EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach.

Andrew G. Nicholson, DM, Jennifer L. Sauter, MD, Anna K. Nowak, MD, Hedy L. Kindler, MD, Ritu R. Gill, MD, Martine Remy-Jardin, MD, Samuel G. Armato, III, PhD, Lynnette Fernandez-Cuesta, PhD, Raphael Bueno, MD, Nicolas Alcala, PhD, Matthieu Foll, PhD, Harvey Pass, MD, Richard Attanoos, FRCPath, Paul Baas, MD, Mary Beth Beasley, MD, Luka Brcic, MD, Kelly J. Butnor, MD, Lucian R. Chirieac, MD, Andrew Churg, MD, Pierre Courtiol, Sanja Dacic, MD, Marc De Perrot, MD, Thomas Frauenfelder, MD, Allen Gibbs, MD, Fred R. Hirsch, MD, Kenzo Hiroshima, MD, Aliya Husain, MD, Sonja Klebe, MD, Sylvie Lantuejoul, MD, Andre Moreira, MD, Isabelle Opitz, MD, Maurice Perol, MD, Anja Roden, MD, Victor Roggli, MD, Arnaud Scherpereel, MD, Frank Tirode, PhD, Henry Tazelaar, MD, William D. Travis, MD, Ming Sound Tsao, MD, Paul van Schil, MD, Jean Michel Vignaud, MD, Birgit Weynand, MD, Ian Cree, PhD, Valerie W. Rusch, MD, Nicolas Girard, MD, Francoise Galateau-Salle, MD

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EURACAN/IASLC proposals for updating the histologic classification of pleural mesothelioma: towards a more multidisciplinary approach.

Andrew G Nicholson DM[a], Jennifer L. Sauter MD[b], Anna K Nowak MD[c], Hedy L Kindler MD[d], Ritu R Gill MD[e], Martine Remy-Jardin MD[f], Samuel G Armato III PhD[g], Lynnette Fernandez-Cuesta PhD[h], Raphael Bueno MD[i], Nicolas Alcala PhD[j], Matthieu Foll PhD[k], Harvey Pass MD[l], Richard Attanoos FRCPath[m], Paul Baas MD[n], Mary Beth Beasley MD[o], Luka Brcic MD[p], Kelly J Butnor MD[q], Lucian R.Chirieac MD[r], Andrew Churg MD[s], Pierre Courtiol[t], Sanja Dacic MD[u], Marc De Perrot MD[v], Thomas Frauenfelder MD[w], Allen Gibbs MD[x], Fred R. Hirsch MD[y], Kenzo Hiroshima MD[z], Aliya Husain MD[aa], Sonja Klebe MD[bb], Sylvie Lantuejoul MD[cc], Andre Moreira MD[dd], Isabelle Opitz MD[ee], Maurice Perol MD[ff], Anja Roden MD[gg], Victor Roggli MD[hh], Arnaud Scherpereel MD[ii], Frank Tirode PhD[jj], Henry Tazelaar MD[kk], William D Travis MD[b], Ming Sound Tsao MD[ll], Paul van Schil MD[mm], Jean Michel Vignaud MD[nn], Birgit Weynand MD[oo], Ian Cree PhD[pp], Valerie W Rusch MD[qq], Nicolas Girard MD[rr], Francoise Galateau-Salle MD[ss].

[a]Department of Histopathology, Royal Brompton and Harefield NHS Foundation Trust and National Heart and Lung Institute, Imperial College, London. a.nicholson@rbht.nhs.uk

[b]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA. sauterj@mskcc.org and travisw@mskcc.org

[c]Medical School, University of Western Australia, Perth Australia. anna.nowak@uwa.edu.au

[d]Department of Medicine, Section of Hematology/Oncology, University of Chicago Medicine, Chicago, Illinois, USA. hkindler@medicine.bsd.uchicago.edu

[e]Department of Radiology, Beth Israel Deaconess Medical Center, Boston, Massacheusetts, USA. rgill@bidmc.harvard.edu

[f]Department of Thoracic Imaging, Hospital Calmette, University Centre of Lille, France. martine.remy@chru-lille.fr

[g]Department of Radiology, The University of Chicago, Chicago, Illinois, USA. s-armato@uchicago.edu

[h]International Agency for Research on Cancer (IARC/WHO), Section of Genetics, Lyon, France. FernandezCuestaL@iarc.fr

[i]Division of Thoracic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, Massacheusetts, USA. rbueno@bwh.Harvard.edu

[j]International Agency for Research on Cancer (IARC/WHO), Section of Genetics, Lyon, France. alcalan@fellows.iarc.fr

[k]International Agency for Research on Cancer (IARC/WHO), Section of Genetics, Lyon, France. follm@iarc.fr

[l]Cardiothoracic Surgery, NYU Langone Health, New York, New York. USA. harvey.pass@nyumc.org

[m]Department of Cellular Pathology, University Hospital of Wales, School of Medicine, Cardiff University, UK. richard.attanoos@wales.nhs.uk

[n]Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands. p.baas@nki.nl

[o]Department of Pathology, Mount Sinai Medical Center, New York, New York, USA. mbbeasleymd@yahoo.com

[p]Diagnostic and Research Institute of Pathology, Medical University of Graz, Graz, Austria. luka.brcic@medunigraz.at

[q]Department of Pathology & Laboratory Medicine, The University of Vermont Medical Center, Burlington, Vermont, USA. kelly.butnor@uvmhealth.org

[r]Department of Pathology, Brigham and Women's Hospital, Boston, Massacheusetts, USA. lchirieac@bwh.harvard.edu

[s]Dept of Pathology, Vancouver General Hospital, Vancouver, BC, Canada. achurg@mail.ubc.ca

[t] Owkin Inc. pierre.courtiol@owkin.com

[u]Department of Pathology University of Pittsburgh Medical Center, Pennsylvania, USA. dacics@upmc.edu

[v]Division of Thoracic Surgery, Princess Margaret Cancer Centre, Toronto, Canada. marc.deperrot@uhn.ca

[w]Institute of Diagnostic and Interventional Radiology, University Hospital Zurich, Zurich, Switzerland. thomas.frauenfelder@usz.ch

[x]Department of Cellular Pathology, Cardiff and Vale UHB, Cardiff, Wales, UK. allenrg@btinternet.com

[y]Center for Thoracic Oncology, Mount Sinai Health System, New York, New York, USA. Fred.Hirsch@ucdenver.edu

[z]Department of Pathology, Tokyo Women's Medical University, Yachiyo Medical Center, Tokyo, Japan. hiroshima.kenzo@twmu.ac.jp

[aa]Department of Pathology, University of Chicago, Chicago, Illinois, USA. Aliya.Husain@uchospitals.edu

[bb]Department of Anatomical Pathology, SA Pathology and Flinders University, Adelaide, Australia. Sonja.Klebe@sa.gov.au

[cc]Department of Biopathology and of Translational Research and Innovation, CNR MESOPATH, Centre Leon Berard Lyon, and Grenoble Alpes University, France. sylvie.lantuejoul@lyon.unicancer.fr

[dd] Department of Pathology, New York University Langone Health, New York, new York, USA. Andre.Moreira@nyulangone.org

[ee]Department of Thoracic Surgery, University Hospital Zurich, Zurich, Switzerland. isabelle.schmitt-opitz@usz.ch

[ff]Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France. maurice.perol@lyon.unicancer.fr

[gg]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA. roden.anja@mayo.edu

[hh]Department of Pathology, Duke University Medical Center, Durham, North Carolina, USA. victor.roggli@duke.edu

[ii]Pulmonary and Thoracic Oncology Department, Univ Lille, CHU Lille, France. arnaud.scherpereel@chru-lille.fr

[jj]Université Lyon, Université Claude Bernard Lyon 1, INSERM 1052, CNRS 5286, Centre Léon Bérard, Cancer Research Center of Lyon, France. franck.tirode@lyon.unicancer.fr

[kk]Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, Arizona. tazelaar.henry@mayo.edu

[ll]Department of Pathology, University Health Network , Princess Margaret Cancer Centre, Toronto, Canada. ming.tsao@uhn.ca

[mm]Department of Thoracic and Vascular Surgery, Antwerp University Hospital and Antwerp University, Belgium. paul.van.schil@uza.be

[nn]CHU Nancy, Université Lorraine, Nancy, France. JM.VIGNAUD@chru-nancy.fr

[oo]Department of Pathology, UZ Leuven, Leuven, Belgium. birgit.weynand@uzleuven.be

[pp]International Agency for Research on Cancer (IARC), Lyon, France. creei@iarc.fr

[qq]Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA. ruschv@mskcc.org

[rr]Institut Curie, Institut du Thorax Curie Montsouris, Paris, France. nicolas.girard2@curie.fr

[ss]MESOPATH Centre Leon Berard, Lyon, France. francoise.galateau@lyon.unicancer.fr

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Abstract

Introduction: Molecular and immunologic breakthroughs are transforming the management of thoracic cancer, although advances have not been as marked for malignant pleural mesothelioma (MPM) where pathologic diagnosis has been essentially limited to three histologic subtypes.

Methods: A multidisciplinary group (pathologists, molecular biologists, surgeons, radiologists and oncologists), sponsored by EURACAN/IASLC met in 2018, to critically review the current classification.

Results: Recommendations include: 1) classification should be updated to include architectural patterns, and stromal and cytologic features that refine prognostication 2) subject to data accrual, malignant mesothelioma in situ could be an additional category, 3) grading of epithelioid MPMs should be routinely undertaken, 4) favorable/unfavorable histologic characteristics should be routinely reported, 5) clinically relevant molecular data (PD-L1, BAP1, *CDKN2A*) should be incorporated into reports, if undertaken, 6) other molecular data should be accrued as part of future trials 7) resection specimens (i.e. extended pleurectomy/decortication and extrapleural pneumonectomy) should be pathologically staged with smaller specimens being clinically staged, 8) ideally, at least 3 separate areas should be sampled from the pleural cavity, including areas of interest identified on pre-surgical imaging, 9) image-acquisition protocols/imaging terminology should be standardized to aid research/refine clinical staging, 10) multidisciplinary tumor boards should include pathologists to ensure appropriate treatment options are considered, 11) all histologic subtypes should be considered potential candidates for chemotherapy, 12) patients with sarcomatoid or biphasic mesothelioma should not be excluded from first line clinical trials unless there is a compelling reason, 13) tumor subtyping should be further assessed in relation to duration of response to immunotherapy, 14) systematic screening of all patients for germline mutations is not recommended, in the absence of a family history suspicious for BAP1 syndrome.

Conclusion: These multidisciplinary recommendations for pathology classification and application will allow more informative pathologic reporting and potential risk stratification, to support clinical practice, research investigation and clinical trials.

Introduction

Malignant pleural mesothelioma (MPM) is a challenging rare cancer comprising less than 0.3% of all malignances. It is aggressive and rarely curable. The World Health Organisation (WHO) 2015 classifies MPM into three major histological subtypes of prognostic importance: epithelioid, biphasic and sarcomatoid (including those with desmoplastic features).[1] Clinically, these are viewed as two classes, epithelioid and non-epithelioid (sarcomatoid and biphasic). The sarcomatoid type is associated with the worst prognosis. MPM has an extremely poor prognosis with a median survival of 7–9 months if untreated and a 5-year survival rate of 5%, and all currently approved systemic or locoregional therapies fail in the vast majority of patients.[2] These failures call for a better understanding of the disease, for multidisciplinary discussion and consensus for the clinical care of these patients and for definition of key components that allow robust classification of the disease.

There have been many recent molecular and immunologic additions to the pathologic diagnosis of malignancies in directing both targeted and immunologic therapies, in particular transforming the field of lung cancer, leading to a more multidisciplinary patient management structure. However, these advances have not been as marked in the management of patients with mesothelioma.[2]

Therefore, a multidisciplinary group was convened to review the histologic classification of MPM. Sponsored by the European Reference Network for Rare Cancers (EURACAN) and the International Association for the Study of Lung Cancer (IASLC), a group of pathologists, molecular biologists, surgeons, radiologists and oncologists met on 5th and 6th July 2018, to critically review the current histologic classification of MPM in light of recent advances.

Initial feedback from specialties other than pathology commented on the need for greater standardization in reporting, with classification based on evidence and validated to be useful in clinical practice. Classification also needed to be consistent among pathologists and to comprise of biologically and clinically relevant subtypes and features, which could be applied to routine practice and clinical trials. Specifically, it was

felt that there could be more granularity than simply the three current subtypes. More precise histologic diagnosis with improved risk stratification could be important for patient selection for surgery, multimodal therapy or chemotherapy alone. Inclusion of non-tumoral features within the tumor micro-environment might also be of value in relation to understanding the molecular pathogenesis of MPM. Other suggestions included more consistent guidance for use of immunohistochemistry (IHC) and molecular analysis. Finally, all groups commented on a lack of standardization in tissue acquisition and how variability in the number and size of tissue samples might affect histologic classification.

Each specialty, namely pathology, surgery, imaging, molecular pathology, oncology, then met to discuss gaps between the current histologic classification and their own practices, leading to a set of recommendations that will hopefully provide a template for future clinical management, WHO classification, and research across all specialties.

The focus of the discussion was on pleural mesothelioma and prognostic features of MPM. Prognostic relevance of these features has yet to be validated in mesothelioma of extrapleural sites. Additionally, questions for further investigation included herein were developed from a thoracic perspective, but expansion to mesotheliomas involving extrapleural sites including peritoneal mesothelioma will be an important future direction.

1. PATHOLOGY

1.1.1 Sample types and classification

WHO classifications are primarily based on resection specimens. Indeed, for lung carcinoma, the 2015 edition was the first to include a specific classification system for biopsies as well as resections, following the 2011 IASLC/American Thoracic Society/European Respiratory Society (ATS/ERS) updated adenocarcinoma classification proposals.[3] Histologic classification of mesothelioma creates its own issues as often only biopsy samples, and sometimes only cytology samples, are available for many patients. In addition, there is considerable variation in the size and number of samples obtained, as biopsy samples may be transthoracic (needle biopsies

and aspirates) or taken at thoracoscopy. The distinction where “biopsy” ends in terms of thoracoscopic biopsy and pleural decortication is not clearly defined, although there is recognition of specific operations that allow maximal surgical cytoreduction, including “extended pleurectomy/decortication (EPD)” and “extrapleural pneumonectomy (EPP)”.[4] A more detailed discussion on the many issues of tissue acquisition for mesothelioma diagnosis are provided in Section 3. It was agreed that, where relevant, specific terminology and criteria should be proposed for biopsy and cytology specimens, to be distinguished from those undergoing “definitive surgery” EPD/EPP or diagnosis at autopsy. Furthermore, only those undergoing EPD/EPP would undergo pathological staging, with the remainder being clinically staged via multidisciplinary team (MDT) review (see section 3).

1.1.2 Recommendations:

- ***Pathologic classification should have terminology and criteria that allow classification across the spectrum of cytology/biopsy and “definitively resected” material.***
- ***Cases undergoing maximal surgical cytoreduction (EPD and EPP) should be pathologically staged. Cases sampled to a lesser degree should be clinically staged.***
- ***Recommendations on number and size of samples are discussed in Section 3.***

1.2 Proposals for updating the histologic subtyping of mesothelioma

Table 1 lists the current subtypes of MPM in the 2015 WHO classification.[1]

1.2.1. Localized malignant mesothelioma

Although rare, localized mesotheliomas are important to recognize as they are potentially treatable by complete (pR0) resection and carry a favorable prognosis compared to diffuse mesotheliomas.[5,6] Classification requires correlation with imaging and surgical findings to ensure that there is no evidence of unsampled diffuse disease.

Localized mesotheliomas have been shown to have distinctive genetic features, with both similarities to and differences from diffuse malignant pleural mesothelioma.[7]

1.2.2 Diffuse malignant mesothelioma

The 2015 WHO classification divides diffuse malignant mesotheliomas into epithelioid, biphasic and sarcomatoid subtypes (table 1 and figure 1), recognizing desmoplastic features in the sarcomatoid subtype.[1] In addition, there have been numerous publications in the past thirty years that report prognostic relevance of both common and rare features seen in epithelioid, and to a lesser degree, sarcomatoid mesothelioma. Some of these carry adverse prognostic significance, such as solid, pleomorphic, rhabdoid and transitional features,[8-13] whilst others are reported as favorable, such as lymphohistiocytoid, and possibly myxoid features.[8,14-16]

1.2.3 Well differentiated papillary mesothelioma

When localized, well differentiated papillary mesotheliomas (WDPM) (figure 1) are also potentially treatable by complete (pR0) resection, and carry a favorable prognosis compared to diffuse mesotheliomas.[17] Likewise, classification requires correlation with imaging and surgical findings to ensure there is no evidence of different subtypes of disease. Diagnosis of WDPMs also requires application of strict criteria in order not to misdiagnose invasive diffuse mesotheliomas with prominent surface papillary architecture,[18] which may be facilitated by the recent recognition of mutually exclusive mutations in *TRAF7* and *CDC42* reported to distinguish peritoneal WDPM from diffuse malignant mesothelioma.[19] Additionally, WDPMs in this study did not harbor alterations in *BAP1*, *CDKN2A*, *NF2* and *SETD2* genes, further distinguishing WDPM from diffuse malignant mesothelioma. These findings suggest that BAP1 IHC and p16 fluorescence in situ hybridization (FISH) may be diagnostically useful in identifying WDPM and that the diagnosis of WDPM should be questioned when BAP1 expression is lost by IHC or homozygous deletion in *CDKN2A* is detected by p16 FISH. PAX8 expression is also commonly seen in WDPM, whilst is rare in diffuse malignant mesothelioma, although extent of overexpression may differ between clones.[20-22]

1.2.4 Current patterns

Epithelioid mesothelioma

A critical review of the literature shows that reported features in epithelioid mesothelioma can be stratified as a mixture of architectural patterns, and cytologic and stromal features (Tables 2 and 3, and figure 2).[23] Their identification is important for several reasons. First, they allow pathologists to diagnose epithelioid mesothelioma correctly and avoid misdiagnoses due to histologic similarity with other tumor types. Secondly, some features have prognostic value which could be incorporated into a grading system and/or a prognostic index.[9] However, most publications are small case cohorts and criteria are, to a degree, arbitrary. Nevertheless, more precise diagnostic criteria would likely improve both reproducibility and assessment of the individual significance of these features.

Biphasic mesothelioma

The current WHO classification requires at least 10% of the tumor to have sarcomatoid elements along with an epithelioid component for the diagnosis of biphasic mesothelioma. However, this cut-off is arbitrary and not based on evidence. One study suggested a <80% cut-off for sarcomatoid areas afforded a better prognosis,[13] and another study showed prognostic significance with a cut-off of 50%.[24] However, more data are required before changes are made to the WHO criteria. The consensus agreement was that the use of percentages to define biphasic mesothelioma should be limited to EPDs and EPPs. Since criteria have never been proposed for smaller samples, the group recommended that the definition for the diagnosis of biphasic mesothelioma should be changed for smaller samples, so that any sample can be diagnosed as biphasic mesothelioma with a comment providing the percentages of each component in the sample.

A stricter definition of what constitutes sarcomatoid features also may improve interobserver (IO) reproducibility among pathologists for characterization of biphasic mesothelioma, which currently only has a kappa of 0.45.[13] Immunohistochemical staining for cytokeratins may be beneficial in identifying a sarcomatoid component, as well as FISH analysis for p16 deletion in suspicious but non-diagnostic cases.[25]

Sarcomatoid mesothelioma

The group concluded that the current definition should remain, although the diagnostic criteria should be strengthened to improve diagnostic reproducibility, particularly the difficult area of the *desmoplastic* variant. The WHO defines sarcomatoid mesothelioma tumor cells as “elongated and tapered” (Figure 1). Sarcomatoid mesothelial cells can be difficult to identify and/or distinguish from reactive fibrosis in some cases by histology alone, and in these cases, the extent and distribution of cytokeratin IHC may be helpful in reaching a diagnosis of sarcomatoid MPM.

There was also a focus on mesotheliomas with a *transitional* pattern. Given its cohesive nature, the transitional pattern is classified under epithelioid MPM in the current WHO classification. However, it is reported to have a prognostic significance closer to sarcomatoid as opposed to epithelioid subtypes.[13] Since kappa values for diagnostic reproducibility were only 0.42, a stricter set of definitions to distinguish transitional from both epithelioid and sarcomatoid types is needed. The group concluded that there is insufficient data available currently to determine whether the transitional pattern should be classified under the epithelioid or sarcomatoid type of MPM. Therefore, the consensus was to include the transitional pattern under both epithelioid and sarcomatoid types until more data is available. A similar conclusion was reached for a *pleomorphic* pattern.

1.2.5 Malignant mesothelioma in situ (MMIS)

Malignant mesothelioma in situ (MMIS) was first proposed in 1992 based on a small series in which there was a single layer of small papillary projections of cytologically atypical mesothelial cells on the pleural surface associated with microscopically invasive mesothelioma.[26] The group discussed whether this pattern of growth really represented mesothelioma in situ or surface growth of an underlying invasive mesothelioma that was not recognized or biopsied, and also the challenge of making this diagnosis and distinguishing it from reactive/atypical mesothelial proliferations. The consensus view was that MMIS must exist as a starting point for some tumors but, until recently, the

issue has always been how to diagnose those MMIS without the presence of coexistent invasion.

Advances in the molecular understanding of mesothelioma, in particular loss of BAP1 expression by IHC and/or the presence of a homozygous deletion of *CDKN2A* (p16) identified by either FISH [27-36] or by methylthioadenosine phosphorylase (MTAP) IHC, potentially allow identification of genetic abnormalities in cases where the mesothelial proliferation is limited to the serosal surface and allow distinction between non-neoplastic and neoplastic cells.[37-40] There has been recent publication of eleven cases of MMIS (nine pleural, two peritoneal) with only surface single layer of mesothelial cells, no gross tumor on imaging or direct examination and no invasive mesothelioma for at least one year.[41,42] In the larger series of 10 patients, seven developed invasive disease 12 -92 months after biopsy, with 3 patients still free of invasive disease at 12, 57 and 120 months. (Figure 3).

The diagnosis of MMIS would be based on a combination of clinical, imaging and histologic criteria, and only made in the absence of clinical and radiologic evidence of tumor. Patients may have a pleural effusion but would not show any mass lesions on imaging or thoracoscopy (unless biopsies show the mass not to be mesothelioma), and the biopsy material shows a mesothelial proliferation limited to the serosal surface with either BAP1 loss and/or *CDKN2A*/p16 homozygous deletion. Testing should only be done in laboratories with experience using validated tests and appropriate antibodies, with the committee view that the Santa Cruz C4 clone is currently the best commercially available option for BAP1 IHC, and that FISH for homozygous deletion of p16 should only be performed in accredited laboratories, with a cut-off of 20% being the most commonly used.

Recognition of either BAP1 loss and/or CDKN2A/p16 homozygous deletion in cytologic material from a pleural effusion without any mass lesion, should prompt histologic sampling to confirm a lack of invasion, although not all cases carry these molecular

abnormalities so the diagnosis of MPM cannot be excluded in the absence of these molecular changes.

Another major issue discussed, but without supporting evidence, is the challenge of what population of patients should be assessed for BAP1 loss and/or *CDKN2A*/p16 deletion. Opinions varied and potential patient populations that were suggested included those with exposure to asbestos, presence of morphologically atypical mesothelial proliferations, and clinical suspicion of MPM (e.g. repeated unexplained effusions). However, identification of these patient populations is subject to potential lack of consistency (germline versus somatic BAP1 mutations, definition of "exposure", extent of atypia, etc). The group consensus was that, at this point in time, a molecular work up using BAP1 IHC, p16 FISH or MTAP IHC as a marker for p16 deletion, should be limited to patients for whom there is clinical suspicion of MPM. More work is clearly needed in this area, and individual institutions were encouraged to embark on a detailed assessment of this topic and data accrual.

There is currently insufficient evidence to support a category of minimally invasive MPM, but the group agreed this was a subject for research. It was recognized that data is limited but the clinical importance of identifying MMIS was a major factor in making this proposal at this early stage of literature accrual.

1.2.6 Recommendations:

- ***The current classification system should be updated to include architectural patterns, and stromal and cytologic features that might improve prognosis, permit early treatment and/or avoid misdiagnosis.***
- ***Subject to accrual of additional supportive data, malignant mesothelioma in situ could potentially be added as a category in future classification systems.***

A proposed update is presented in Tables 2 and 3. Questions for future investigation are in supplementary data 1, section 1.2.7.

1.3.1 Grading of MPM

Since 2010, there have been several papers proposing a pathologic grading system for epithelioid MPM that would provide prognostic stratification.[43-45] Although grading does not yet have therapeutic implications, because a uniform grading system has not been previously recommended, distinction between low and high grade has potential management implications such as intervals for imaging follow-up. Thus grading may be of benefit as part of inclusion or stratification criteria when planning future trials, and may provide better risk stratification than assignment of some rare architectural, stromal or cytologic features of epithelioid MPM (see previous section).

The purpose of applying a grading system to epithelioid MPM would be to identify those tumors that behave more aggressively. This grading system can be applied to biopsies and resection specimens to determine prognosis.[45] Although there have also been studies of grading mesotheliomas across all subtypes, including biphasic and sarcomatoid,[45] there does not seem to be a role yet for more granular risk stratification of these tumors since data consistently show a poorer prognosis for tumors containing a sarcomatoid component and dividing sarcomatoid areas into low and high grade groups has shown low interobserver agreement.[13] Therefore, the consensus view was that grading should be limited to epithelioid MPM since patients with epithelioid histology would benefit the most from improved risk stratification.

Proposals for grading systems in the literature vary, but are primarily based on a combination of nuclear features, mitotic rate and the presence or absence of necrosis. The pathology group favored a two-tier system of low and high grade based on an international multi-institutional paper that showed consistency amongst several institutions and provided risk stratification for epithelioid MPM.[44] Areas showing the highest grade features should be used to assign the tumor to low (any nuclear grade 1 and nuclear grade 2 without necrosis) or high grade (nuclear grade 2 with necrosis and any nuclear grade 3) (Figure 4 and Table 4).

The group considered the addition of certain published "features" that had been based on architectural patterns into the high grade category (solid, pleomorphic, rhabdoid, micropapillary, transitional).[8-11,44] Deciduoid mesotheliomas have also been reported as being more aggressive but this was associated with high-grade nuclear features, and therefore, the application of grading to these tumors would place them into the higher grade category.[46,47] However, it was decided that these should be documented separately until there was evidence that adding patterns to a two tier grading system added sufficient value in prognostication (Supplementary data 2, table 1).

1.3.2 Recommendation:

- ***All specialty groups recommended that grading of epithelioid MPMs should be routinely part of reporting for all types of samples, favoring a two-tier system of low and high grade based on nuclear atypia, mitotic activity and the presence or absence of necrosis.***

- ***Favorable and unfavorable histologic characteristics (architectural patterns, cytologic features, stromal features) should also be reported (a template is proposed in Supplementary data 2- table 2)***

Questions for future investigation are in supplementary data 1, section 1.3.3.

1.4.1: Use of diagnostic and predictive immunohistochemical and molecular assays.

There is considerable literature on the use of IHC in the diagnosis of mesothelioma, until recently all relating to problems in diagnosis, such as distinguishing mesothelioma from reactive mesothelial hyperplasia and reactive fibrous pleuritis, epithelioid MPM from metastatic carcinoma and sarcomatoid mesothelioma from the other spindle cell neoplasms. These have been exhaustively reviewed elsewhere.[23] The recent introduction of IHC for BAP1 and use of p16 FISH and MTAP IHC to identify *CDKN2A* deletion,[37-40,48] however, offer exciting new tools to distinguish benign from malignant mesothelial proliferations, including MMIS (see previous section), both in histology and cytology specimens.[49]

There are no current targeted treatment options for routine use that warrant standardized screening of mesotheliomas for a molecular signature, and pathologists were not in agreement on whether such testing should be routinely recommended. A minority of individuals with loss of BAP1 may have a germline rather than a somatic mutation, although immunohistochemical screening was not considered the best methodology for identifying such patients.[50]

The consensus view on BAP1 staining was that, although it clearly has value in confirming MPM in atypical mesothelial proliferations, further work is required to understand why some mesotheliomas show discordance between epithelioid and sarcomatoid areas. Furthermore, it was noted that some institutions report partial loss

and it is uncertain whether this is due to a lack of standardization in application of the antibody, or a true reflection of tumoral heterogeneity.

Several trials are ongoing on the utility of PD-L1 IHC, and there are early data to suggest some correlation between positive staining and sarcomatoid subtypes.[51-53] However, the majority of epithelioid mesotheliomas generally show a low level of positivity and other markers of tumor response should be sought.[54] Currently, if requested, pathologists should score PD-L1 IHC in mesotheliomas in similar fashion to lung cancers, providing a percentage of positively staining tumor cells. Scoring should be undertaken according to the recommendations for the clone of antibody used, most being based on membrane staining of tumor cells, reporting the number of positively staining tumor cells within the tumor cell population as a percentage.[55]

1.4.2 Recommendations

- ***Although BAP1 IHC is recommended as part of the diagnostic work up of mesothelial proliferations, it should not be used in isolation from other clinical, morphologic and immunohistochemical data to distinguish malignancy from reactive mesothelial hyperplasia.***
- ***No biologic markers are currently sufficiently clinically validated to warrant a recommendation for routine use, but should be undertaken on request and data collection is encouraged within the context of research trials (see molecular section)***

Questions for future investigation are in supplementary data 1, section 1.4.3.

2. MOLECULAR PATHOLOGY

2.1.1 Current inter-relationship between molecular pathology and cellular pathology

The limited use of molecular testing in mesothelioma compared to other cancers might be explained by the lack of knowledge of the molecular characteristics of these diseases. Studies have proposed using gene expression tests to predict prognosis, but these have not become part of routine reporting.[56] Recently, there have been several sequencing efforts to provide insights into the genomic characteristics of these understudied diseases. In a recent study including a large number of cases, Bueno and colleagues reported a molecular classification of MPM based on expression patterns, which partially matched the 3-types in the 2015 WHO histological classification.[57] In this study, four molecular cluster groups were identified: sarcomatoid (consisting of all sarcomatoid, numerous biphasic and a few epithelioid samples), epithelioid (consisting almost exclusively of epithelioid samples), epithelioid-biphasic (predominantly epithelioid, with some biphasic samples) and biphasic-sarcomatoid (predominantly biphasic samples, with some sarcomatoid samples). These groups were shown to recapitulate the epithelial to mesenchymal transition. The epithelioid and sarcomatoid groups constituted the most distinct molecular groups, with the epithelioid group having the longest overall survival.[58] In line with the fact that *CLDN15* and *VIM* were among the most significantly upregulated genes in the epithelioid and sarcomatoid groups respectively, the authors found that the log2 ratio of *CLDN15/VIM* gene expression was significantly different between the four groups, allowing their distinction.[57] In a recent

study, in which Alcala and colleagues reanalyzed the expression data of 211 MPM from Bueno and colleagues, and 73 from the TCGA,[58] the authors found that the molecular profile and the prognosis of MPM was better explained by a continuous model rather than by one based on discrete groups. (submitted for publication) They also found that the main source of variation of this continuum was explained by immune and vascular pathways. The authors found that the extreme of this continuum had very specific molecular profiles, with specific expression patterns of genes involved in angiogenesis and immune response. These findings were replicated in an independent series of 77 MPM from the French MESOBANK, and may assist the clinical management of MPM. The overexpression of the V-domain Ig Suppressor of T-cell Activation (VISTA) immune checkpoint protein has been validated by IHC by the TCGA in an independent series of MPM samples.[58,59] They found VISTA overexpressed in epithelioid MPM, correlated with mesothelin expression, and diffusely expressed in benign mesothelium. In the same line, unpublished targeted RNAseq data suggest the existence of subsets of MPMs with very characteristic immune environment signatures: one enriched for pleomorphic mesotheliomas with a CD8 T-lymphocyte signature, and a set of epithelioid samples with a very strong signature of B lineage cells (Franck Tirode, personal communication). Overall, the available genomic data suggest that while the molecular and histological classifications do not match perfectly, both classifications can complement each other and also provide unique information for the clinical management of this deadly disease.

The use of blood-based biomarkers for either the diagnosis or prognosis of mesothelioma remains exploratory. The gold standard biomarker, soluble mesothelin-related peptides (SMRP) or mesothelin, has consistent sensitivities and specificities of 40% and 98%, respectively. Essentially only 16-40% of asbestos exposed individuals will be detected by the marker to have mesothelioma on longitudinal follow-up, and only 15% will have a change in the marker within 6 months prior to diagnosis of the disease. SMRP is useful, however, for the monitoring of disease after or during treatment. SMRP is elevated in the majority of epithelioid mesotheliomas and a portion of biphasic but will not be able to detect sarcomatoid tumors. The use of fibulin 3 to diagnose mesothelioma remains controversial, but levels are generally elevated in all types of mesothelioma. There are no validated data on using microRNAs in serum or plasma to predict types of tumor, and the use of immuno-oncologic methods to diagnose MPM using transcriptional panels is in its infancy. Most recently, serum levels of calretinin measured by ELISA in males with mesothelioma have been able to differentiate MPM types in a case-control study: differences between sarcomatoid (n=28) and epithelioid (n=103) (p= 0.0041) as well as sarcomatoid and biphasic (n=44) (p=0.0001) were statistically significant. These promising data should lead to further validation trials.[60]

2.1.2. Tissue acquisition for molecular studies.

The success of the future research strongly relies on the quality of the tissue specimens and the levels of detail of the clinical and epidemiological annotations. Close collaboration between experts from different disciplines is therefore warranted. As discussed in the pathologic and surgical sections, there is a need to better define what

constitutes an adequate biopsy, as well as providing as much reproducible and detailed information about the sample as possible (i.e., type, subtype, tumor content, percentage of sarcomatoid content, fibrosis, detailed information about the microenvironment such as percentage and type of inflammatory cells etc.). This will hopefully allow accrual of information that will inform what is required to ensure successful genomic testing. Depending on the type of scan, the radiologist can provide information about the maximum metabolic activity (SUV), distribution and extent of disease from PET scans, tumor distribution, invasion into adjacent structures, and quantitative measures such as tumor volume and fissure thickness from CT scan and tumor heterogeneity, cellularity and perfusion parameters from MRI scans. Oncologists would need to work much closer with molecular biologists and ensure that the costly clinical trials are always paired with the collection of tumor material and blood before and after treatment. Finally, an overview with detailed information regarding available bio-repositories and datasets would promote collaborations and help in advancing the research in this field.

2.1.3 Recommendations for the use of the molecular characteristics and blood biomarkers to inform the histological classification

- ***Molecular characteristics that might inform clinical management (PD-L1 status, loss of BAP1, CDKN2A* deletion*) should be incorporated into reports, if undertaken.***
- ***Although molecular analysis currently is primarily a research topic, molecular data should be part of future trials looking at prognostic indices. This includes data on the tumor microenvironment.***

- ***As calretinin levels in the blood might inform histologic classification, further validation studies should be considered.***

Questions for future investigation are in supplementary data 1, section 2.1.4.

3. SURGERY

3.1.1. Tissue acquisition, volume and processing

As discussed in the pathology section, there is a need to refine classification so that it has relevance across all sample types received from the thorax, with recognition of distinction between maximal cytoreductive surgery, namely EPD and EPP, versus smaller samples.[4]

While the use of cytology specimens for the diagnosis of MPM remains controversial, occasionally, the combination of both pleural effusion cytology and pleural biopsy can complement one another diagnostically, particularly when a pleural biopsy shows mainly fibrosis and the cell block shows a cellular effusion. Emerging data suggest that the use of ancillary tests including BAP1 IHC, p16 FISH and/or MTAP IHC[32-34,39] can be helpful in the diagnosis of MPM on pleural effusion cytology specimens, which can be important in patients who are unable to undergo transthoracic or thoracoscopic biopsy procedures. However, given the limitations inherent to cytology specimens as well as limitations in the application and interpretation of these ancillary tests, MPM cannot always be reliably diagnosed on cytology specimens.

3.1.2 Depth, number and location of surgical samples

It was emphasized that ideal biopsy samples included subpleural fat (as opposed to chest wall fat), so that the extent of invasion can be assessed as this is a particularly useful diagnostic feature in better differentiated superficial mesotheliomas. It was also

felt that there was minimal published data and no standardization on the optimal number of biopsies to ensure the presence of histologic subtypes that might impact on future management, such as sarcomatoid areas in patients being considered for surgery. A higher number of tissue blocks in biopsies have been shown to provide better concordance with tumor subtype in resection specimens, as well as thoracoscopic biopsies showing better concordance than needle biopsies.[61] There may also be value in the assessment of tumor volume derived from CT scans as a prognostic factor and maximum PET avidity for targeting particularly active areas that may have prognostic relevance.

3.1.3 Staging

Discussion also included staging issues, and there was agreement that mesotheliomas diagnosed by maximal cytoreductive surgery (i.e. EPD and EPP) should be pathologically (p) staged, whilst any smaller samples should be clinically (c) staged. The importance of discussing intraoperative findings with the surgeon before completion of the pathological staging was also emphasized.

3.1.4. Recommendations:

- ***Studies to assess the ideal number of samples needed to obtain an accurate assessment of tumor type should be undertaken. Until available, expert consensus was that at least 3 separate areas should be sampled from the pleural cavity, if not compromised by fibrosis, including any area of interest identified on pre-surgical imaging. Samples should also include subpleural fat, if feasible.***
- ***Additional tumor and normal control samples should be taken and stored as appropriate for molecular testing, with appropriate consent if for research. Pathologists need to ensure this can be enabled.***
- ***Maximal cytoreductive surgical resections (EPD and EPP) should be pathologically staged. Cases sampled to a lesser degree should be clinically staged.***

Questions for future investigation are in supplementary data 1, section 3.1.5

4. IMAGING

The radiologic appearance of MPM is nonspecific, ranging from pleural effusion in early stages to lobulated circumferential pleural thickening and/or lobulated pleural masses in later stages of disease. Imaging findings include unilateral pleural effusion, circumferential nodular pleural thickening, and thickening of the interlobular septa.[62] Although the tumor tends to grow as circumferential pleural thickening, MPM also may present as localized pleural masses. Occasionally the involved hemithorax exhibits significant volume loss due to circumferential tumor without obvious chest wall invasion ("contracted hemithorax"); these cases generally demonstrate infiltrative tumor involvement through diffuse invasion of the endothoracic fascia. In advanced disease, the tumor may invade adjacent structures including the chest wall, mediastinum, pericardium, and diaphragm, or the tumor may metastasize to lymph nodes, lungs, bones, or distant sites.[63]

Contrast-enhanced CT is the most widely available modality for evaluation of MPM, while magnetic resonance imaging (MRI) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) provide complementary information especially in the assessment of resectability and response to therapy.[62] The diagnostic performance of CT is influenced by the scanning conditions. Special mention should be made to venous phase imaging at single- or dual-energy CT.[64] MRI is superior to CT in detecting occult chest wall and diaphragmatic involvement, particularly with contrast-enhanced T1-weighted sequences with fat suppression, and can result in reclassification of up to 30% of surgical candidates into an unresectable stage.[65] MRI also has been reported superior to CT for detecting involvement of bone, interlobar fissures, diaphragm (particularly transmural involvement and extension through the diaphragm), and endothoracic fascia.[66] Diffusion-weighted MRI can provide information on MPM tumor histology.[67,68] Perfusion CT and MRI also have been explored for the enhancement of diagnostic accuracy and for assessment of response to therapy.[69-72]

The diagnosis of localized mesothelioma and MMIS is especially problematic. No reported studies have evaluated the role of imaging in this setting. Diagnosis would benefit from a temporal sequence of images to track change, with diffusion-weighted MRI as perhaps the most promising modality in this regard; however the role of DWI in early disease has not been assessed previously. An unexplained pleural effusion (particularly in a patient with a history of asbestos exposure) should prompt the need for a pleural biopsy as the effusion might mask underlying tumor. In the event of a non-diagnostic or benign result on pathology, longitudinal follow up with CT in 6-12 months should be considered to ensure resolution of the pleural effusion and exclude progression to malignancy.

The main benefit of FDG-PET/CT is its ability to detect distant and occult metastatic lesions that would not be apparent by other modalities and that, when present, contraindicate surgery. FDG-PET/CT may have a role in the assessment of tumor histology, with epithelioid tumors being less FDG avid than their sarcomatoid or biphasic counterparts; higher metabolic activity is prognostic of shorter survival.[73] In early MPM, the effusion tends to lack avidity, especially if there is no associated pleural thickening or nodularity. FDG-PET/CT should not primarily be used for follow-up in patients who have undergone prior pleurodesis. Positive PET findings following pleurodesis must be interpreted with caution, as the resulting inflammatory response can cause increased FDG avidity in the pleura for a prolonged period of time and could also potentially increase the size and FDG uptake of mediastinal and hilar lymph nodes.

Image-guidance is a useful tool to aid acquisition of tissue at biopsy, with the various methods having both advantages and disadvantages. In addition to CT, ultrasound is a useful modality for the guidance of diagnostic and intraoperative biopsies. FDG-PET/CT and/or MRI can be used to assist in the initial identification of target sites for biopsy and to guide thoracoscopy. A multidisciplinary discussion with the surgeon prior to an intra-operative pleural biopsy is needed to maximize the diagnostic yield.

Clinical staging, which is based predominantly on CT imaging, continues to be problematic primarily due to the qualitative nature of the current approach. Therefore, quantitative measures derived from imaging such as tumor volume and fissural, pleural, and diaphragmatic thickness are being explored for their potential to enhance clinical staging.[74-77] CT-derived tumor volume also provides prognostic information,[78,79] and a quantitative stage derived from volume and maximum fissural thickness demonstrated improved prognostic performance relative to the current clinical standard.[74] PET/CT does not substantially improve clinical staging and has very low sensitivity and specificity for the detection of nodal involvement.[80] Modified RECIST criteria 1.1, as recently updated, are most suited to assess response in these tumors.[81-83].

4.1. Recommendations:

1. **Standardize image-acquisition protocols across centers to allow for the pooling of imaging data for future research. For CT, the contrast delay should be set to optimize the visualization of tumor (the timing of contrast administration during arterial [40 seconds] and venous [55-70 seconds] phases, with ≤1.25-mm axial sections (to allow for multiplanar reformatting and reliable volumetric estimation) displayed in a soft tissue window.**
2. **Develop a standard imaging lexicon to harmonize reporting and improve clinical staging.**
3. **A multidisciplinary discussion of tumor distribution and involvement of adjacent chest wall, diaphragm, and mediastinal structures (and, in particular, involvement of the endothoracic fascia) is necessary for surgical planning and for the assessment of resectability.**

Questions for future investigation are in supplementary data 1, section 4.2

5 MEDICAL ONCOLOGY

5.1.1 The impact of histopathologic subtypes of mesothelioma on decision making for systemic treatment

Decisions on the systemic treatment of advanced mesothelioma require consideration of timing of initiation, selection of agent, as well as consideration of individual patient issues that may affect treatment tolerance or supportive care requirements. The prognostic value of histopathologic subtypes has been assessed primarily in early-stage, resected mesothelioma. Nevertheless, histologic subtyping also plays a role in the decision making as sarcomatoid and biphasic histologic subtypes of mesothelioma are associated with poor outcome, which may reinforce the importance of earlier initiation of systemic therapy.[84,85] Conversely, selected patients with epithelioid subtype of disease who are not candidates for surgical treatment may be considered for active surveillance prior to initiation of systemic therapy.[86]

5.1.2. Recommendation: Multidisciplinary tumor boards should include pathologists to ensure that appropriate treatment options are considered, especially if classification is further refined (section 1).

Questions for future investigation are in supplementary data 1, section 5.1.3

5.2.1 The impact of histopathologic subtypes of mesothelioma on the outcome after cytotoxic chemotherapy

The current standard-of-care for first-line chemotherapy is the combination of cisplatin and pemetrexed for which there has been no clear interplay between histology and outcomes.[87]. In the pivotal EMPHACIS study that demonstrated the benefit of this combination, around 68% of patients on each arm had epithelioid histology, around 10% sarcomatoid histology, and around 16% biphasic histology, however efficacy of chemotherapy was not reported according to subtype. Similarly, other historical clinical trials of systemic chemotherapy either did not report, or did not demonstrate any differences in outcome by histological subtype.[88,89]

5.2.2. Recommendation: Based on current evidence, patients with all histologic subtypes should be considered potential candidates for chemotherapy.[86] Overall, despite the prognostic impact of sarcomatoid elements, there is no clear evidence that chemotherapy, based on cisplatin and third-generation cytotoxic agent, provides less proportional benefit to patients with biphasic or sarcomatoid disease.

5.3.1 Histopathologic subtype as a criterion for treatment with antiangiogenic agents

Clinical trials of antiangiogenic agents in mesothelioma included histologic subtypes as stratification or selection criteria. The first positive randomized phase III trial with antiangiogenics was the MAPS study, assessing cisplatin and pemetrexed with or without bevacizumab.[90] In this trial, patients were stratified by histology - epithelioid vs. sarcomatoid or mixed histology - with approximately 80% in each arm of epithelioid histology, and 20% of sarcomatoid or mixed histology. The trial demonstrated the benefit of bevacizumab in the intent-to-treat population with a hazard ratio (HR) of 0.77 [0.62–0.95]; p=0.0167). Histology had a non-significant interaction with outcomes, with sarcomatoid and biphasic subtypes being associated with a more favorable HR for OS as compared to epithelioid histology but a non-significant interaction test.

In trials assessing nintedanib, histological subtype was used as selection criteria for enrolment of patients. The LUME-Meso phase II study tested cisplatin/pemetrexed with nintedanib or placebo, enrolling only those with epithelioid (89%) or biphasic (n=10, 11%) histology and excluding patients with sarcomatoid disease.[91] The trial showed a statistically significant benefit of nintedanib in terms of PFS and a trend toward improved overall survival. The observation of greater benefit in epithelioid subtypes triggered restriction of the phase III study to epithelioid histology only, despite the low numbers on which this decision was based.[92] However, the subsequent LUME-MESO phase III study in epithelioid-only patients did not confirm any benefit of adding nintedanib to chemotherapy.[93]

1.3.2. Recommendation: Based on evidence as of 2019, all histologic subtypes are candidates for chemotherapy with or without bevacizumab based on clinical eligibility.

1.3.3. Recommendation: Patients with sarcomatoid or biphasic mesothelioma should not be excluded from first line clinical trials unless there is a compelling biological rationale to do so. Where subgroups in clinical trials are defined based on epithelioid vs. non-epithelioid histologies; the relevance of such clustering has to be assessed.

5.4.1 Does histopathological subtype modulate the efficacy of immune checkpoint inhibitors in mesothelioma?

Immunotherapy using immune checkpoint inhibitors targeting PD-1/PD-L1 or CTLA-4 is, as of 2019, not approved in the treatment of mesothelioma; however, results from phase I/II trials have been made available in the advanced, refractory setting, leading to the off-label use of some of those agents.[94-96] CTLA-4 inhibition using tremelimumab alone was assessed in the large randomised phase 2b trial DETERMINE, that enrolled 564 patients in the second/third-line setting vs. placebo.[97] This trial found no benefit of tremelimumab in the predominantly epithelioid (83%) intent-to-treat population. The MAPS2 study randomized 125 patients (83% epithelioid) in the second/third-line setting to treatment with nivolumab or nivolumab plus ipilimumab.[98] The primary endpoint was disease control rate (DCR) at 12 weeks. DCR was 44% with nivolumab and 50% for nivolumab plus ipilimumab with median PFS of 4.0 and 5.6 months, respectively, and

median OS of 13.6 months and not reached, respectively. Subgroups analyses showed a tendency towards greater OS benefit from nivolumab plus ipilumumab for sarcomatoid/biphasic histologies. Other phase II studies assessing nivolumab, pembrolizumab, or combining durvalumab plus tremelimumab, enrolled limited numbers of patients, most with epithelioid disease, precluding clear assessment of the role of histologic subtypes on outcomes.[99-102] A real-world cohort of 93 patients who received pembrolizumab second-line or beyond reported greater efficacy in non-epithelioid mesotheliomas (n=73), with a response rate of 24% vs. 16% (p=0.54), and a median PFS of 5.6 vs. 2.8 months (p=0.02) in epithelioid mesotheliomas (n=27).[94] Finally, a single-centre phase 2 trial using a combination of nivolumab plus ipilimumab showed marked efficacy in patients with recurrent malignant pleural mesothelioma.[103]

5.4.2. Recommendation: As of 2019, there is evidence of efficacy for immunotherapy with anti-PD-1/PD-L1 inhibitors alone or combined with anti-CTLA-4 antibodies in all histologic subtypes of mesothelioma, although the efficacy of immunotherapy may vary according the histologic subtype (non-epithelioid subtypes may be associated with a more prolonged duration of response).

Questions for future investigation are in supplementary data 1, section 5.4.3

5.5.1 The use of biomarkers in the clinic for systemic treatments

Biomarker studies have been important components of recent phase III trials: notably, angiogenesis serum biomarkers, and PD-L1 expression by IHC. Exploratory analyses of VEGF concentration as a predictor of the benefit of bevacizumab and nintedanib were conducted part of the MAPS[90] and the LUME-MESO phase II trial,[104] not reporting significant predictive value for the benefit of antiangiogenics. In the MAPS trial, patients with higher baseline VEGF concentrations than the median value treated in the bevacizumab group derived a 2.3 month, non-statistically significant benefit. Expression of PD-L1 by IHC is observed in 16-40% of mesothelioma cases;[98] PD-L1 expression is associated with non-epithelioid histology and poorer outcome.[53,59] In the MAPS2 trial, positive PD-L1 tumor expression (with a cutoff of 1%) was associated with objective response in both treatment groups, whereas high PD-L1 tumor expression (≥25% of tumor cells) was associated with objective response or disease control in both groups. Conversely, positive PD-L1 tumor expression (≥1%) tended to result in a longer overall survival only in the nivolumab group. Similar trends were reported in some of the other smaller trials. [99-102] PD-L1 expression was a selection criterion in a pembrolizumab phase I trial.[105]

The need for the characterization of predictive biomarkers will depend on the results of future clinical trials; currently the potential observed predictive value of PD-L1 for the efficacy of immunotherapy in the late line setting remains to be validated in phase III trials.

Other promising predictive biomarkers include mesothelin, as anetumab ravtansine is a drug-conjugated antibody targeting mesothelin;[106] ; BAP1 deficiency, which may predict the efficacy of EZH2 inhibitors;[107] and NF2 alterations in use of FAK inhibitors. When

mesothelioma develops in carriers of germline BAP1 mutations, these malignancies have a better prognosis.[108] Mesothelin may also be a target for chimeric antigen receptor-modified T cells, given its frequent expression in mesotheliomas, especially the epithelioid subtype.[109-111]

5.5.2 Recommendations:

- **Routine incorporation of the above biomarkers into standard reports is not recommended, but data should be accrued in a regulated manner within clinical trials and recorded in reports, if requested.**
- **Given the rarity of germline BAP1 mutations, systematic screening of all patients for germline mutations is not proposed in the absence of family history suspicious for BAP1 syndrome; oncogenetic counseling is not recommended in a systematic manner.**

- Questions for future investigation are in supplementary data 1, section 5.5.3

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LEGENDS:

Figure 1. A) Epithelioid malignant mesothelioma shows malignant rounded epithelioid cells. B) Sarcomatoid malignant mesothelioma shows malignant spindle cells lying within fibrous stroma. C) Biphasic malignant mesothelioma shows a combination of epithelioid and sarcomatoid areas. D) Well differentiated papillary mesothelioma shows prominent papillary architecture, with the surface covered by bland mesothelial cells.

Figure 2: Architectural patterns, cytologic and stromal features in malignant mesothelioma (see table 2 for definitions).

Figure 3: Malignant mesothelioma in situ: A) the pleural surface is covered by a single layer comprising a mildly atypical mesothelial proliferation. B) the cells show loss of BAP1 staining. The patient developed an invasive mesothelioma at 36 months after initial presentation.

Figure 4: Nuclear grading features; A) Nuclei are small, uniform and round with inconspicuous nucleoli and finely granular chromatin. B) Nuclei are intermediate in size with limited anisonucleosis and pleomorphism, Nucleoli are more conspicuous and chromatin is coarser. C) Nuclei are large with anisonucleosis and pleomorphism. Nucleoli are prominent and chromatin is coarse.

TABLE 1: Current (2015) WHO classification of mesothelioma[1]

Diffuse malignant mesothelioma
- Epithelioid mesothelioma
- Sarcomatoid mesothelioma
  - Desmoplastic mesothelioma
- Biphasic mesothelioma

Localized malignant mesothelioma
- Epithelioid mesothelioma
- Sarcomatoid mesothelioma
- Biphasic mesothelioma

Well differentiated papillary mesothelioma

Adenomatoid tumor

Epithelioid: A mesothelioma, composed of rounded rather than spindle shaped cells (see definition under sarcomatoid below) usually showing a cohesive architecture, although epithelioid cells can show single cell growth within fibrous stroma.

Sarcomatoid: A mesothelioma, composed of spindle shaped (greater than two times longer than wide). The spindle cells may lie in varying amounts of fibrous stroma, or they can form solid sheets.

Biphasic: A mesothelioma, showing at least 10% of both epithelioid and sarcomatoid morphology. This rule is limited to definitive resections, namely extended pleurectomy/decortication and extrapleural pneumonectomy (EPD and EPP). For smaller samples, until more data are collected, the group proposes that the diagnosis of “biphasic” can be rendered regardless of the percentages of each component present and that the diagnosis should be accompanied by a comment indicating the percentages of each component.

Well differentiated papillary mesothelioma: A rare localized mesothelial neoplasm characterized by an exophytic papillary architecture lined by relatively bland

mesothelium with no or only minimal areas of invasion. Diagnosis requires exclusion of diffuse malignant mesothelioma with papillary architecture.

TABLE 2: Proposed changes to subtyping of mesothelioma

DIFFUSE MALIGNANT MESOTHELIOMA*
Epithelioid malignant mesothelioma ➢ **Architectural patterns** *(give percentages for EPD/EPP** and document patterns present for all other samples)* ➢ **Tubulopapillary** ➢ **Trabecular** ➢ **Adenomatoid** ➢ **Microcystic** ➢ **Solid** ➢ **Micropapillary** ➢ **Transitional pattern^** ➢ **Pleomorphic^** ➢ **Cytologic features** *(give percentages for EPD/EPP. For all other samples, state "with … features present".* ➢ **Rhabdoid** ➢ **Deciduoid** ➢ **Small cell** ➢ **Clear cell** ➢ **Signet ring** ➢ **Lymphohistiocytoid#^** ➢ **Stromal features** *(give percentages for EPD/EPP. For all other samples, state "with … features present".* ➢ **Myxoid**

Sarcomatoid malignant mesothelioma

- **Features** *(give percentages for EPD/EPP. For all other samples, state "with … features present".*
- **Desmoplastic**
- **With heterologous differentiation**
- **Lymphohistiocytoid#^**
- **Transitional pattern^**
- **Pleomorphic^**

Biphasic malignant mesothelioma

- *For EPD/EPP, any combination of patterns of epithelioid and sarcomatoid mesothelioma with at least 10% of each component. For all other samples, the consensus was to propose that the diagnosis of "biphasic" can be made regardless of percentages of each component and to include a comment indicating the percentages of each component in the sample.*

LOCALIZED MALIGNANT MESOTHELIOMA

- *Any of the above subtypes may be present, with tumor limited to an isolated mass lesion*

WELL-DIFFERENTIATED PAPILLARY MESOTHELIOMA

ADENOMATOID TUMOR

*Some architectural patterns and cytologic and stromal features are important for prognostic significance while some are included only for clarity to avoid pathology misdiagnoses. When generating reports, please note that multiple architectural patterns and cytologic and stromal features may be present in a tumor and all patterns/features seen in a tumor should be included in the report.

** EPD: Extended pleurectomy/decortication, EPP: extrapleural pneumonectomy

^Classification of transitional and pleomorphic patterns is currently difficult due to limited data available. Therefore, the consensus is to include transitional and pleomorphic patterns under both epithelioid and sarcomatioid types until more data emerge.

#Histiocytoid refers to morphology of actual tumour cells, not the presence ofackground macrophages.

Table 3: Definitions for architectural patterns, cytologic features and stromal characteristics in pleural mesothelioma:

Histologic patterns:

A. **Tubular:** Round to oval spaces surrounded by a single layer of malignant epithelioid cells.
B. **Papillary:** Malignant epithelioid cells growing over a fibrovascular core.
C. **Tubulopapillary:** In many cases, tubular and papillary patterns are seen together.
D. **Trabecular:** An interconnected single or dual linear arrangement of malignant epithelioid cells
E. **Solid:** An architectural feature comprising continuous sheets of malignant epithelioid cells.
F. **Micropapillary:** Small groups of epithelioid cells forming a papillary structure, but lacking a fibrovascular core. Micropapillary can also include a single cell pattern.
G. **Adenomatoid:** A pattern of malignant mesothelioma composed of gland-like structures lined by flat to cuboidal malignant epithelioid cells resembling adenomatoid tumor.
H. **Microcystic:** A cribriform network of malignant epithelioid cells with small acinar spaces forming round holes like a sieve.

CYTOLOGIC FEATURES

I. **Pleomorphic:** Tumor cells show marked nuclear atypia, often with bizarre nuclei and tumour giant cells.
J. Transitional: Tumor cells are intermediate between epithelioid and sarcomatoid morphologies, having lost their rounded morphology but not being overtly sarcomatoid.
K. **Rhabdoid:** Tumor cells resemble those seen in rhabdomyoblastic tumors, typically with a cytoplasmic eosinophilic globule that is positive for cytokeratins and generally negative for muscle markers.

L. **Deciduoid:** Tumors cells have a significant excess of richly eosinophilic cytoplasm resembling the decidua from the placenta . This carries no prognostic significance as a cytologic feature, but is important for avoiding misdiagnosis.

M. **Small cell:** Small hyperchromatic tumor cells morphologically resembling small cell carcinoma, but showing a mesothelial phenotype. This carries no prognostic significance but is important for avoiding misdiagnosis.

N. **Clear cell:** Tumor cells with clear cytoplasm. This carries no prognostic significance, but is important so metastatic clear cell carcinoma is not incorrectly diagnosed.

O. **Signet ring:** Tumor cells with intracytoplasmic vacuoles pushing the nucleus to the side. This carries no prognostic significance in mesothelioma, but is important so metastatic signet ring carcinomas from other sites are not incorrectly diagnosed.

P. **Lymphohistiocytoid:** This feature is seen in predominantly sarcomatoid mesothelioma where the neoplastic cells are histiocytoid in appearance but are obscured by a prominent infiltrate of lymphocytes. The morphology raises the differential diagnosis of malignant lymphoma. This definition requires that the actual tumour cells resemble histiocytes and does not simply represent prominent lymphocytic infiltration in an epithelioid mesothelioma. Focal lymphohistiocytoid features occur in otherwise conventional sarcomatoid mesotheliomas.

STROMAL FEATURES

Q. **Myxoid:** Tumour cells lie within a pale hematoxyphilic mucoid stroma. This should be noted when > 50% of a tumor with < 50% solid component shows this feature.

R. **Desmoplastic:** A sarcomatoid mesothelioma with prominent dense hyaline fibrous stroma, haphazard slit-like spaces, bland collagen necrosis, cellular proliferation nodules and invasive growth.

S. **Heterologous elements:** Sarcomatous elements such as osteosarcoma (as seen in figure), chondrosarcoma and rhabdomyosarcoma.

TABLE 4 – Grading of pleural epithelioid malignant mesothelioma

Nuclear Grade:

Nuclear atypia score: _____ (1 for mild, 2 for moderate, 3 for severe)

Mitotic count: ____ (1 for low [≤1 per 2mm^2], 2 for intermediate [2-4 per2mm^2], 3 for high [5+ per 2mm^2])

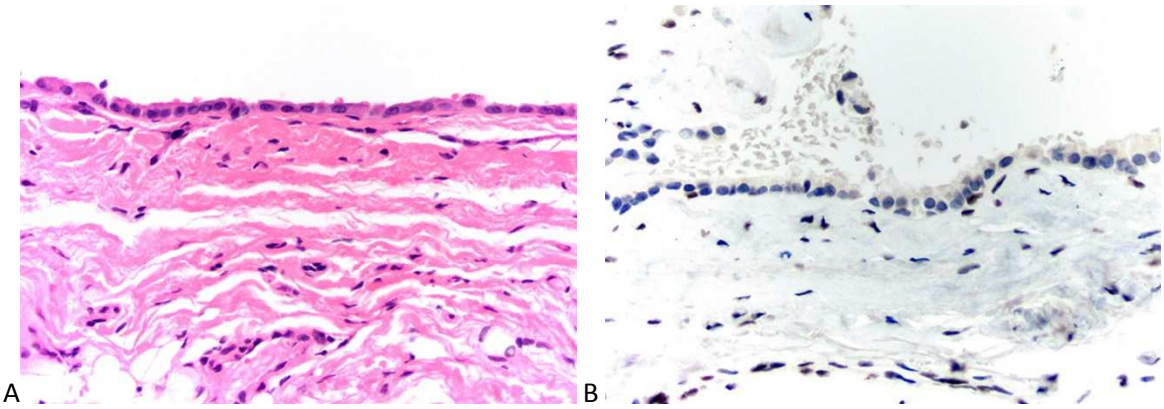
Sum: _____ (2 or 3 = nuclear grade I, 4 or 5 = nuclear grade II, 6 = nuclear grade III)

Necrosis: Present / Absent

Low-grade = Nuclear grades I and II without necrosis

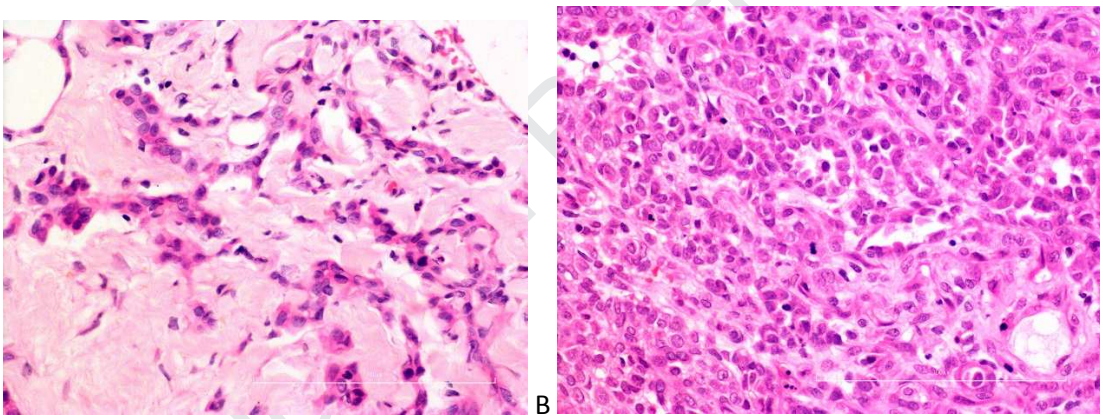
High-grade = Nuclear grade II with necrosis, Nuclear grade III with or without necrosis

Figure 3



A B

Figure 4



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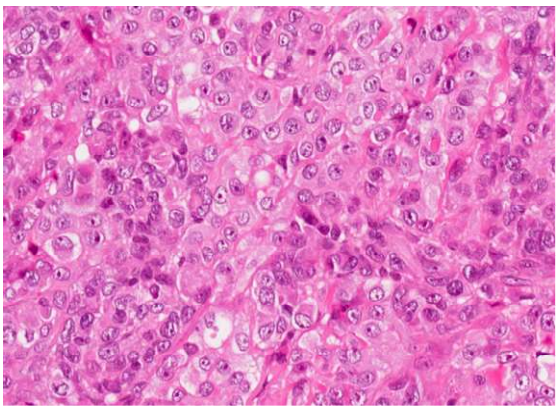

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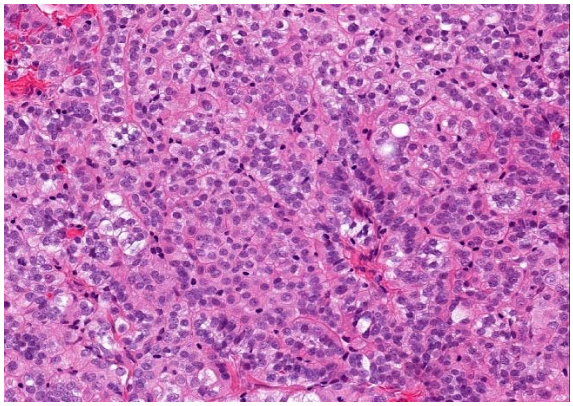
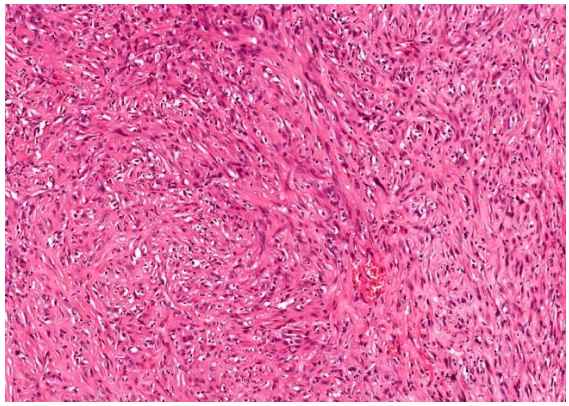
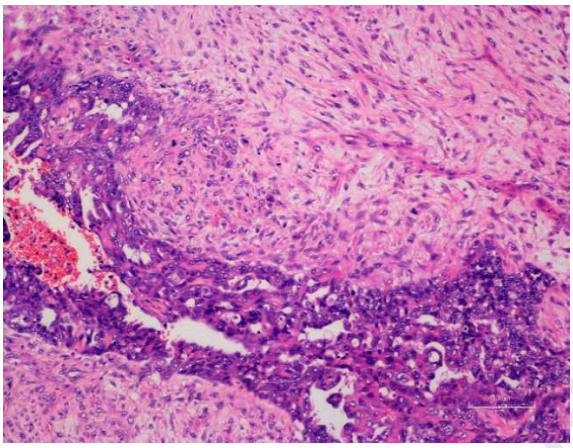
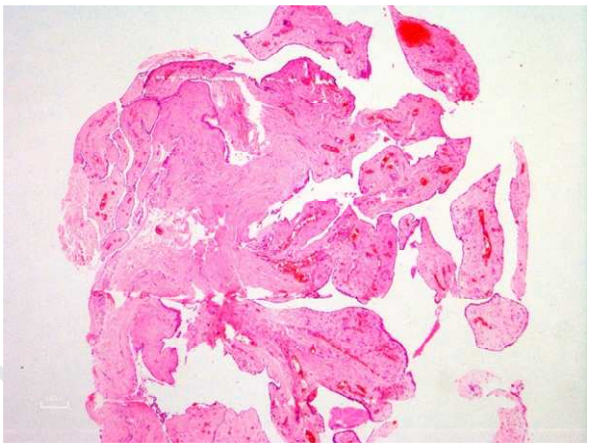
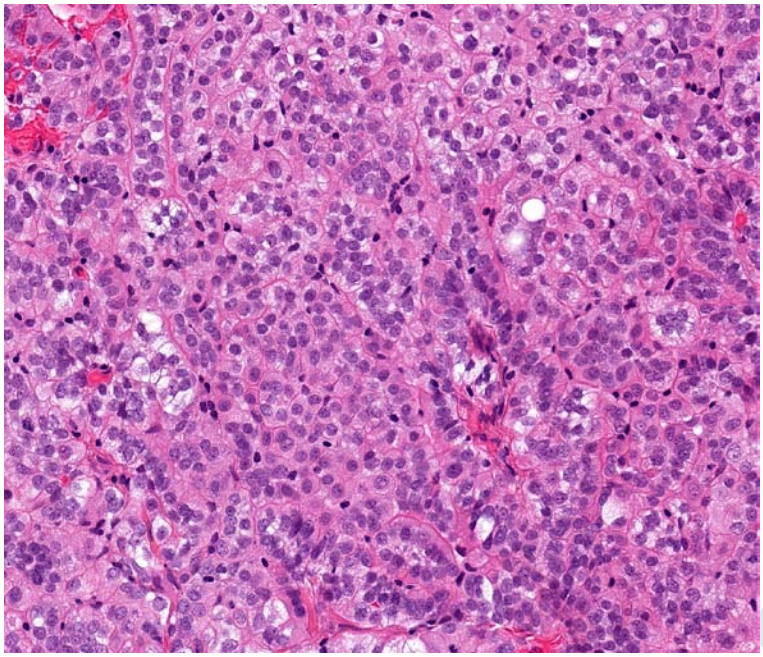
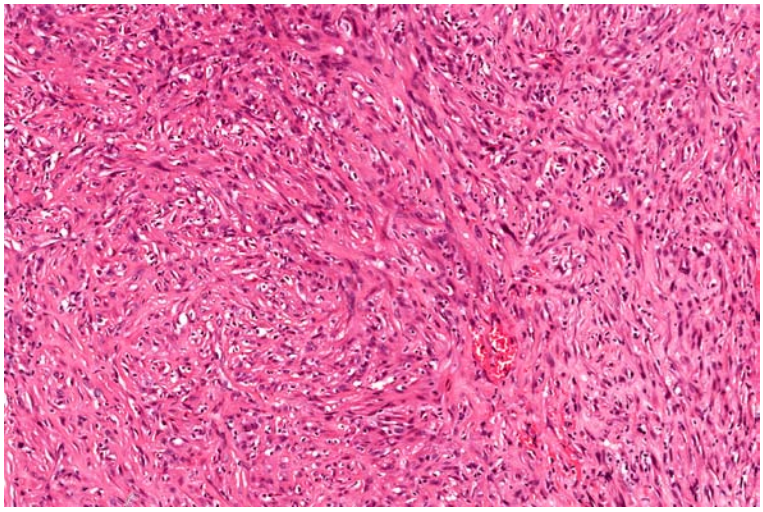
A 

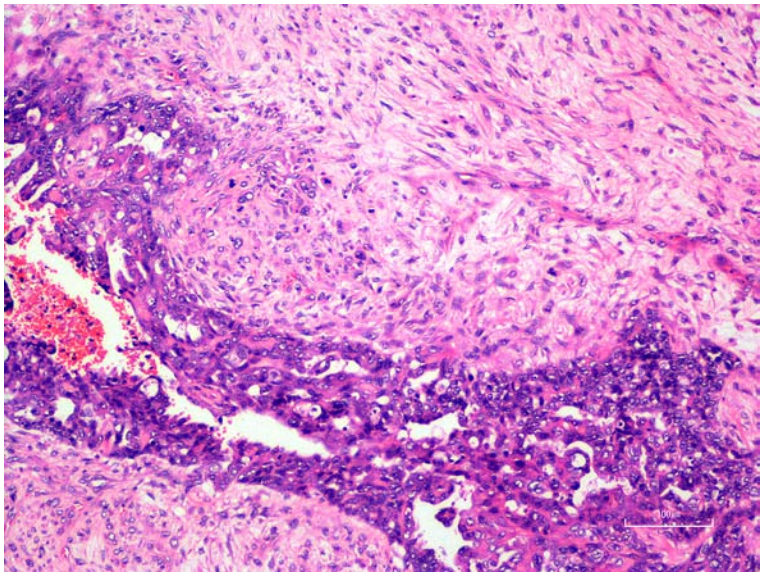
B 

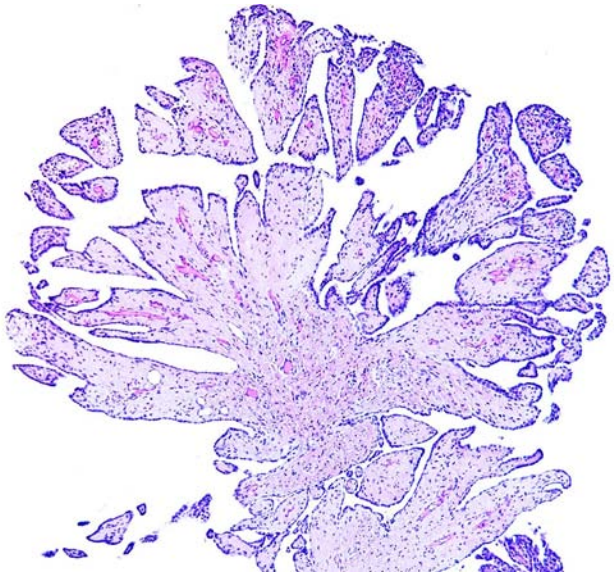
C 

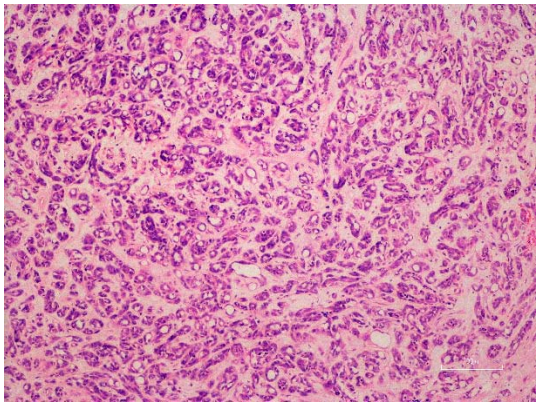
D 

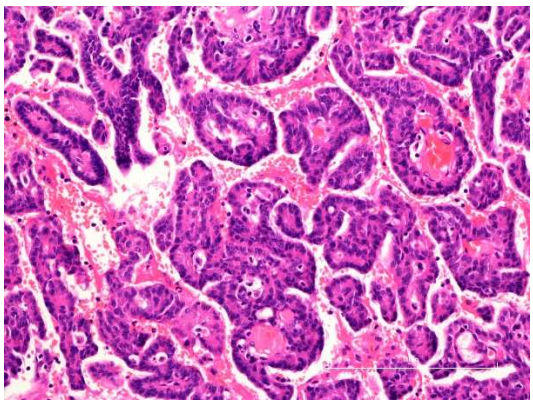


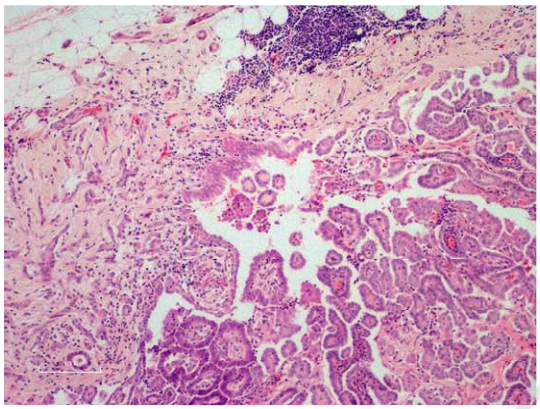


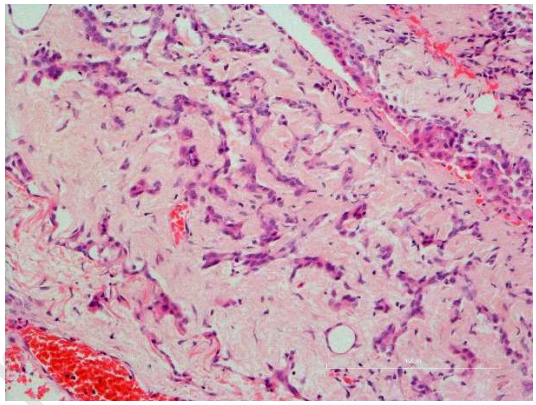


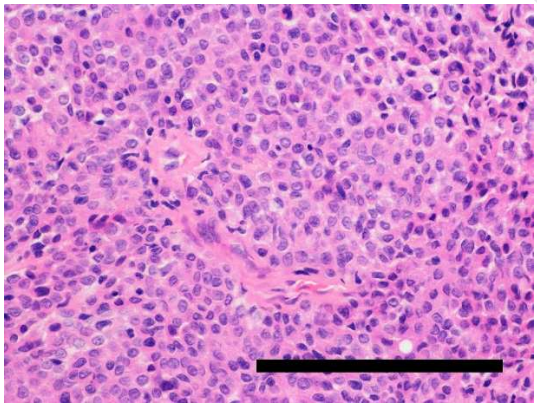


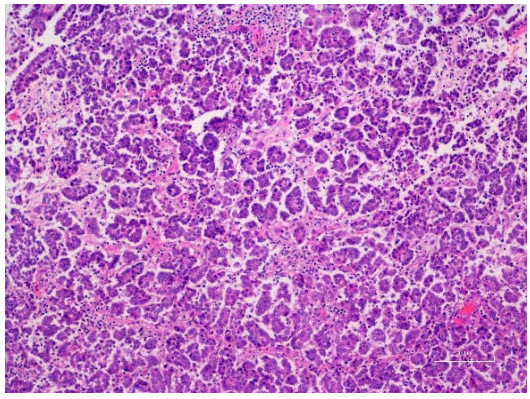
A 

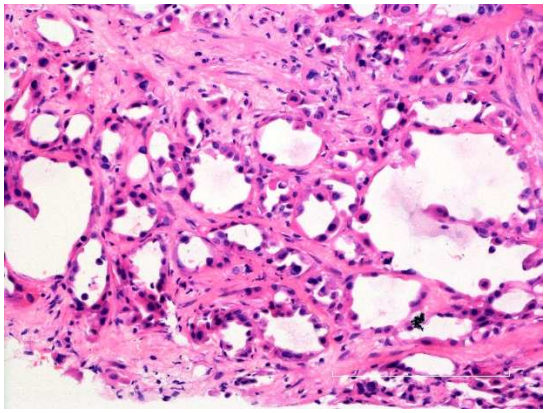
B 

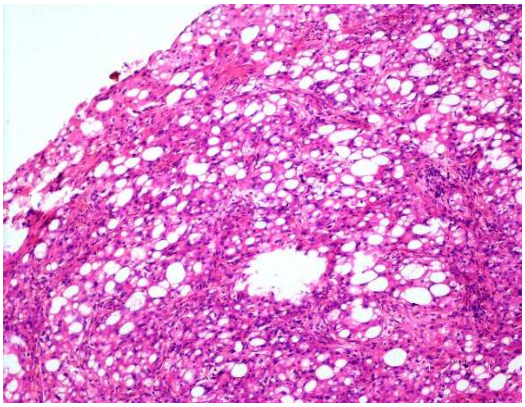
C 

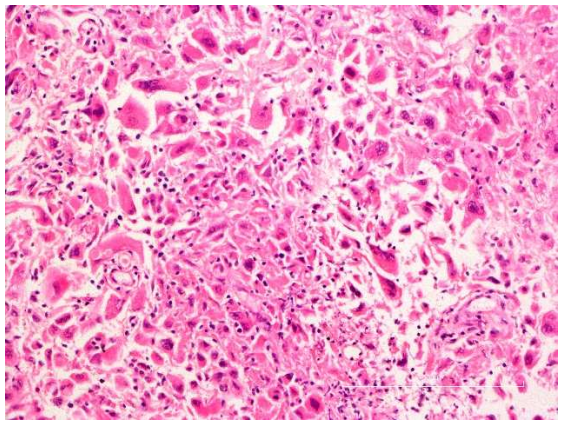
D 

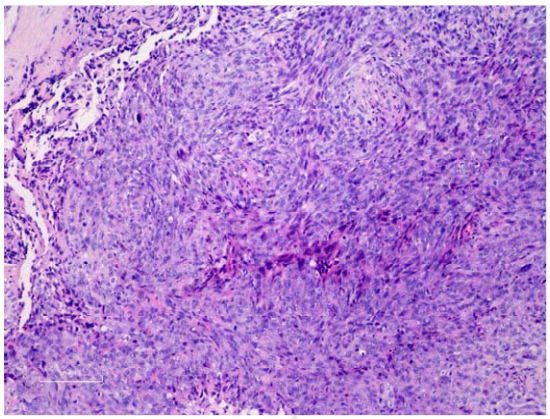
E 

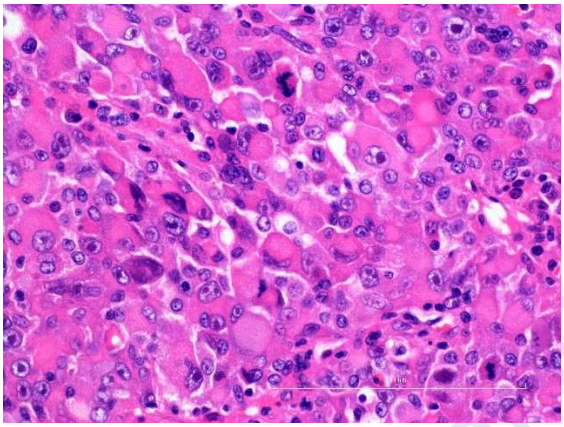
F 

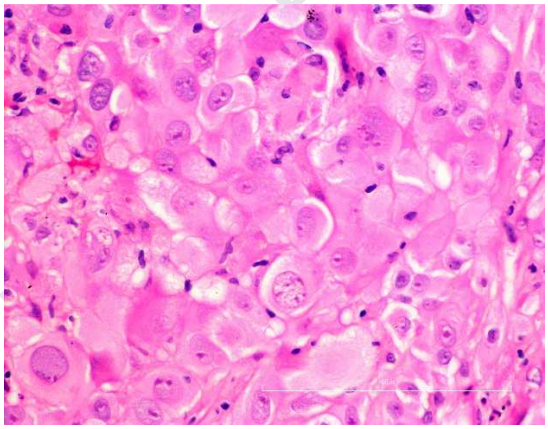
G 

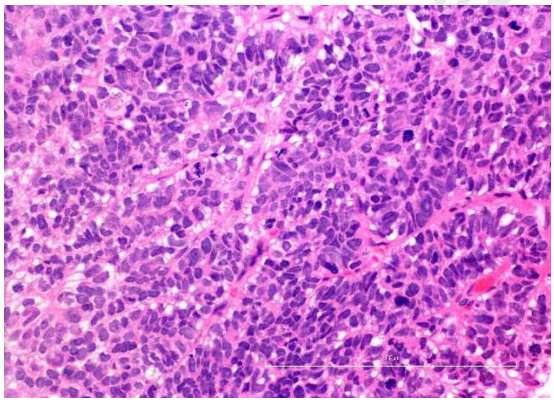
H 

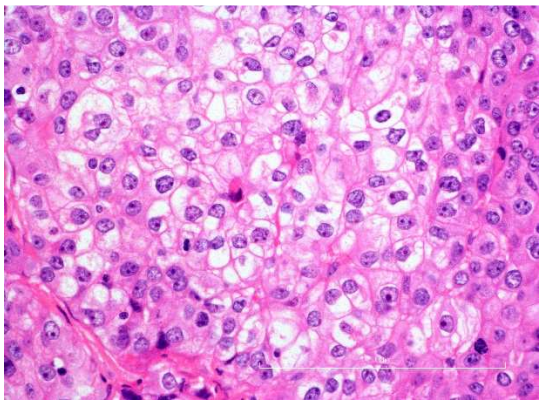
I 

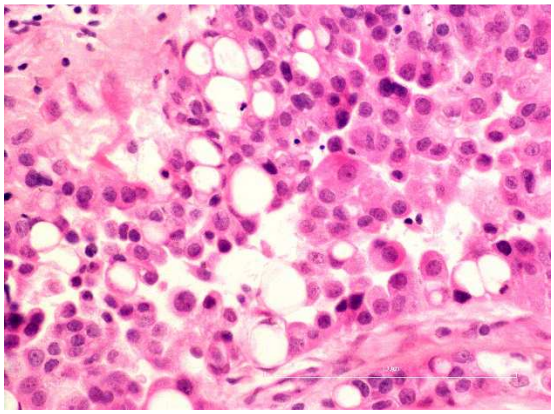
J 

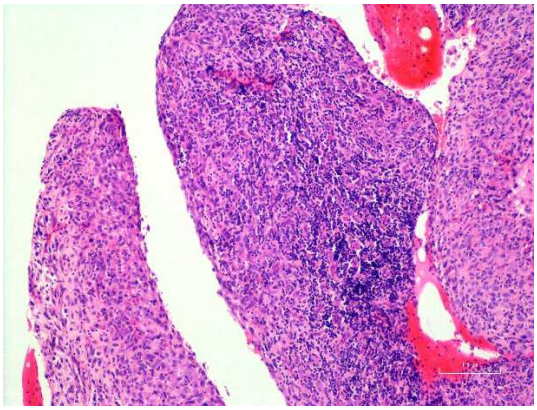
K 

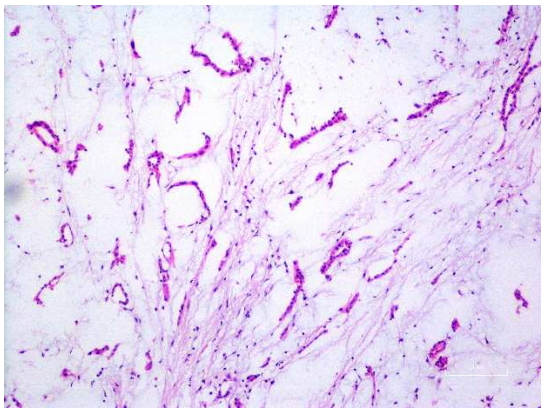
L 

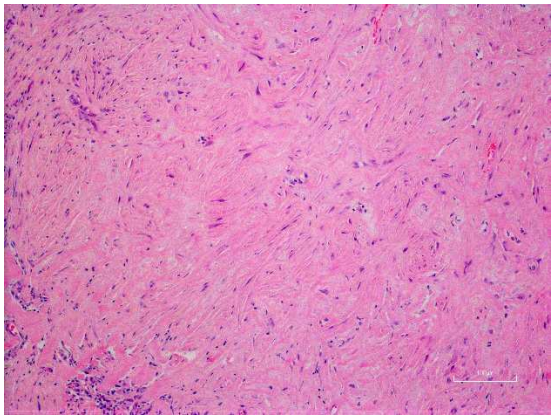
M 

N 

O 

P 

Q 

R 

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