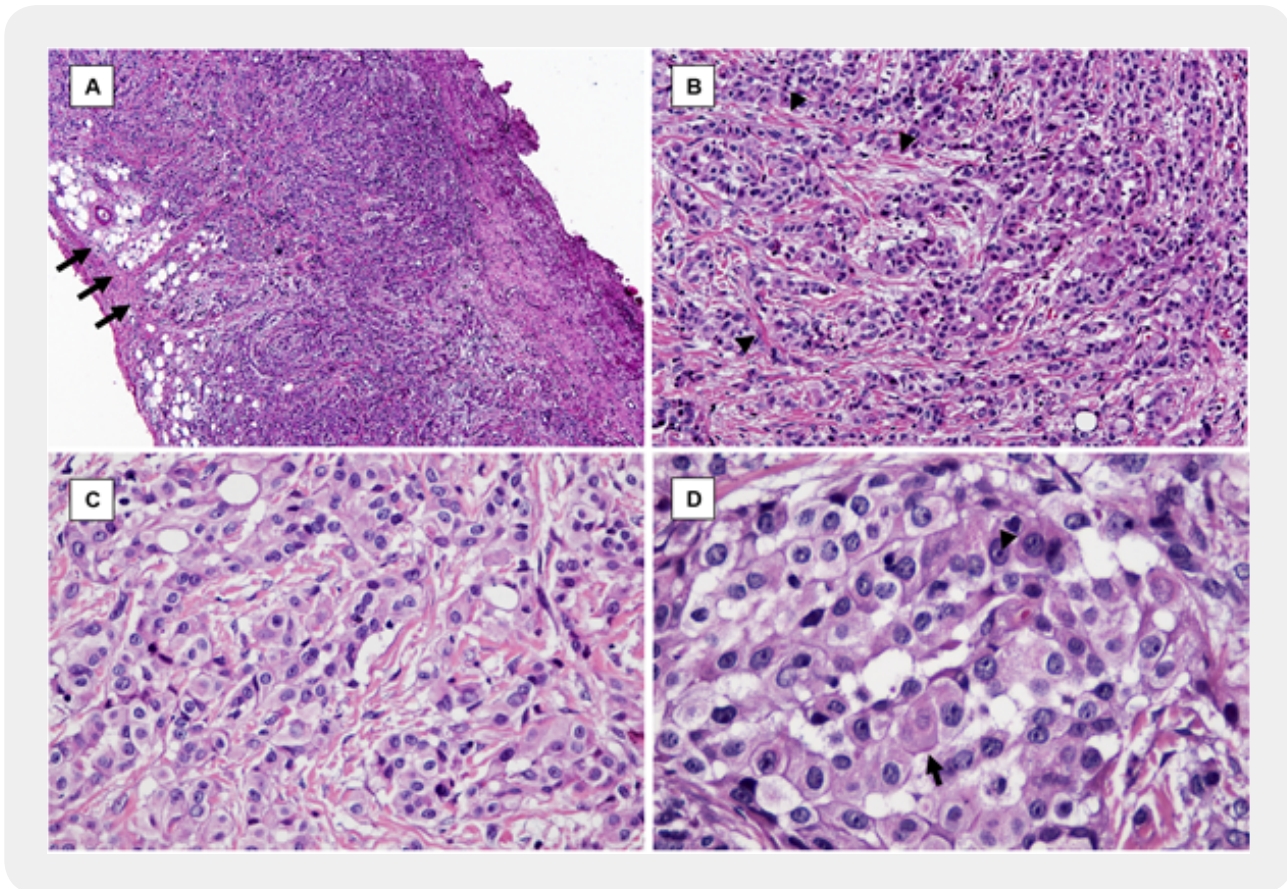


Figure 1: *Epithelioid Malignant Mesothelioma Morphology Features – Hematoxylin and Eosin (H&E) stained slide of pleural resection. (A) Hypercellular infiltrative neoplasm, extending in a plaque fashion throughout visceral pleura, from superficial mesothelial lining, where it arises from, through conjunctival submesothelial and adipose layers (arrows in adipose tissue infiltration), extending to parietal pleura. (B) Intercellular matrix dissociation by malignant epithelioid cellularity (arrowheads on eosinophilic collagenic response as part of desmoplasia); (C, D) epithelioid neoplastic cells in infiltrative and dissociative fashion composing a predominantly solid arrangement, with delineated and coherent cytoplasm (arrow), with prominent nucleoli (arrowhead).*

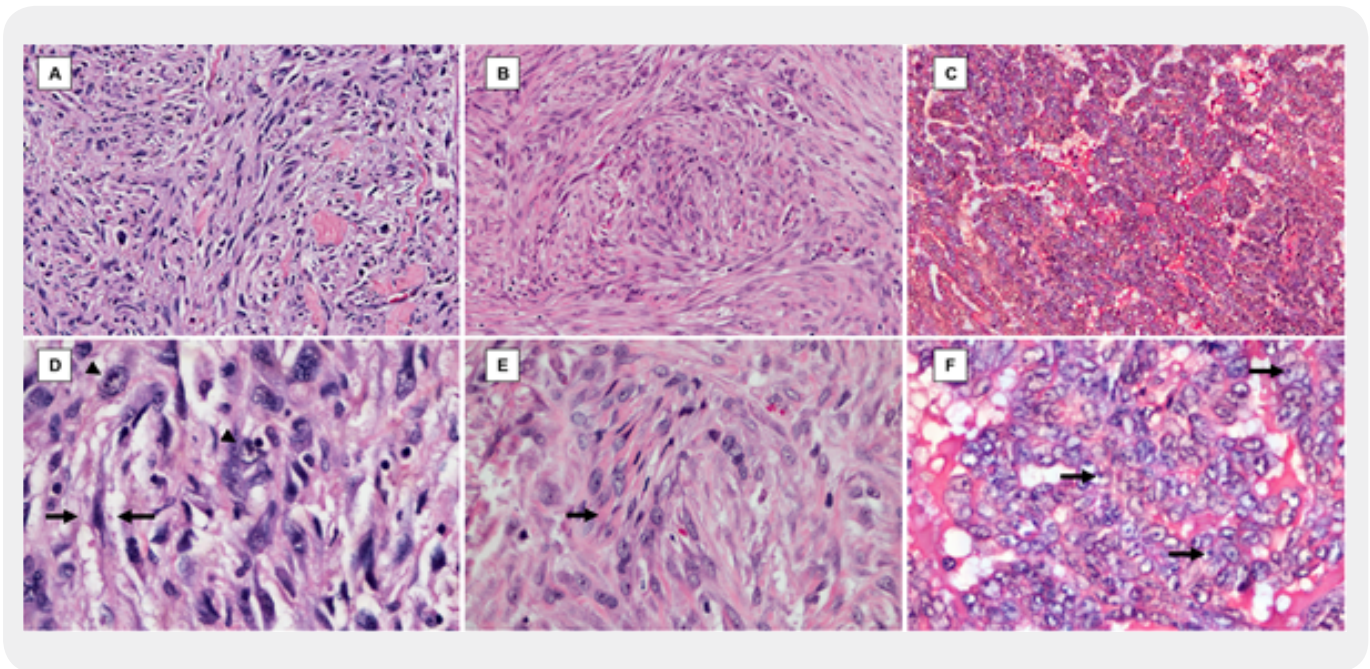


Figure 2: Hematoxylin and Eosin (H&E) stained slide of pleural resection showing infiltrative features of Malignant Mesothelioma. (A, D) Sarcomatoid type, composed by hypercellular spindle cells (arrows, D) with intense nuclear pleomorphisms (arrowheads); (B, E) Desmoplastic type, a less cellular spindle cell neoplasm, in storiform pattern, with intense extracellular matrix (arrow); (C, F) Epithelioid type, with pleomorphic features (arrows on prominent nucleoli).

Pathological Diagnosis - 2017 Update of the Consensus Statement from the International Mesothelioma Interest Group (iMIG)

The pathological diagnosis relies on the cornerstone bases of adequate sampling, which might not be commonly obtained, especially in non-epithelioid neoplasms. The diagnosis of biphasic mesothelioma should be spared to representative sampling, as surgical resection specimens [12,18], once the proper observation of both components in at least 10% of the specimen is mandatory, which might not be sufficed in a small biopsy or cytology sample. Exfoliative cytology and cell blocks may be employed, although with caution, as the published sensitivity for the cytological diagnosis of mesothelioma ranges from 30-75%, probably due to inadequate sampling. Immunocytochemical and molecular techniques (as p16 FISH) may be employed in all of these specimens [18].

An adequate immunohistochemical panel should be effective, in order to balance the necessity and utility of potential markers. It should be constructed through a Bayesian approach, employing pre-analytical clinical data, including radiological and surgical findings, correlated with morphology. Location and gender strongly influence the differentials, especially in non-pleural MM; asbestos exposure should not be taken into consideration as a necessity to conform the diagnosis [18].

Considering the morphological aspects, gender and location of the lesion, an epithelioid or sarcomatoid infiltrative pleural with the characteristics described earlier should elect the differential diagnosis of MM. In our practice, it is not uncommon to deliver a preliminary report of “Malignant epithelioid neoplasm” or “Malignant spindled cell neoplasm” and continue investigation from an immunohistochemical standpoint. There is no current consensus as to a mandatory panel; from a good practice point-of-view, the consensus is to elect, at least, two positive and two negative antibodies, which are, each, minimally 80% sensitive to MM and they should be evaluated in conjunction [18]. These recommendations are from actual iMIG Guidelines [19], originated from long-date suppositions, since Ordonez suggested the highly specific use of mesothelin [20] as a highly sensitive and specific marker. Curiously, nowadays, this maker might not play an exclusive diagnostic role, playing a more therapeutic role in targeted-therapy [21].

As a golden rule, in our practice, we follow the suggestions from the 2006 Ordonez paper [22], sustained by the iMIG and actual guidelines [18], as a two-panel approach in a Bayesian fashion for suspicious lesions, taking location, age, sex and previous oncologic data into account. For epithelioid suspicious lesions, we build a first approach-panel excluding MM by counterpointing expected mesothelial markers (Calretinin, D2-40, Wt1, CK5/6) to adenocarcinoma markers, which should be negative (Ber-EP4, MOC31). If this panel leads us into a possible adenocarcinoma, an expanded second panel is proposed. For pleural lesions, for example, common differentials are carcinomas, including lung adenocarcinoma and squamous cell carcinoma. For these, a broad keratin cocktail is employed (as AE1/AE3) to demonstrate the epithelial nature of the neoplasm, followed by primary lung adenocarcinoma antibodies (as TTF1, Napsin A, with sensitivity around 80-90% for lung adenocarcinomas [18]) and squamous cell (as p63 or p40). Caution is taken to evaluate this panel alongside the previous, as CK5/6 can be focally positive in a small subset of lung adenocarcinoma 2-20%; WT1 and Podoplanin D2-40). For a cytokeratin negative epithelioid neoplasm, the next step is to broaden its scope, employing other cytokeratins, as CAM 5.2, CK7/20, CK5/6 and considering other epithelioid malignant neoplasms, as Malignant Melanoma, Epithelioid Hemangioendothelioma or Angiosarcoma, and Malignant Lymphoma. For peritoneal epithelioid mesothelioma, differentials should consider also metastatic adenocarcinoma, especially renal cell carcinoma (PAX-8 positive) and papillary serous carcinoma, as well as nongynecologic adenocarcinoma (biliary, pancreatic, gastric and colonic). In Table 1, our approach is contextualized and in Figure 3 an example of typical epithelioid mesothelioma with positive mesothelial markers (D2-40, Calretinin and Negative Adenocarcinoma markers (Ber-EP4, MOC31).

For sarcomatoid suspected lesions, carcinomas still should be ruled out, as sarcomatoid carcinomas may present these features. Also, caution is advisable, as specific mesothelial markers do not behave in the same fashion in epithelioid and sarcomatoid MM, as summed in Table 1.

Table 1: Immunohistochemistry Workup for Malignant Mesothelioma and Differential Diagnosis

First Panel Approach – Consider Morphology			
Morphology	Markers	Result	Conclusion
Epithelioid	Mesothelial (Calretinin, Cytokeratin 5/6, WT1, D2-40, Mesothelin)	2 Positive Mesothelial AND 2 Negative Adenocarcinoma	Epithelioid Malignant Mesothelioma*
	Adenocarcinoma (MOC31, BER-EP4, Claudin 4)	If any positive AND Mesothelial Negative	Adenocarcinoma, expand panel
Sarcomatoid	Mesothelial (Calretinin, Cytokeratin 5/6, WT1, D2-40, Mesothelin)	Calretinin (30% positive) Podoplanin (D2-40) CK 5/6 is limited	Consider Molecular Testing (homozygous deletion 9p21 (p16) FISH, as well to exclude differentials (X;18 translocation for Synovial Sarcoma)
	Sarcomatoid Carcinomas	Lung, renal cell	
	Sarcomas	Synovial sarcoma Epithelioid Angiosarcoma Liposarcoma	
	Exclude negative-cytokeratin sarcomatoid mesothelioma with heterogeneous elements		
Expanded Panel for Adenocarcinomas – Consider Localization			
Morphology	Markers	Result	Conclusion
Pleural	Lung Adenocarcinoma (TTF1, Napsin A)	If positive AND Mesothelial Negative	Adenocarcinoma, exclude Thyroid Papillary Carcinoma
	Squamous Cell Carcinoma (p40, p63)	If positive AND Mesothelial Negative	Squamous Cell Carcinoma

Peritoneal	Renal Cell Carcinoma (PAX8, PAX2), avoid CD10, use RCC with caution	If positive AND Mesothelial Negative RCC can be positive in 30% of mesotheliomas	Metastatic Renal Cell Carcinoma
	Papillary Serous Carcinoma (Claudin 4, MOC31, PAX8, BG8, BER-EP4 Estrogen Receptor)	If positive AND Mesothelial Markers Negative	Metastatic Papillary Serous Carcinoma
	Nongynecologic Adenocarcinoma	CDX2 (colon, small intestine, gastric carcinomas) BER-EP4 (pancreas, bile duct, colon) CK7, CK20	Metastatic Adenocarcinoma, suggest primary

*The differential diagnosis between benign mimickers (Well Differentiated Papillary Mesothelioma and Benign Multicystic Mesothelioma) and localized (“*in situ*”) malignant mesothelioma, as well as Desmoplastic Mesothelioma relies on morphological grounds. BAP1 immunohistochemistry and p16 fluorescent hybridization (FISH) can be employed in dubious cases.

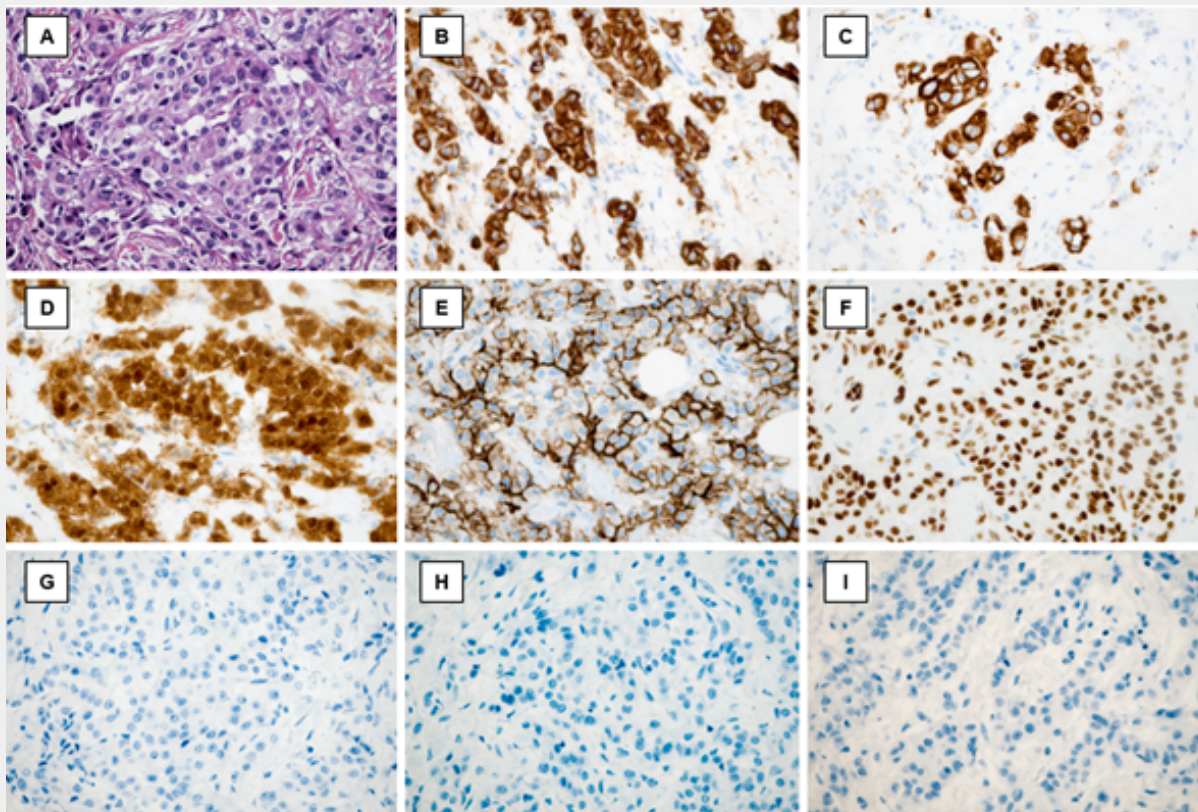


Figure 3: Immunohistochemical aspects - (A) H&E stained slide, Malignant Mesothelioma, Epithelioid type; (B-F) Typical positive immunohistochemistry markers - (B) Cytokeratin AE1/AE3, (C) Cytokeratin CK7, (D) Calretinin, (E) Podoplanin (D2-40); (F) Wilms tumor-1 (WT1); (G-I) Typical negative immunohistochemistry markers, (G) Cytokeratin 20, (H) Ber-EP4, (I) MOC31.

Nuclear Grading and Pleomorphic Features

Mesothelial Nuclear Grading System was proposed in 2011 [16]. This system revealed prognostic significance under a three-tier nuclear score grade, composed of cytological features, investigated in epithelioid MM (nuclear atypia, nuclear/cytoplasmic ratio, chromatin pattern, intranuclear inclusion, nucleoli prominence, mitotic count and presence of atypical mitosis). Some have replicated, modified and validated nuclear grading systems, as a large 2018 series report [15]. In this multi-institutional cohort of 776 cases, it was observed a significant global survival difference between Nuclear Score 1 and 3 (31 vs 11 months).

Nuclear grading is tendency to be incorporated in synoptic report; in our series we have observed nuclear grading differences between pleural and non-pleural mesotheliomas, accounting for significant higher grade for the last ones, possibly owned to worse survival (unpublished data).

TNM/AJCC Staging - 8th Edition

MM staging is a continuous work in progress, since its first 1994 iMIG classification [23]. For the 2018 TNM edition, pathologic staging was proven to show no striking differences between adjacent stages, except

T3 and T4. In the last years much effort has been made into enhancing morphological and predictive classification of MM and new data, as tumor morphology [18], pleomorphism [15,16], tumor volume [23] has not yet been incorporated into the actual edition of TNM, as current populational data and evidence does not subside unbiased conclusions. Further data collection, as well as accurate sampling of multiple sections and regions in resection specimens are encouraged for continuous data gathering.

Treatment Guidelines: American Society of Clinical Oncology Practice Guideline, 2018

In January 2018, the American Society of Clinical Oncology has updated its practices guidelines on MM [24]. Some key recommendations are summarized and discussed below according to the corresponding topic:

Diagnosis

Pathological diagnosis should be warranted, from initial evaluation of symptomatic pleural effusion (pleural fluid cytology), through treatment (thoroscopic biopsy should be performed before anti-neoplastic therapy, for adequate histological type diagnosis, immunohistochemistry or molecular biology confirmation and target therapy tests). Non-tissue biomarkers are under evaluation and there is no formal evidence of its utility for monitoring treatment and response; the same applies to tumor genomic sequencing.

Staging

Imaging studies are a requisite (initial CT scan of chest and upper abdomen with IV contrast, complemented with FDG PET/CT and MRI to evaluate disease extent), mediastinoscopy and/or endobronchial US should be considered if enlarged or PET-avid mediastinal nodes are detected; laparotomy should be considered with suspicious intra-abdominal findings. RECIST criteria should be employed for follow-up; although CT tumor volume assessment may enhance clinical follow-up, it is not formally recommended, as this data remains investigations.

Chemotherapy

Chemotherapy should be offered to MM patients with adequate minimal conditions; in asymptomatic patients with epithelial histology and minimal pleural disease, not surgical eligible, close observation may be offered prior to chemotherapy. First-line therapy is combined pemetrexed plus a platinum-derived agent (cisplatin / carboplatin); enrollment to clinical trials should be offered as an option, given the limited activity of second-line chemotherapy (vinorelbine). Pemetrexed should not be used as maintenance therapy due to its low quality of evidence.

Surgical Cytoreduction

Maximal surgical cytoreduction is strongly advised in early-stage disease (either lung sparing or non-lung sparing, meeting specific preoperative cardiopulmonary functional criteria, without evidence of extra thoracic disease and preserving the ability to receive multimodality treatment, except for those diagnosed with sarcomatoid mesothelioma), although it is insufficient as a single modality treatment option, requiring additional antineoplastic treatment (chemotherapy and/or radiation therapy). Neoadjuvant treatment should

be reserved for criteria as: transdiaphragmatic disease, multifocal chest wall invasion, contralateral mediastinal or supraclavicular lymph node involvement. N3 (contralateral or supraclavicular) node involvement should be an absolute contraindication to maximal surgical cytoreduction. Lung sparing cytoreduction should be preferred over non-lung sparing; chemotherapy may be delivered pre or post-surgically; intracavitary therapies may be administered in reference centers.

Radiation Therapy

Neo-adjuvant treatment should be offered with caution and criteria (e.g., not as prophylaxis of interventional faults); may be offered for local asymptomatic recurrence and as a palliative resource, specially to symptomatic disease patients.

New Drug Targets

Thoracic oncology is under an era of new perspectives due to targeted therapy, which includes tyrosine kinase agents, immunobiologicals, immune checkpoint inhibitors and other agents. The first thoracic neoplasms to be at the spot of improved survival were the lung non-small cell carcinoma (NSCC) [25]. Prognosis for mesothelioma is often dismissal, with some trials reporting about 13 months with combination

platinum-based chemotherapy opposite to 10 months without treatment. PD-L1 inhibitors, for instance, have been reported to shown medium survival up to 18.8 months in combination with traditional combination chemotherapy approach [26].

Immune checkpoints inhibitors, as anti PD-1, PD-L1 and CTLA-4, have been regarded as promising drugs: around 20–40% of PD-L1 expression has been observed in mesothelioma and stromal cells in tissue immunohistochemical essays [27]. Overall survival and disease-free data is still poorly available in the literature, although encouraging its prescription, yet there is no sufficient data to sustain FDA approval, as most clinical trials are phase I and II trials [28,29]. Besides this, histopathological PD-L1 evaluation is still under a strong debate, once it has been clinically validated as an OncoDx marker, coupling the clone election to the drug choice, with resulting different interpretation points between different clones [26].

Another on-going class of promising anti-neoplastic agents on development are Mesothelin (MSLN) Immunobiological agents. MSLN is a membrane glycoprotein specific to the mesothelial cells; this class of agents, under development and initial phase trials, relies I specific mesothelial cancer cells elimination through diverse immunological mechanisms, immunotoxins, vaccines, chimeric monoclonal antibodies, chimeric antigen receptor T cells (CART) and antibody-drug conjugates [21].

We have summarized the latest target-therapy trials on course enlisted at Clinicaltrials.gov, up to May 1st 2018. Of those, active and recruiting trials, 70 were selected, encompassing a total of 8732 expected patients to be enrolled in the United States and Europe, most of them on Immune Chekpoints therapy (PD-1, PD-L1, CTLA-4 and novel drugs, as LAG-3, anti-FAK and anti-NanogStemness); MSLN directed therapy also is ongoing, including CAR-T. Data is enlisted on Table 2 and illustrated on Table 4. For further discussion, a comprehensive review is approached elsewhere [30].

Table 2: Ongoing Clinical Trials on Mesothelioma Immunotherapy and Novel Agents (May-2018, *clinicaltrials.gov*)

Biological Action	Target	Agents	Phase	Studies (n=70)	Enrollment (n=8732)	Status
Immune Check-point	PD-1	Pembrolizumab	I II	9	2188	A / R
	PD-1	Nivolumab	I II III	7	1407	A / R
	CTLA-4	Tremelimumab	I II	3	631	A / R
	LAG-3	LGA525 PDR001	I II	1	515	R
	PD-L1	Atezolimumab / Avelumab / Durvalumab	I II	4	199	R
	FAK	Defactinib	II	1	38	A
Mesothelin Im-muno-targeting	Monoclonal Antibody	Amatuximab, Antumab	I II	3	490	A / R
	Vaccine	Dendritic Cell	I II	6	338	A / R
	CAR-T	CAR-T	I II	6	248	A / R
		Immunotoxin	I II	3	109	A / R
		Virus Vector	I II	2	70	A / R
EC Ligands	CD30	Brentuximab	II	1	50	R
	CD26	YS110	I II	1	48	R
	Biological	Autologous TILs	I II	2	28	A / R
Angiogenesis Inhibitor	PDGFR, FGFR	Nintedanib	I II	5	757	A / R
	VEGF	Cediranib	I II	1	116	A
Cell cycle related	PEG-Arginine	ADI-PEG 20	I II III	2	470	A / R
	CDK4/6	Abemaciclib	I	1	150	R
	BCR-ABL	Bosutinib, Dasatinib	I	2	84	A / R
	NAE	Pevonedistat	I II	1	42	R
	Aurora A	Alisertib	II	1	28	A
	Hsp90	Ganetspib	I II	1	27	A

Histone Complex	EZH2	Tazemetostat	II	2	367	R / A
	DART B7-H3	MGD009	I	1	114	R
DNA-repair	PARP	Niraparib	II	1	47	NR
Cancer Stem-Cell	DD3	Rovalpitumab	I	1	116	R
	Nanog-Stemness	BBI608	I II	1	24	A

Abbreviations: PD-1: Programmed cell death protein 1, CTLA-4: Cytotoxic T-lymphocyte-associated protein 4, LAG-3: Lymphocyte-activation gene 3, Mesothelin Mab, Mesothelin Monoclonal Antibody, PEGArginine, Pegylated Arginine Deiminase, EZH2: Histone-lysine N-methyltransferase enzyme (H3K27), PD-L1: Programmed cell death protein ligand-1, CDK4/6: Cyclin-dependent kinase 4/6, VEGF: Vascular Endothelium Growth Factor, DD3: Delta protein 3, DART B7-H3: Dual-affinity re-targeting protein B7-H3 histone complex, BCR-ABL: BCR-ABL mutation, PARP: Poly(ADP-ribose) polymerase, NAE: NEDD8-activating enzyme, FAK: Focal Adhesion Kinase, MET: mesenchymal-epithelial transition factor, AAK: Aurora A Kinase, Hsp90: Heat Shock Protein 90, A: Active, R: Recruiting, NR: Not Recruiting.

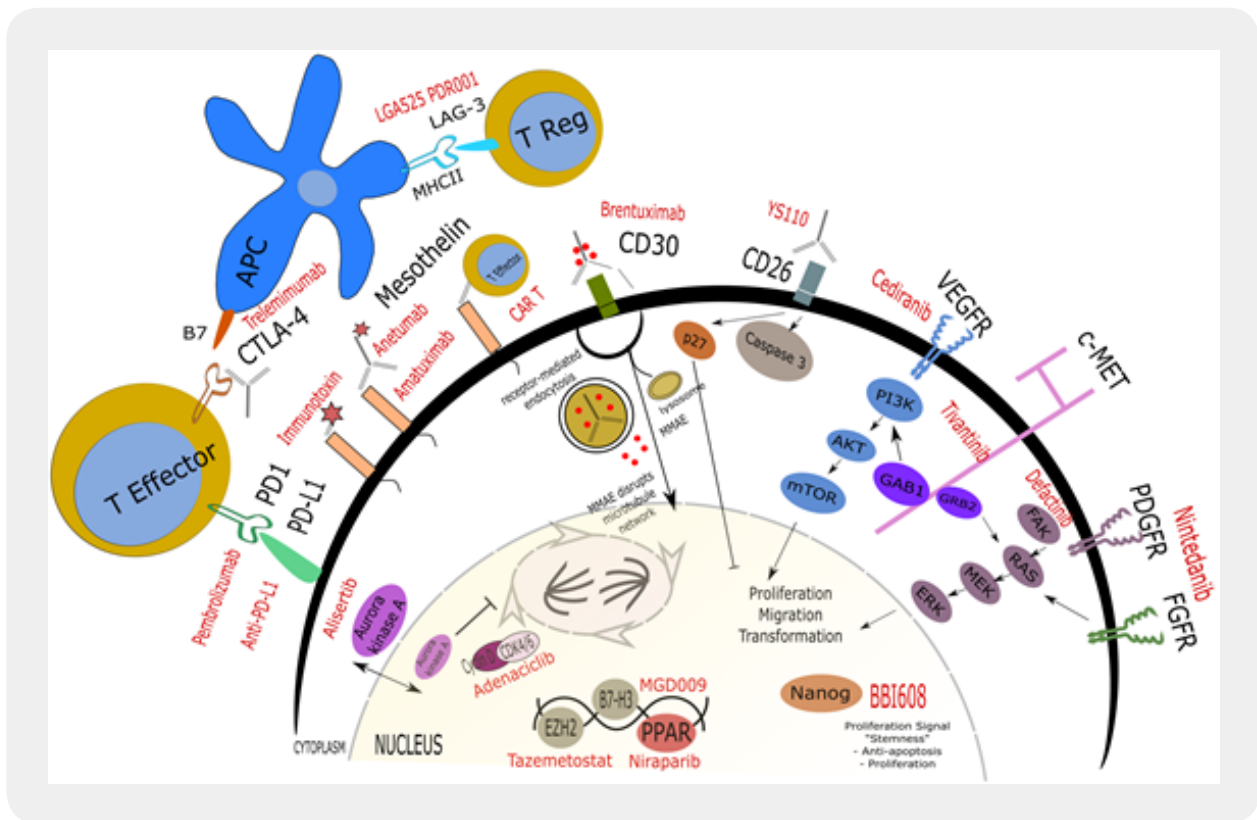


Figure 4: Mechanistic approach to the main novel and on trial drugs, as discussed on Table 2.

Conclusion

In this review, we have reviewed the major 2018 updates for MM, from its recently published guidelines addressing diagnosis, treatment and new drugs on trials. Morphology, adequate sampling and combination chemotherapy remain cornerstones in MM management. Nuclear grading and new drugs on trial are promising, possibly offering most effective treatment options, as well as more predictive and prognostic information to patients in encouraging times for mesothelioma investigators.

Disclosures / Conflicts of Interests

Dr. Balancin has received speaker fees from Roche Diagnostics on Breast Cancer Her-2 ISH for training conferences. The remaining authors declare no conflict of interest.

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