IASLC
2019 World Conference on Lung Cancer
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Conquering Thoracic Cancers Worldwide

Pathology section II: What you should know on mesothelioma in 2019
Mis- or under diagnosis of MPM still a problem today

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CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

mesoPATH mesoBANK

No disclosure to declare

Mis- or under diagnosis of MPM still a problem today

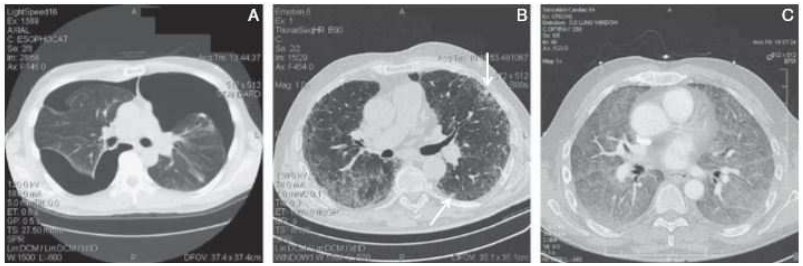
Pleural mesothelioma is a rare cancer <0.3% of all cancers (Francim Registry Network)

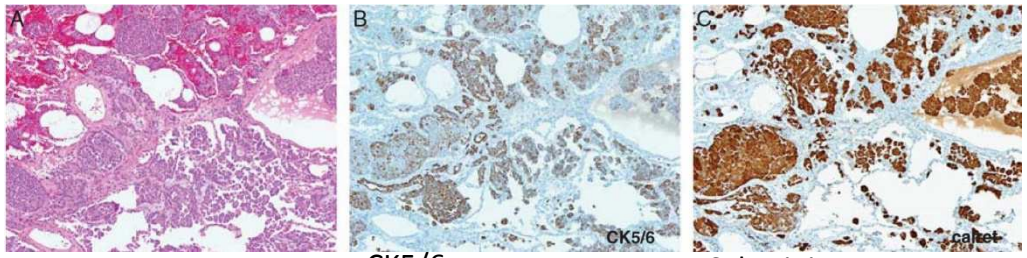
1) Mesothelioma is an heterogeneous cancer a great mimickers of other malignancies that metastazise to the pleura

2) The separation between benign lesions and malignant pleural mesothelioma is morphologically challenging

Clinically

1° Diffuse Intrapulmonary Malignant Mesothelioma Masquerading as Interstitial Lung Disease A Distinctive Variant of Mesothelioma

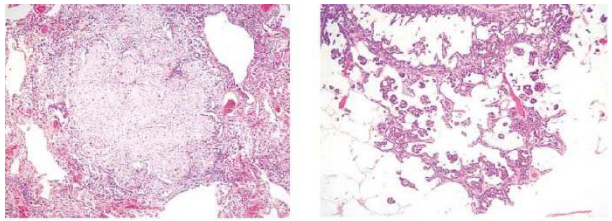




CK5/6 Calretinin

Larsen B et al, Am J Surg Pathol 2013;37:1555–1564

2° Intraparenchymal growth with lepidic carcinoma like pattern…. Nind et al, Histopathology 2003 vol 42 issue 2.150-55

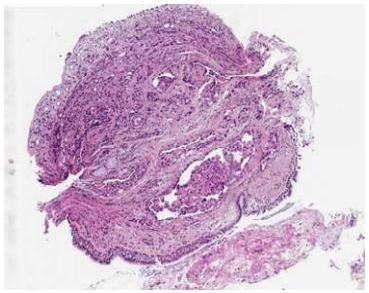


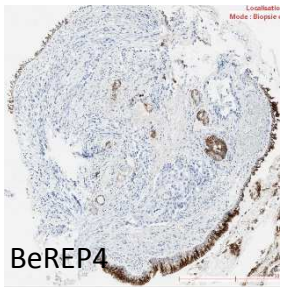
- 3° Bone marrow metastasis of MPM Ihari et al Intern Med 2018 or Brain metastasis revealing a localized MPM Ertan G, et al. BMJ Case Rep 2016. doi:10.1136/bcr-2016-21734

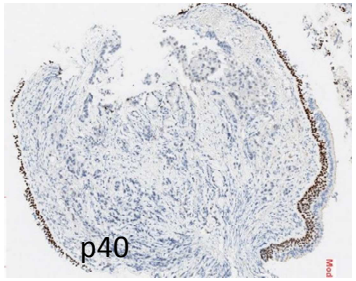
4° Malignant mesothelioma mimicking rheumatoid pleurisy. Nanke et al, J Clin Oncol. 2001 Sep 1;19(17):3782-4.

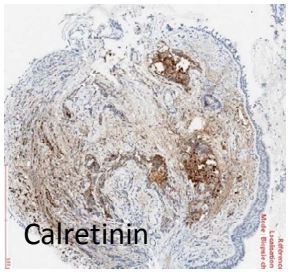
Small biopsies and unusual location

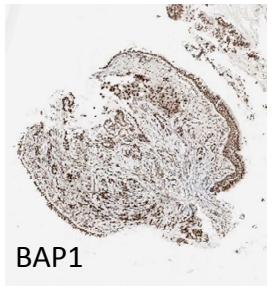
Male 83 years old with a pleural tumor on CT scan



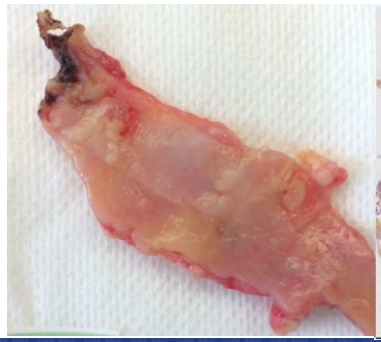


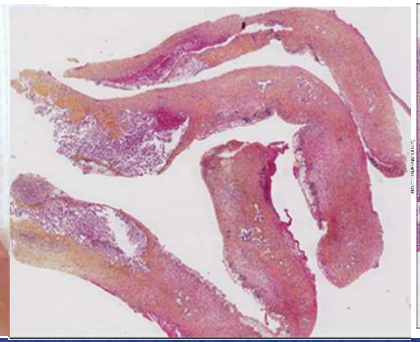


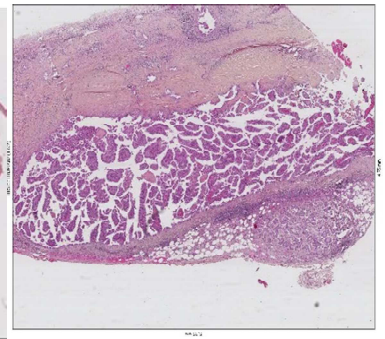




- Female 75 yrs, smoker, workers in the mills
- Diminution of general health and loss of weight
- Unilateral pleural effusion
- Went to hospital for thoracoscopy
- CT scan hilar mass
- Surgical evaluation showed contained pleural effusion
- Multiples biopsies.







Cagle et al, concurrent mesothelioma and Adenocarcinoma Mod Pathol 1993

Pathologically the major causes of misdiagnosis are:

- Metastasis
  - EMM versus carcinoma metastasis lung and breast & renal, ovarian
- SMM versus Sarcomatoid carcinoma , versus primitive sarcoma of the pleura
- Mesothelioma versus other tumors of mesothelial origin

The major causes of underdiagnosis are:

- Benign/reactive lesions versus mesothelioma or question of sampling

MESOPATH 2018:results of the standardized procedure of certification period 1998-2018 Activity report INCA and French NIH SpF

By year of incidence	<1998		1998-2007		2008-2017		Total	
	N	%	N	%	N	%	**N**	**%**
Mesothelioma	**531**	**61%**	**5655**	**76%**	**7060**	**83%**	**13246**	**79%**
Epithélioïd	435	82%	4815	85%	5480	78%	**10730**	**81%**
Biphasic	56	11%	459	8%	817	12%	**1332**	**10%**
Sarcomatoïd	22	4%	263	5%	547	**8%**	**832**	**6%**
Desmoplastic	13	2%	99	2%	95	1%	**207**	**2%**
Mesothelioma in situ	5	1%	19	0%	121	2%	**145**	**1%**
Other tumor of mesothelial origin	**17**	**2%**	**83**	**1%**	**143**	**2%**	**243**	**1%**
WDPM	16	94%	70	84%	94	66%	**180**	**74%**
Adenomatoid tumor	0	0%	0	0%	2	1%	**2**	**1%**
SFT	1	6%	8	10%	5	3%	**14**	**6%**
Multicystic mesothelioma	0	0%	5	6%	42	29%	**47**	**19%**
Dg uncertain-We can'tell	**39**	**6%**	**506**	**9%**	**516**	**8%**	**1061**	**6%**
AMH	10	26%	150	30%	138	27%	**298**	**28%**
Unclassified tumor	9	23%	294	58%	351	68%	**654**	**62%**
Others	20	51%	62	12%	27	5%	**109**	**10%**
Excluded for another Dg	**218**	**25%**	**877**	**15%**	**559**	**6%**	**1654**	**10%**
Benign	18	8%	257	29%	232	42%	**507**	**31%**
Metastasis	179	82%	535	61%	307	55%	**1021**	**62%**
Other primitive tumor	21	10%	85	10%	20	4%	**126**	**8%**
Excluded for inadequacy	**71**	**8%**	**275**	**4%**	**186**	**2%**	**532**	**3%**
TOTAL	**876**	**100%**	**7396**	**100%**	**8464**	**100%**	**16736**	**100%**

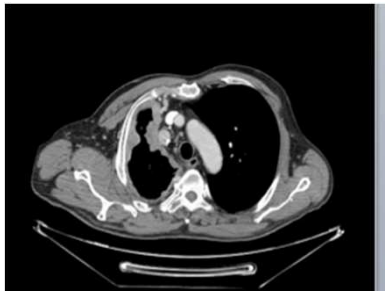
MoleculaLar markers
IHC, FISH, RNAseq

MESOPATH/MESOBANK 2018:results of the standardized procedure of certification period 1998-2018 Activity report INCA and French NIH SpF

Aide au diagnostic en 2019

- ✓ RCP et les confrontations des ACPs avec les cliniciens et l'imagerie
- ✓ Immunohistochimie et les nouveaux marqueurs (BAP1, MTAP, PAX8, GATA3)
- ✓ La biologie moléculaire en routine dans certains laboratoires spécialisés
  - FISH: HD *CDKN2A*(p16), EWSR1, ALK etc.. Daniel Pissaloux
  - RNASeq: analyse du profil transcriptomique (Franck Tirode
- ✓ L'Intelligence Artificielle (Deep Learning)

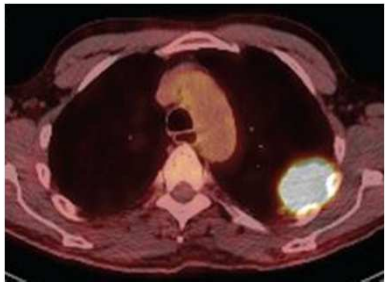
Attention au mesotheliome localisé car peut beneficier d'une exerese chirurgicale
Marchevesky et al, Hum Pathol 2019

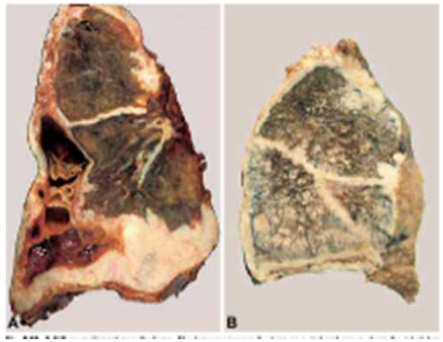


Allen et al, Am J Surg Pathol. 2005 Jul;29(7):866-73.

23 cas.
mean age 63 ans
sex ratio 2:1 (M/F).
Loc: 21 Pleu/ 2 Per
Hist: 16 MME – 6 BMM- 1 MMS et autres
Exérèse chirurgicale:
10/21 en vie de 18 mo à 11 ans
DCD de MM diffuse pour les autres

MESOBANK
N< 10/8800



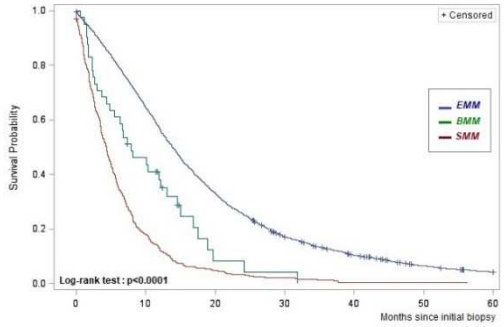


Marchevesky et al, Hum Pathol 2019

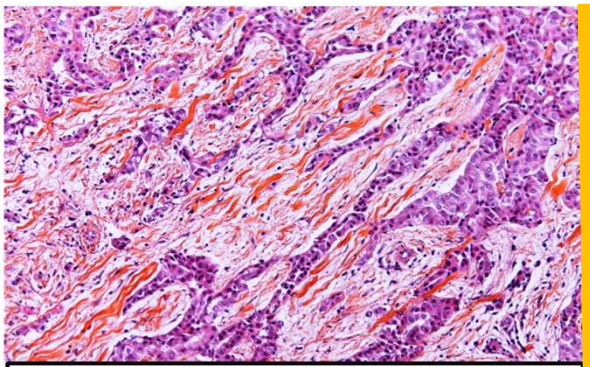
Sixty tumors (83%) were intrathoracic,
others presented in intraabdominal sites.
Tumors varied in size from 1.2 to 19 cm.

Median and mean survivals for 51 cases were 134 and 101 months,

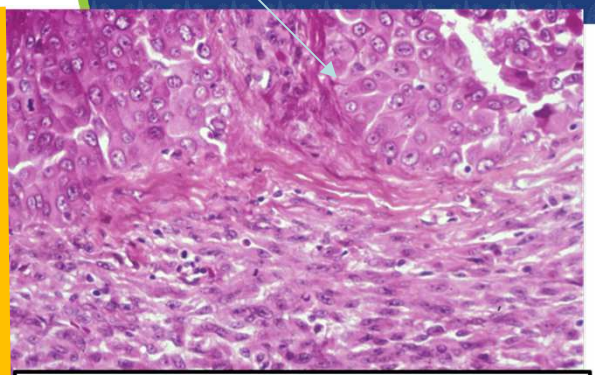
WHO 2015 CLASSIFICATION-Classic subtypes



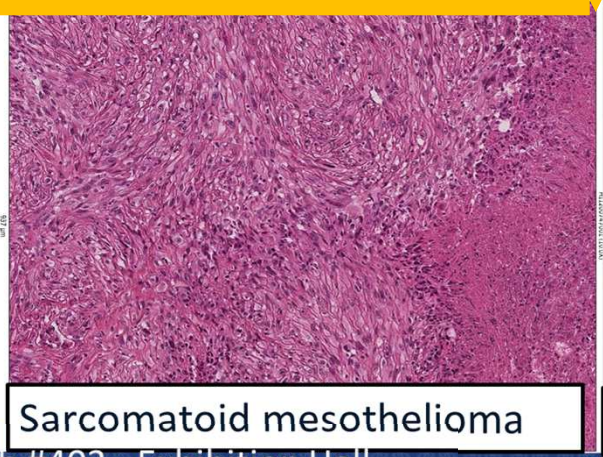
	N	Median	1 yr-survival [CI95%]	2 yrs-survival [CI95%]	5 yrs-survival [CI95%]
EMM	5219	14 mos	55% [53%; 57%]	24% [23%; 26%]	4% [3%; 5%]
BMM	42	8 mos	38% [23%; 53%]	8% [0%; 19%]	0%
SMM	465	4 mos	12% [9%; 15%]	3% [1%; 5%]	0%



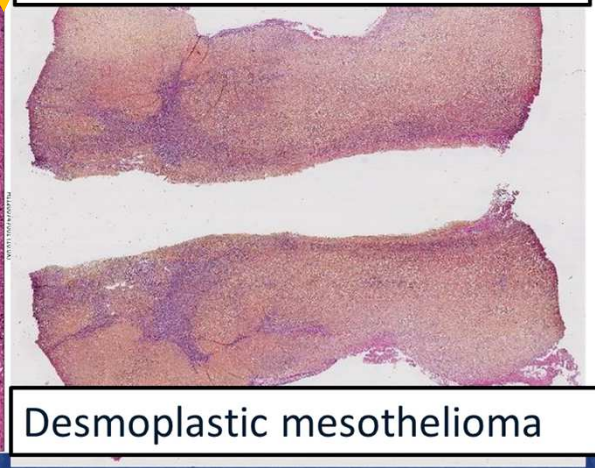
Epithelioid mesothelioma



Biphasic mesothelioma



Sarcomatoid mesothelioma



Desmoplastic mesothelioma

th #403– Exhibition Hall

WHO Classification 2015, European and International multidisciplinary workshop

157 Authors from 29 countries

New advances
in the diagnosis, prognosis, treatment

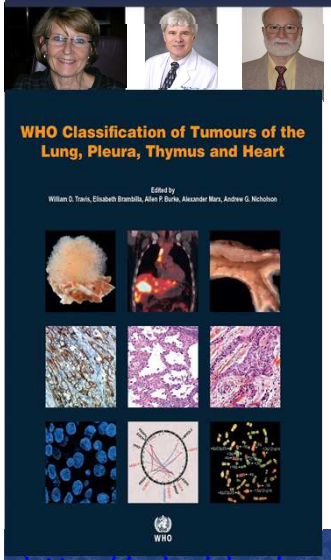
IASLC

European Reference Network
for rare or low prevalence complex diseases
Network Adult Cancers (ERN EURACAN)

IASLC·EURACAN·MULTIDISCIPLINARY·WORKSHOP·ON·MESOTHELIOMA·CLASSIFICATION¶

Lyon·¶

6-7th·JULY·2018¶



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 Nowak MD[c], Hedy Kindler MD[d], Ritu Gill MD[e], Martine Remy-Jardin MD[f], Sam Armato MD[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]

http://whobluebooks.iarc.fr/ WHO Booth #403– Exhibition Hall

Nicholson A et al , Accepted JTO

towards a more multidisciplinary approach, Nicholson et al, JTO in press

1) **Classification should include: Architectural patterns, Stromal response, Cytologic characteristics for prognostication**
2) **Malignant mesothelioma in situ could be an additional category**
3) **Favorable/unfavorable category should be routinely recognized and reported**
4) **Clinically relevant molecular abnormalities BAP1, CDKN2A (p16) HD, PDL-1 should also be incorporated in the reports**
5) **Other molecular data should be accrued as part of future clinical trials (MET etc..)**
6) Resection specimens (Pleurectomy/decortication and EPP) should be pathologically staged while small biopsies should be clinically staged
7) 3 different areas should be samples if possible
8) Correlation with image –acquisition protocol/imaging terminology are needing standardization for clinical staging and research practice
9) **Multidisciplinary board should include pathologists to ensure appropriate treatment**
10) **All histologic subtypes should be considered for chemotherapy**
11) **Patients with Biphasic and sarcomatoid mesothelioma should not be excluded from first line clinical trials**
12) **Tumor subtyping should be assessed in relation to response to immunotherapy**
13) Systematic screening of all patients for germline mutation is not recommended in the absence of family history of BAP1 syndrom

MESOPATH COHORT 1998-2018 selection of 13.246 definitively certified cases of M

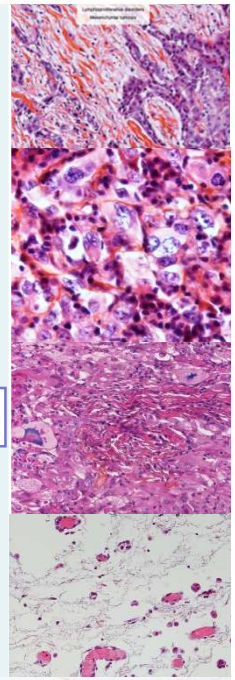
Epithelioid (81%)	Biphasic (10%)	Sarcomatoid (6%)
Architecture Papillary Acinous Trabecular Solid Micropapillary **Cell characteristics** Deciduoid Clear cell Microcystic/adenomatoid-like Signet ring cell Small cell (<1%) Rhabdoid	Any combination of pattern of epithelioid and sarcomatoid with at least 10% of one component	**Stromal characteristics** Desmoplastic (2%)

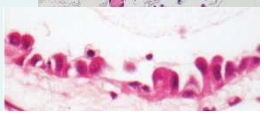
Rare variants MESOPATH cohort selection 10669 cases Pleura 9% Peritoneum 10%

Stromal characteristics	Morphological characteristics	Morphological characteristics
Lymphohistiocytoid (10%) Myxoid stroma (45%)	Transitional 7% Pleomorphic (20%)	With heterologous elements:2%) 1° rhabdomyosarcomatous, (2%) 2°osteosarcomatous, 3°chondrosarcomatous

Early lesions

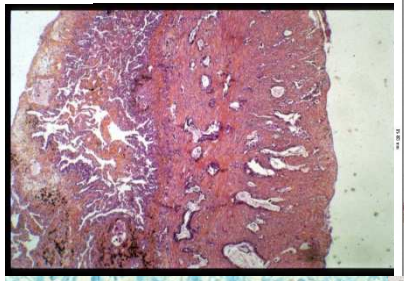
So called ''in situ'' MM (1%)



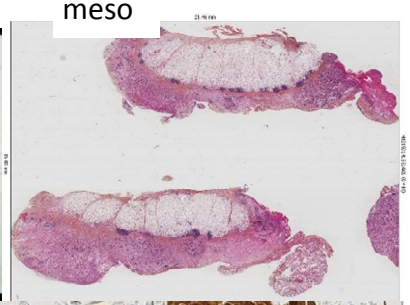


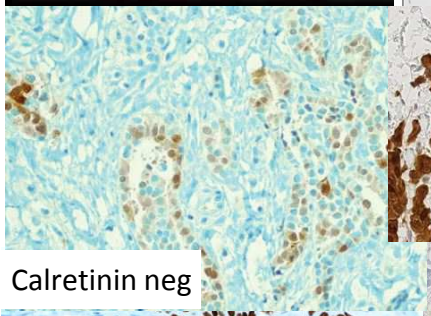
carcinoma metastasis 2 pos & 2 neg IHC markers specific of organs

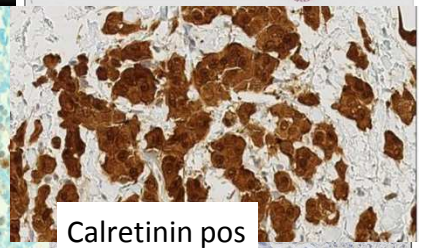
Lung



meso

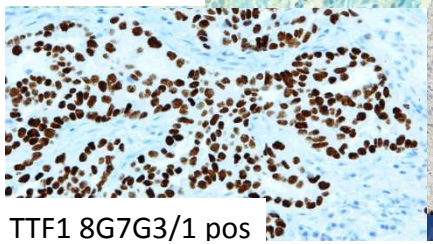


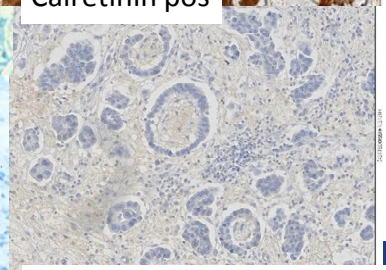




Calretinin pos

Calretinin neg





TTF1 8G7G3/1 pos

TTF1 8G7G3/1 neg

IHC comparison of epithelioid MM and lung and breast ADC

Biomarker	Sensitivity cut-off	EMM			LA			BA		
		N	Se	95%CI	N	Sp	95%CI	N	Sp	95%CI
Calretinin	>10% cells	6,183	95%	[94;96]	146	92%	[86;96]	34	79%	[62;91]
EMA	>10% cells	6,571	83%	[82;84]	138	14%	[9;21]	29	10%	[2;27]
Keratin 5/6	>10% cells	6,564	85%	[84;86]	139	84%	[77;90]	30	67%	[47;83]
Keratin AE1/AE3	>10% cells	4,703	99%	[99;100]	109	2%	[0;6]	21	0%	[0;16]
Mesothelin	>10% cells	2,037	88%	[86;90]	54	72%	[58;84]	11	45%	[16;77]
p53	>10% cells	3,355	78%	[76;80]	88	28%	[19;39]	19	21%	[6;45]
WT1	>10% cells	3,698	86%	[85;87]	36	75%	[58;88]	11	82%	[48;98]
BAP1	<1% cells	1,591	65%	[62;67]	13	100%	[75;100]	9	89%	[56;98]
p16	<1% cells	1,411	63%	[60;66]	12	42%	[19;68]	9	67%	[35;88]

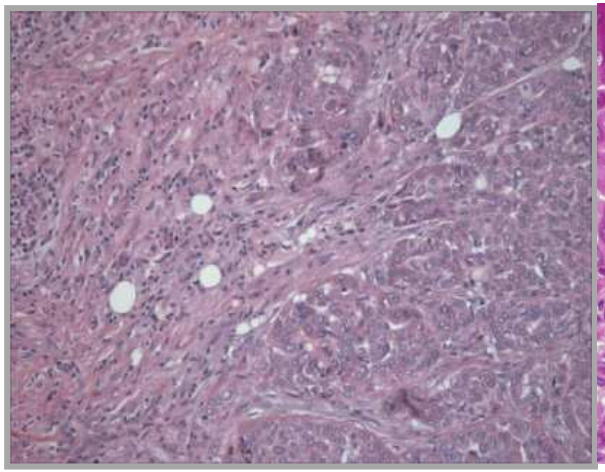
Biomarker	Sensitivity cut-off	LA			BA			EMM		
		N	Se	95%CI	N	Se	95%CI	N	Sp	95%CI
Ber-EP4	>10% cells	130	76%	[68;83]	41	71%	[54;84]	6,273	91%	[90;92]
CEA, II-7	>10% cells	104	30%	[21;40]	34	18%	[6;34]	4,223	100%	[99;100]
ERα	>10% cells	26	0%	[0;13]	41	81%	[63;93]	1,412	100%	[99;100]
TTF-1	>10% cells	149	88%	[81;93]	41	15%	[5;29]	6,265	100%	[99;100]

Le Stang N et al, Systematic review Archiv Pathol Lab 2019

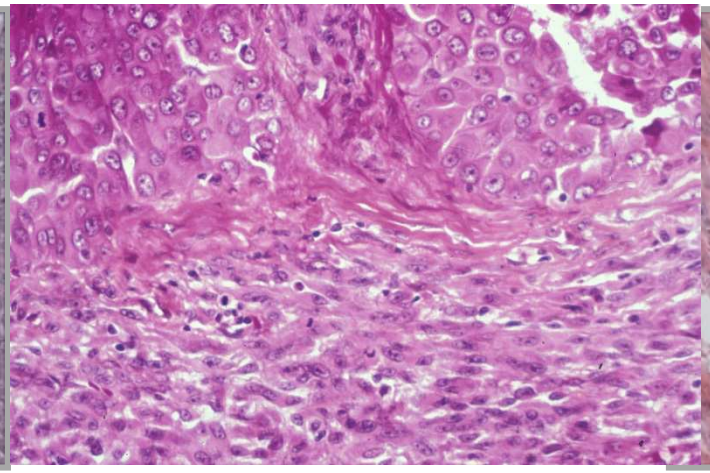
Diagnosis were based on the criteria for each types defined in the last 2015 WHO.

1° **A biphasic is any combination of EMM or SMM component of at least 10%**

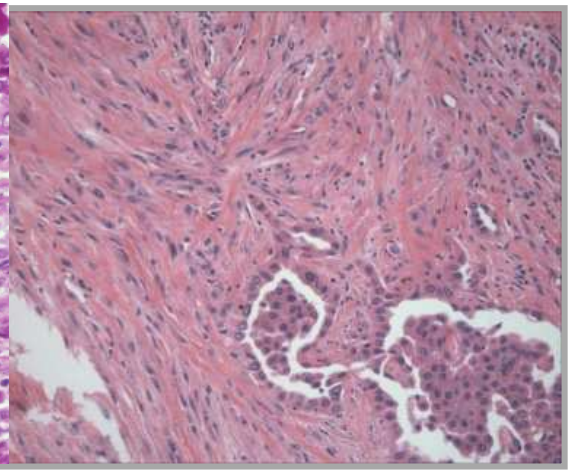
BMM epithelioid predominant



BMM



BMM sarcomatoid predominant



Modern Pathology
https://doi.org/10.1038/s41379-019-0320-y

USCAP

ARTICLE

rcomatoid component

Interobserver variation in the assessment of the sarcomatoid and transitional components in biphasic mesotheliomas

Sanja Dacic[1] · Nolwenn Le Stang[2] · Aliya Husain[3] · Birgit Weynand[4] · Mary Beth Beasley[5] · Kelly Butnor[6] · David Chapel[3] · Allen Gibbs[7] · Sonja Klebe[8] · Sylvie Lantuejoul[2] · Anja C. Roden[9] · Victor Roggli[10] · Henry Tazelaar[11] · Jean-Michel Vignaud[12] · Françoise Galateau-Sallé[2]

Received: 19 April 2019 / Revised: 5 June 2019 / Accepted: 5 June 2019

Thirteen members of the International Mesothelioma Panel reviewed 54 cases of biphasic mesothelioma, completed the survey of 25 questions and rendered 607 interpretations.

Interobserver agreement:
% sarcomatoid component

Weighted Kappa coefficient	Obs 1	Obs 2	Obs 3	Obs 4	Obs 5	Obs 6	Obs 7	Obs 8	Obs 9*	Obs 10	Obs 11
Obs1		0.30	0.38	0.61	0.46	0.58	0.49	0.31	0.64	0.51	0.47
Obs2			0.58	0.52	0.58	0.50	0.37	0.63	**0.96**	0.56	0.70
Obs3				0.75	0.51	0.46	**0.81**	**0.83**	NA	**0.83**	0.65
Obs4					0.59	0.65	0.46	0.61	**0.86**	**0.81**	0.54
Obs5						0.72	0.61	0.64	**1.00**	0.64	0.67
Obs6							0.60	0.57	0.74	0.57	0.70
Obs7								0.53	**0.99**	0.53	0.55
Obs8									**0.91**	0.55	0.70
Obs9										**0.89**	0.61
Obs10											0.44
Obs11											

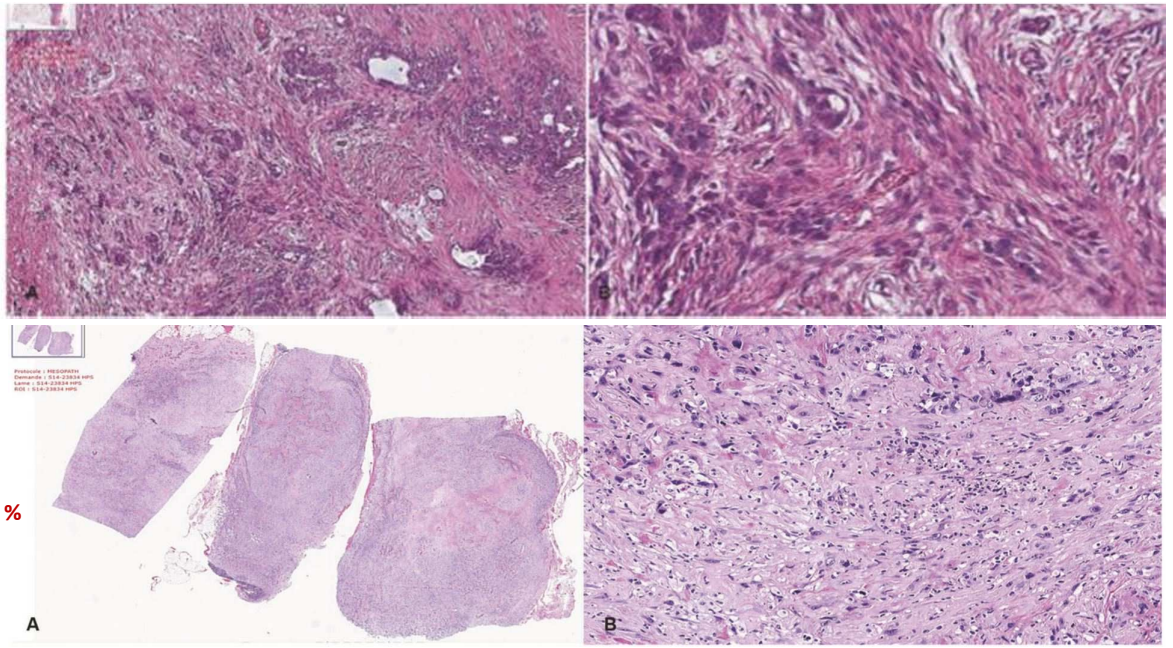
* Only 12 cases

Strength of agreement	Value of wk
Excellent	>0.8
Good	0.61 - 0.80
Moderate	0.41 - 0.60
Fair	0.21 - 0.40
Poor	0.00 - 0.20
Very poor	<0.0

% sarcomatoid component
0-24%,25-49%, 50-74%, 75-100%
Overall Wkappa (2018) = 0.62

[1] Landis J.R., Koch G.G: The Measurement of Observer Agreement for Categorial Data, Biometrics, 1977a, 33, 159-174

A stricter definition of sarcomatoid component and prognostic value of % of sarcomatoid component is under evaluation



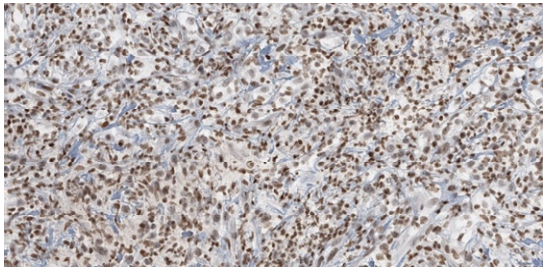
Dacic Mod Pathol, 2019

Biphasic mesothelioma: utility of ancillary technics

Molecular assessment can help in the identification of malignant sarcomatoid component

BAP1 loss on the sarcomatoid component alone was not observed.

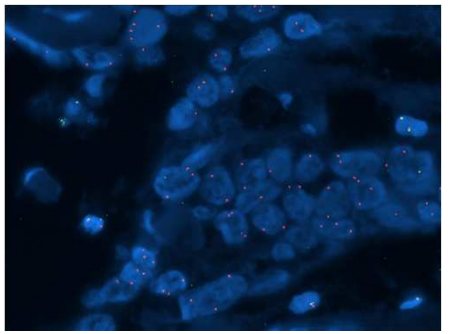
BAP1 loss on EM alone



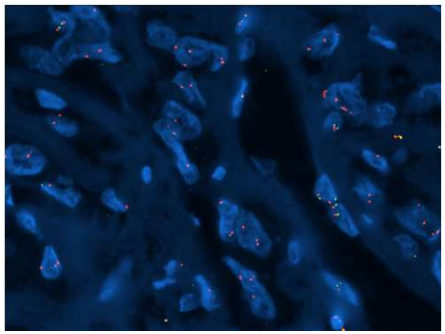
Molecular assessment of exuberant stromal component should be evaluated by p 16 HD

p16 homozygous deletion by FISH was present in **74 %** of the series (n=28/38)

HD p16 EM



HD p16 SM

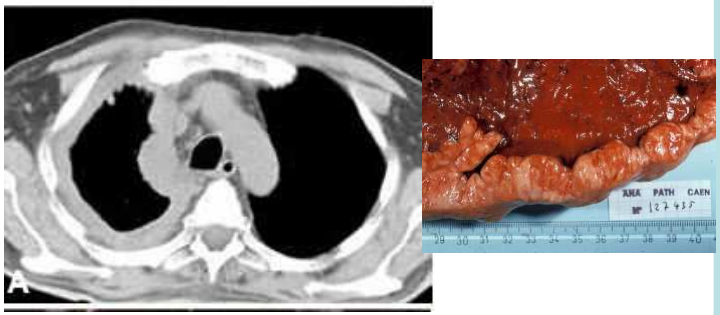


WHO 2015 9051/3 ICD-O code

WHO 2015 8022/3 ICD-O code

Sarcomatoid mesothelioma versus Sarcomatoid carcinoma

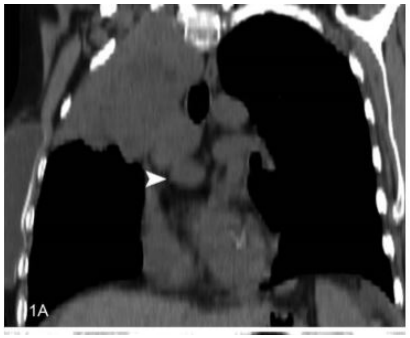
Rare usually<10%
Dyspnoea, chest pain, weight loss and loss of performance status,
Asbestos exposure
Men 96%>women 4%
Older pts>74 yrs
Pleural plaques 79%
Histological asbestosis 27%
Elevated asbestos content in lung tissue 93%

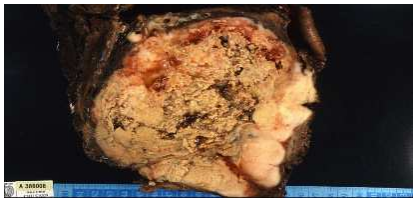


Marked pleural thickening and encasement of the lung parenchyma or pleural based mass

WHO 2015, Klebe S, Roggli V series of 326 cases Mod Pathol, 2010; 23:470-479,

Rare o,3 to 3% of all NSCLC
Heavy smokers 82%, asbestos exposure, chemicals exposure and immunosupression
Men in 61%
68 years (range, 32-89 years





Solitary peripheral mass with a predilection for the upper lobes invading the pleura

Tumor are large 2 to 18 cm large mean 7cm

WHO 2015 & Franks Arch Pathol Lab Med 2010 134:49-54, Maneenil, Clin Lung Cancer, May 2018

Human Pathology (2017) 67, 160–168
ELSEVIER

Original contribution

The differential diagnosis between pleural sarcomatoid mesothelioma and spindle cell/pleomorphic (sarcomatoid) carcinomas of the lung: evidence-based guidelines from the International Mesothelioma Panel and the MESOPATH National Reference Center☆

Alberto M. Marchevsky MD[a,*], Nolwenn LeStang[b], Kenzo Hiroshima MD[c], Giuseppe Pelosi MD[d], Richard Attanoos MD[e], Andrew Churg MD[f], Lucian Chirieac MD[g], Sanja Dacic MD[h], Aliya Husain MD[i], Andras Khoor MD[j], Sonja Klebe MD[k], Silvie Lantuejoul MD[l], Victor Roggli MD[m], Jean-Michel Vignaud MD[n], Birgit Weynard MD[o], Jennifer Sauter MD[p], Douglas Henderson MD[k], Kasuzi Nabeshima MD[q], Francoise Galateau-Salle MD[b]

The study was designed to review the experience at MESOPATH and query the English literature for best available evidence for the immunophenotype of SMM and SPC

Table 1 Demographics of patients diagnosed with sarcomatoid malignant mesothelioma and spindle cell/pleomorphic carcinoma at MESOPATH from 1998 to 2016

Populations	SPC (n = 46)	SMM (n = 587)	Comparison test (*P*)
Gender			.40 [a]
Male	36 (78%)	488 (83%)	
Female	10 (22%)	99 (17%)	
Age			.0003 [b]
Median	68.5 y	74 y	
Range	33-88	40-96	

[a] χ^2 test.
[b] Mann-Whitney test.

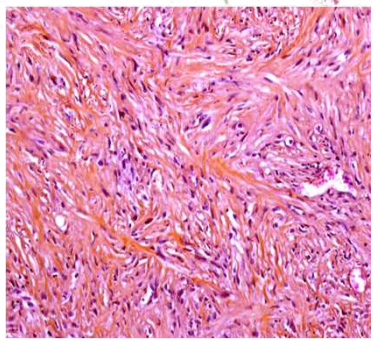
Table 1 Populations	SC (n=46)	SMM (n=892)	Comparison test
Gender			p†=0.43
Male	36 (78%)	748 (84%)	
Female	10 (22%)	144 (13%)	
Age			p‡=0.0003
Median	69 yrs	75 yrs	
Range	33-88	40-96	

p† : Chi2 test p-value
p‡ : Mann-Whitney test p-value

Sarcomatoid mesothelioma versus Sarcomatoid Carcinoma

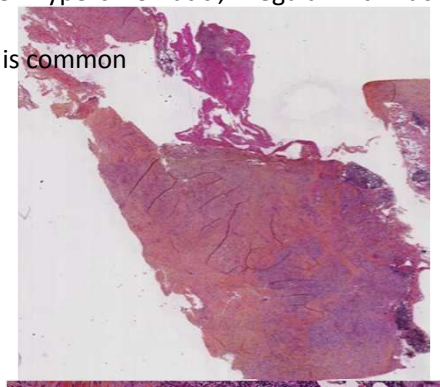
WHO 2015 9051/3 ICD-O code

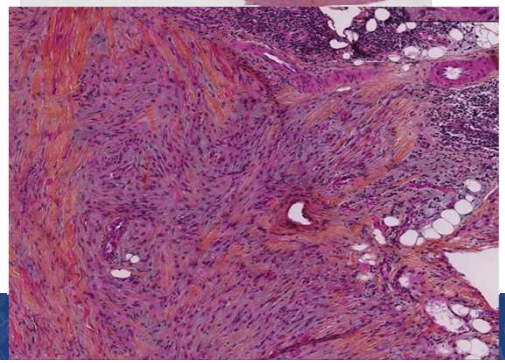
Proliferation of spindle cells arranged in fascicles or with haphazard pattern involving the adipose tissue or lung parenchyma and may present heterologous elements.
Wide range of morphologies but in conventional SM
Nuclear atypia varies from minimal to moderate



WHO 2015 8022/3 ICD-O code

Malignant spindle cell proliferation arranged in fascicular or storiform patterns.
Differentiated elements are absent
Nuclei are often hyperchromatic , irregular with nucleoli and granular chromatin
Inflammation is common





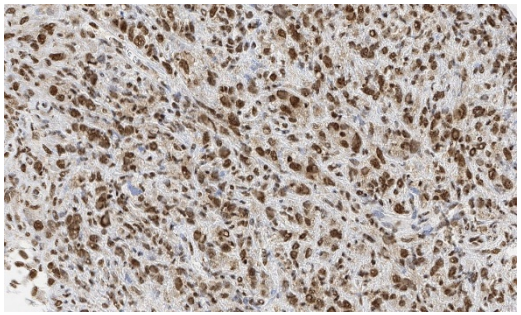
Can we use BAP1 immunostaining for the separation between SMM vs SC.No

NO!!!

Righi et al, JTO 2016 **Loss of BAP1 nuclear staining is rare in SMM and more prevalent in EMM**

Histological Subtype by Morphological Examination Only (N = 143)[a]	Nuclear Grade				BAP1 IHC Staining in Tumor Cells			BAP1 IHC Analysis in Stromal Cells		
	Tumor Cells, n (%)[a]	p Value	Stromal Cells, n (%)	p Value	Positive, n (%)	Negative (NN or NN/CP), n (%)	p Value	Positive, n (%)	Negative (NN or NN/CP), n (%)	p Value
Epithelioid MPM (n = 95)[a]	GI: 59 (62) GII: 35 (37) GIII: 1 (1)	p < 0.0001	Low: 18 (46) Mod: 21 (54) High: 0	p < 0.0001	30 (32)	NN: 65 (68) NN/CP: 44/21	p < 0.0001	39 (41)	0	p < 0.0001
Pleomorphic MPM (n = 12)[a]	GI: 0 GII: 10 (83) GIII: 2 (17)		Low: 0 Mod: 3 (25) High: 9 (75)		3 (25)	NN: 9 (75) NN/CP: 7/2		11 (92)	NN: 1 (8)	
Biphasic MPM (n = 13)[a]	GI: 4 (31) GII: 9 (69) GIII: 0		Low: 0 Mod: 6 (46) High: 7 (54)		3 (23)	NN: 10 (77) NN/CP: 9/1		8 (62)	NN: 5 (38)	
Sarcomatoid MPM (n = 23)[a]	NA		NA		18 (78)	NN: 5 (22) NN/CP: 5/0		NA	NA	
Total	GI: 63 (53) GII: 54 (45) GIII: 3 (2)		Low: 18 (28) Mod: 30 (47) High: 16 (25)		54 (38)	89 (62) NN/CP: 65/24		58 (91)	6 (9)	

[a]Parenthetical numbers from Kadota et al.[12]
BAP1, BRCA1-associated protein 1; IHC, immunohistochemical; MPM, malignant pleural mesothelioma; G, grade; Mod, moderate; NA, not applicable; NN, nuclear negativity; CP, cytoplasmic positivity.



SM

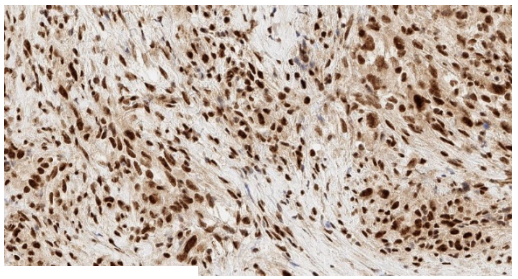
BAP1 staining is low in NSCLC

Carbone et al Oncotarget 2017

Tumor Type	Malignant Mesothelioma				Non-small cell lung cancer		
Histology	Epithelial	Biphasic	Sarc	Total	Adeno	SCC	Total
Sample no.	20	8	7	35	32	13	45
BAP1 Neg	13 (65%)	4 (50%)	5 (71%)	22 (63%)	0	0	0
BAP1 Pos	1 (5%)	1 (13%)	2 (29%)	4 (11%)	30 (94%)	13 (100%)	43 (96%)
BAP1 Focal	6 (30%)	3 (37%)	0	9 (26%)	2 (6%)	0	2 (4%)

Owen et al, Human Pathology (2017) 60, 82–85 **TMA 133 confirmed cases**

BAP1 loss (nuclear) 1%



SC

Can we use GATA3 for the separation between SM and SC: Yes

- GATA binding protein 3 (GATA3) is a transcription factor,
- GATA3 function is important in the regulation of genes such as MUC1/EMA involved in the luminal differentiation of breast epithelium and genes related to T-cell development

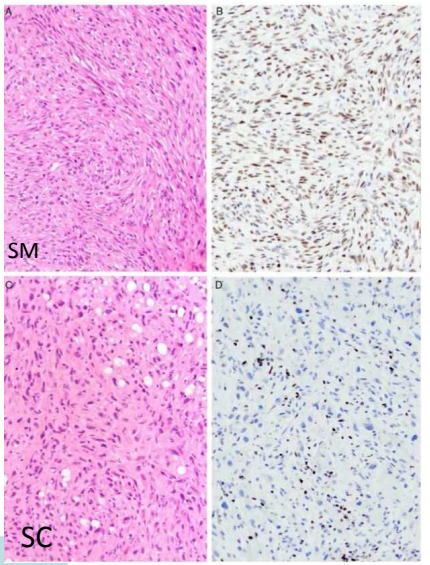
- GATA3 cl.L50-823 has been evaluated in surgical pathology as a marker for breast metastatic carcinoma in 80-90% and 67% of triple neg tumors

Berg & Churg(Am J Surg Pathol 2017;41:1221–1225)

TABLE 1. GATA3 Diffuseness, Intensity, and Total Score

Diffuseness Score	Sarcomatoid Mesotheliomas (N = 19) (n [%])	Sarcomatoid Carcinomas (N = 13) (n [%])	Intensity Score	Sarcomatoid Mesotheliomas (N = 19) (n [%])	Sarcomatoid Carcinomas (N = 13) (n [%])
0	0	11 (84)	0	0	10 (77)
1	2 (10)	2 (15)	1	0	3 (23)
2	2 (10)	0	2	6 (32)	0
3	15 (80)	0	3	13 (68)	0

Total score	Sarcomatoid mesotheliomas (N = 19) (n [%])	Sarcomatoid Carcinomas (N = 13) (n [%])
0-1	0	11 (85)
2-6	19 (100)	2 (15)



Marchevsky et al, Hum Pathol, 2017 67, 160-168 updated

Table 2 Immunohistochemical markers	SC (n=64)	SMM (n=892)	Comparison test
GATA3 <10% ≥10%	n=20 16 (80%) 4 (20%)	n=136 40 (29%) 96 (71%)	p†<0.0001

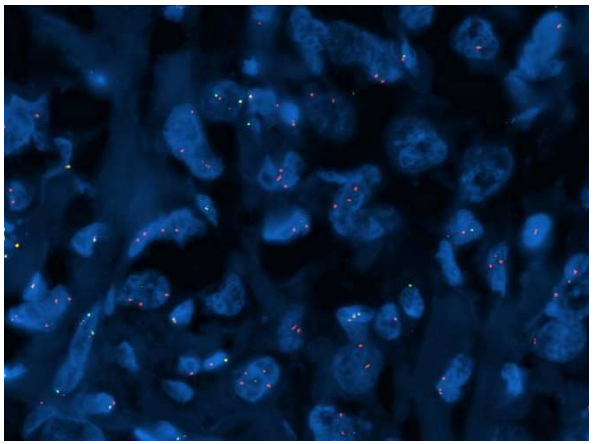
Can we use P16/*CDKN2A* HD for the separation of SMM versus SC=NO

Lung Cancer 67 (2010) 23–30
Contents lists available at ScienceDirect
Lung Cancer
journal homepage: www.elsevier.com/locate/lungcan

p16^{INK4A} inactivation mechanisms in non-small-cell lung cancer patients occupationally exposed to asbestos

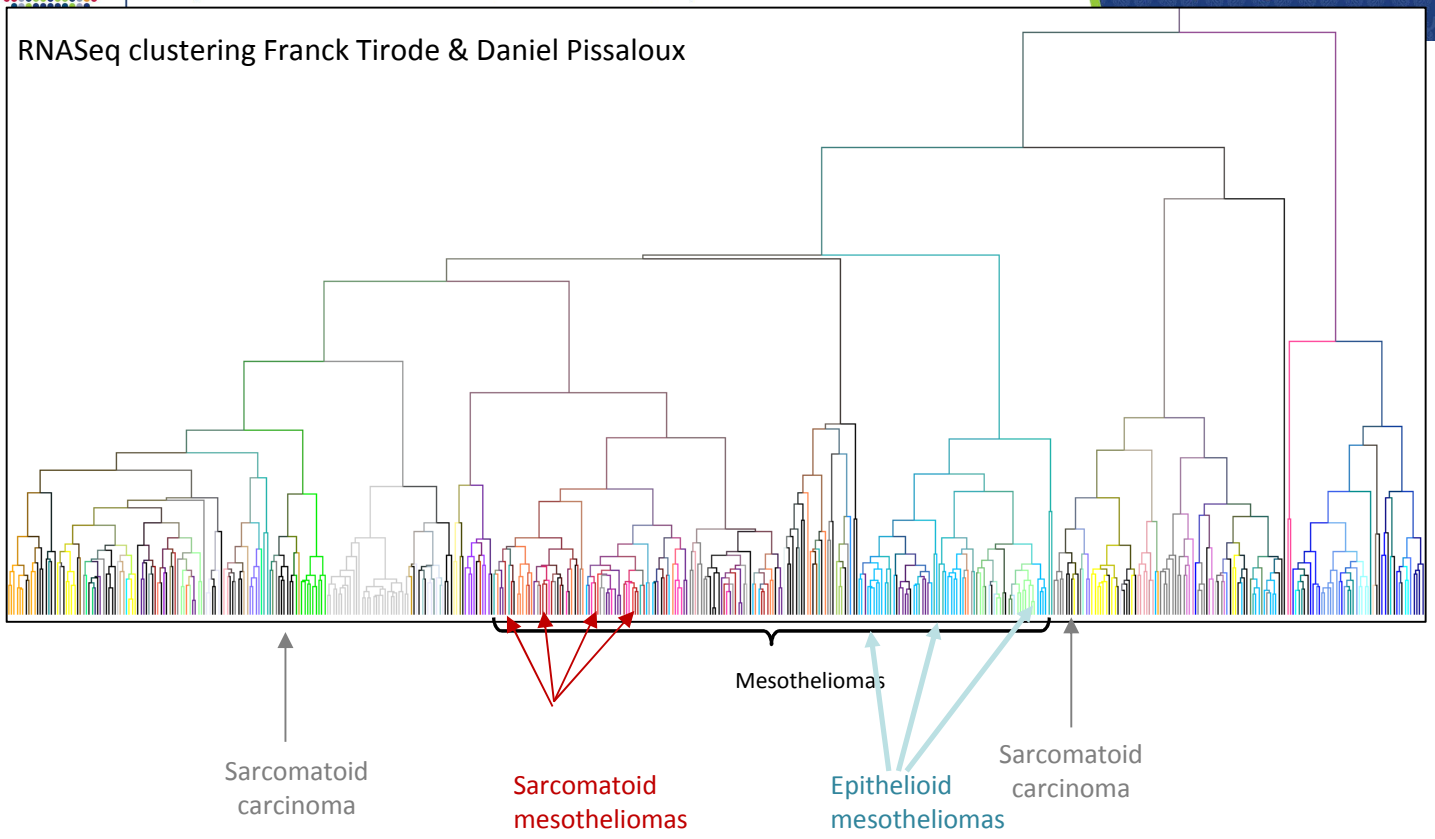
Pascal Andujar[a,b,c], Jinhui Wang[d,1,2], Alexis Descatha[e,f,g], Françoise Galateau-Sallé[h,i], Issam Abd-Alsamad[j], Marie-Annick Billon-Galland[k], Hélène Blons[l,m], Bénédicte Clin[n,o], Claire Danel[o,p,2], Bruno Housset[a,b,c], Pierre Laurent-Puig[l,m], Françoise Le Pimpec-Barthes[q,r], Marc Letourneux[b,s], Isabelle Monnet[a], Jean-François Régnard[k,t], Annie Renier[p,r], Jessica Zucman-Rossi[p,r], Jean-Claude Pairon[a,b,c], Marie-Claude Jaurand[p,r,*]

	NSCLC cases		*P* value
	Asbestos-exposed subjects ($n=34$)	Unexposed subjects ($n=41$)	
Mean age (years ± SD)	64.5 ± 8.8	64.1 ± 9.6	0.85
Gender			
Female	2 (5.9%)	9 (21.9%)	0.052
Male	32 (94.1%)	32 (78.1%)	
Histology			
Squamous cell carcinoma	16 (47.1%)	19 (46.3%)	
Adenocarcinoma	14 (41.2%)	18 (43.9%)	0.62
Others	4 (11.7%)	4 (9.8%)	
Smoking status			
Current smokers	17 (50.0%)	19 (46.3%)	
Former smokers	15 (44.1%)	18 (43.9%)	0.82
Never smokers	2 (5.9%)	4 (9.8%)	
Cumulative tobacco consumption (P-Y ± SD)	39.6 ± 21.4	41.9 ± 25.0	0.67
Age at onset (years ± SD)	22.8 ± 9.2	20.5 ± 8.1	0.42
Duration (years ± SD)	41.0 ± 12.2	40.6 ± 15.5	0.74
Asbestos exposure			
Positive occupational questionnaire	34	0	
AB/g dry lung tissue > 10^3	21	0	
AB/g dry lung tissue (median) [min–max]	1446 [0–21200]	58 [0–484]	$<10^{-4}$

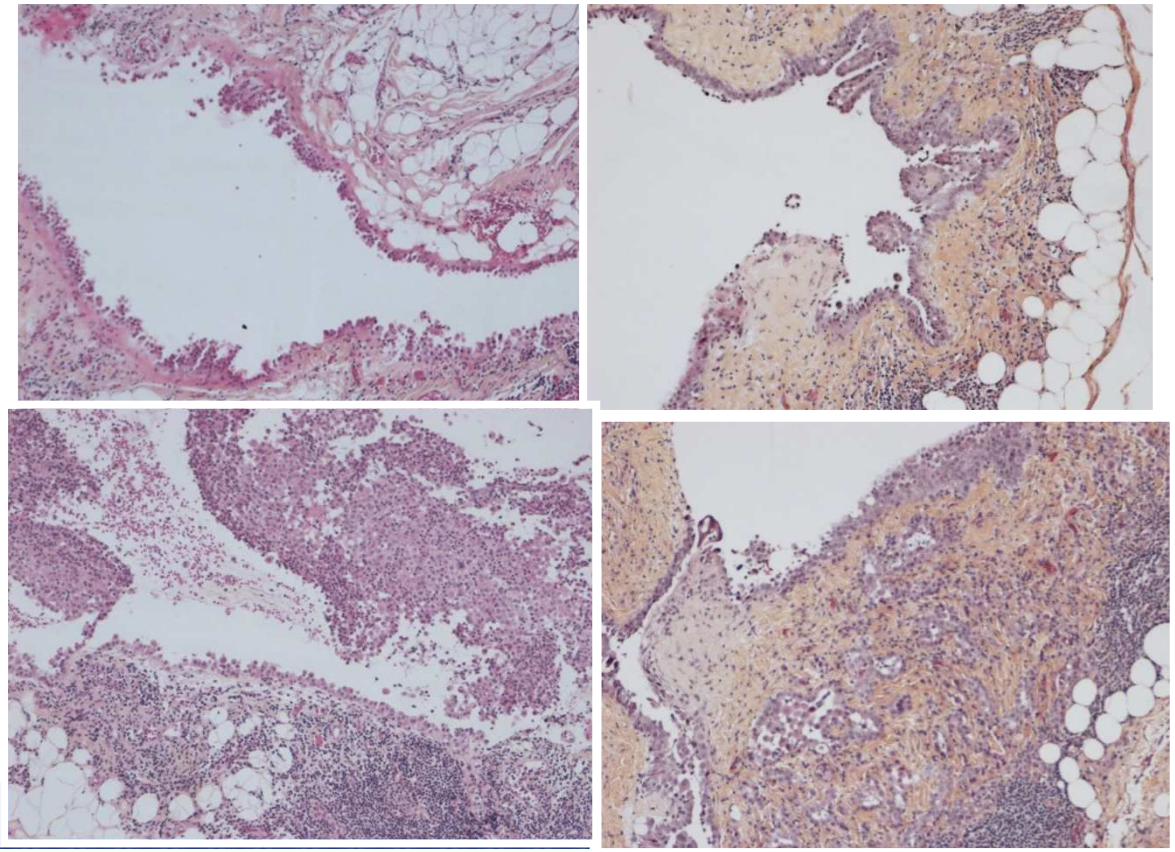


P16/*CDKN2A* promoter hypermethylation was significantly lower in AE pts than in Non AE pts

while P16/*CDKN2A* HD was higher in AE pts than in non AE pts p= 0.0062 after adjustment for age and cumulative tobacco consumption

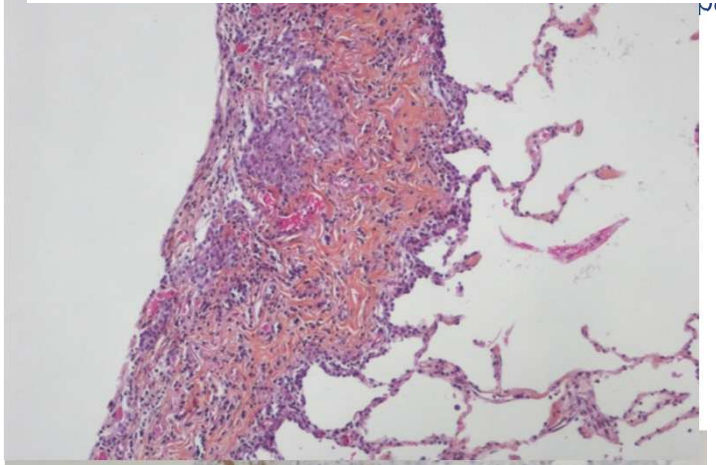

RNASeq clustering Franck Tirode & Daniel Pissaloux
Mesotheliomas
Sarcomatoid carcinoma
Sarcomatoid mesotheliomas
Epithelioid mesotheliomas
Sarcomatoid carcinoma

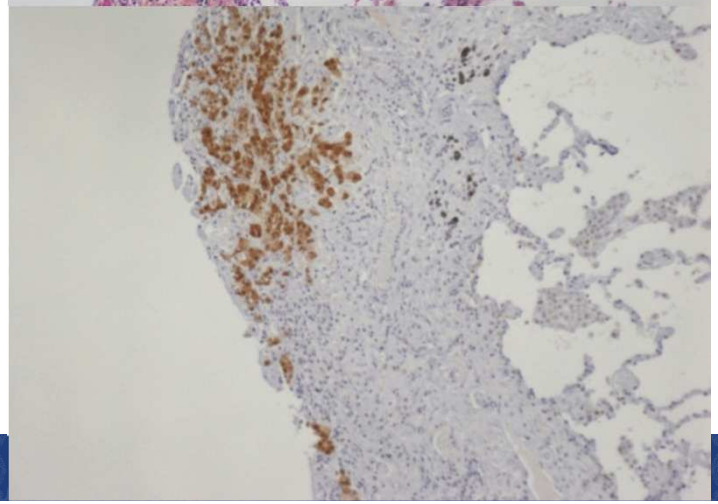
Early lesions are more frequently observed in MESOPATH



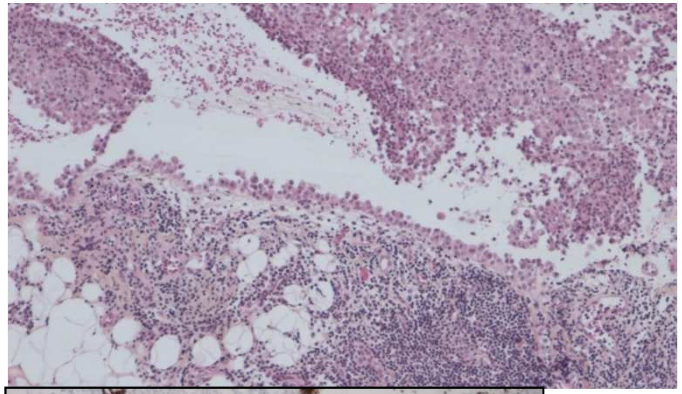
IASLC

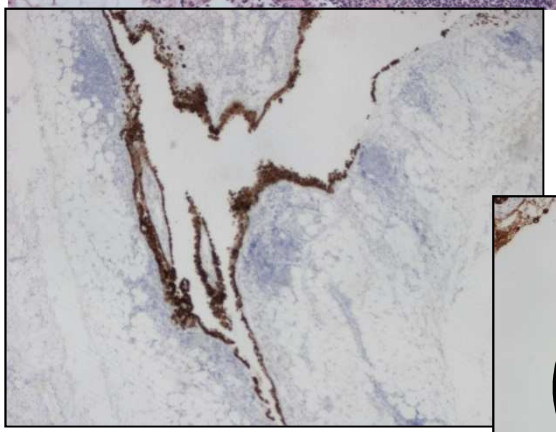
Hyperplasie mésotheliale de signification indéterminée

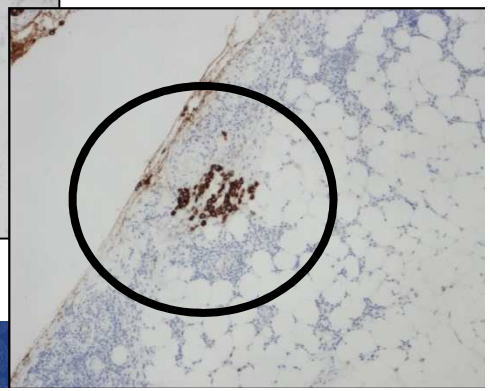


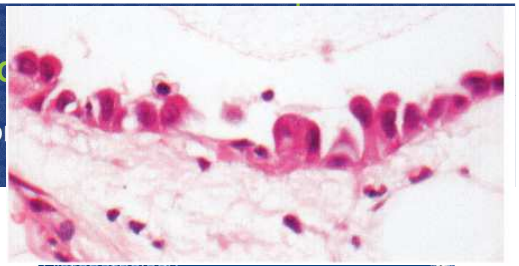


Mésothéliome débutant (invasion minime)

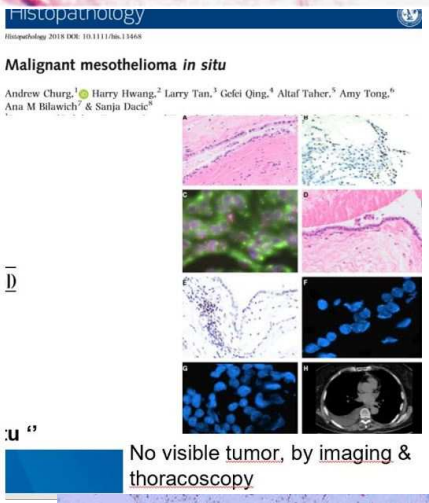








1°Whitaker D, Henderson DW, Shilkin KB. The concept of mesothelioma in situ: implications for diagnosis and histogenesis. *Semin Diagn Pathol.* 1992;9(2):151-161.

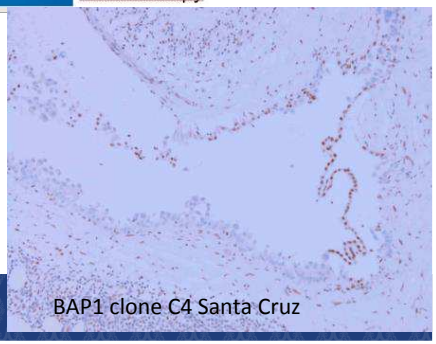


2°Churg A, Hwang H, Tan L, et al. Malignant mesothelioma in situ. *Histopathology.* 2018. 72(6):1033-1038

3°Churg A, Galateau-Salle F, Roden AC, Attanoos R, von der Thusen JH, Tsao MS, Chang N, De Perrot M, Dacic S. Malignant mesothelioma in situ: morphologic features and clinical outcome. Mod Pathol. 2019 Aug 2

10 cases with repeated pleural effusion and with no tumor on imaging

The recommendation of the MDgroup is that MMIS could potentially be added as a category in future classification



nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0583-3

Deep learning-based classification of mesothelioma improves prediction of patient outcome

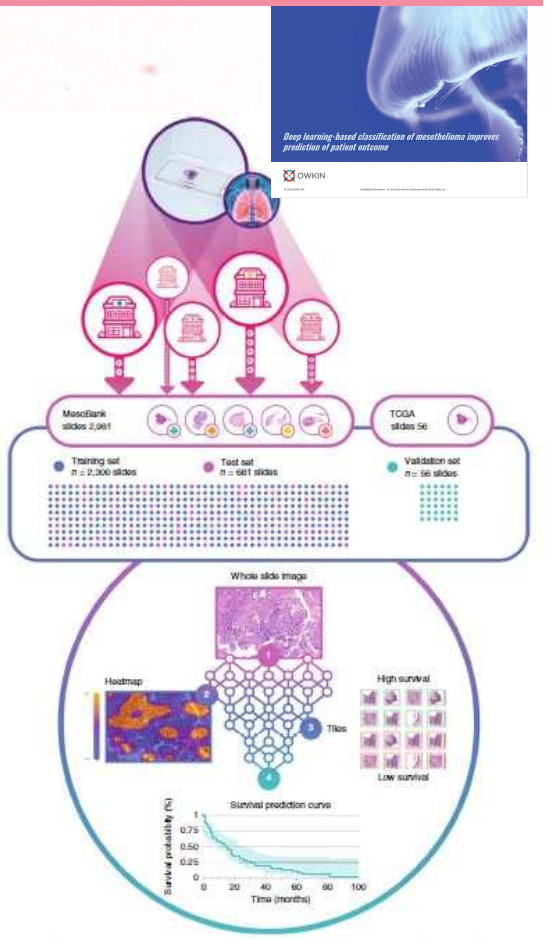
Pierre Courtiol[1,8], Charles Maussion[1,8], Matahi Moarii[1], Elodie Pronier[1], Samuel Pilcer[1], Meriem Sefta[1], Pierre Manceron[1], Sylvain Toldo[1], Mikhail Zaslavskiy[1], Nolwenn Le Stang[2], Nicolas Girard[3,4], Olivier Elemento[5], Andrew G. Nicholson[6], Jean-Yves Blay[7], Françoise Galateau-Sallé[2,8], Gilles Wainrib[1,8] and Thomas Clozel[1,8]*

Malignant mesothelioma (MM) is an aggressive cancer primarily diagnosed on the basis of histological criteria[1]. The 2015 World Health Organization classification subdivides mesothelioma tumors into three histological types: epithelioid, biphasic and sarcomatoid MM. MM is a highly complex and heterogeneous disease, rendering its diagnosis and histological typing difficult and leading to suboptimal patient care and decisions regarding treatment modalities[2]. Here we have developed a new approach—based on deep convolutional neural networks—called MesoNet to accurately predict the overall survival of mesothelioma patients from whole-slide digitized images, without any pathologist-provided locally annotated regions. We validated MesoNet on both an internal validation cohort from the French MESOBANK and an independent cohort from The Cancer Genome Atlas (TCGA). We also demonstrated that the model was more accurate in predicting patient survival than using current pathology practices. Furthermore, unlike classical black-box deep learning methods, MesoNet identified regions contributing to patient outcome prediction. Strikingly, we found that these regions are mainly located in the stroma and are histological features associated with inflammation, cellular diversity and vacuolization. These findings suggest that deep learning models can identify new features predictive of patient survival and potentially lead to new biomarker discoveries.

16 months), whereas SMM patients have the worst prognosis (OS of 5 months) and BMM patients have an intermediate prognosis[6]. This histological classification is of prognostic and therapeutic value[7,8] but is insufficient to cover the extreme variability in clinical features and patient outcomes in MM patients. This highlights the important need for developing new methods to identify predictive biomarkers consistently associated with survival[2,9–12].

The advent of deep learning and the availability of thousands of histology slides provides a new opportunity to revisit classical approaches to diagnosis and predicting patient outcomes[12–21]. However, this approach is usually seen as a black-box, where image features contributing to the prediction are hardly intelligible. To address these limitations, we developed MesoNet, a deep learning algorithm specifically customized to analyze large images, such as whole-slide images (WSIs), without any local annotation by pathologists[22].

To build MesoNet, we adapted a recently described algorithm specifically designed to address this scenario[22]. To create prediction models, our algorithm trains deep learning networks from WSIs[22,24] with only global data labels (Extended Fig. 1). First, WSIs from MM patients were preprocessed and divided into small 112×112 µm squares (224×224 pixels), called 'tiles'. These tiles were fed into the network architecture, which assigned a 'survival score' to each tile, through an iterative learning process. Finally, the network selected the tiles of each WSI that were the most relevant to the prediction and used this limited number of tiles to predict patient OS (for a



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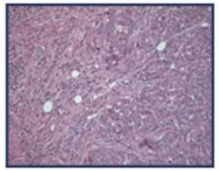
Deux questions à résoudre

1° Peut –on reconnaitre une forme histologique complexe
2° Peut on mieux stratifier les patients à partir d'une lame H&Es

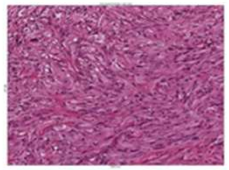
Mesothelioma with transitional pattern: Study conducted with the IMP

° The **Diag of TM was based on experts consensus** when TM features were recognized by at least 7 out of 14 pathologists of the IMP
The criteriafor TM was on the basis of **sheets of plump cells starting to lose their epithelioid morphology but not overtly spindle shaped and lacking frank sarcomatous features**

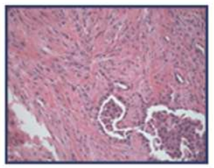
Epithelioid predominant[EM



Transitional??????[TM] pattern



Sarcomatoid predominant[SM]



Demographic, clinical, histopathological treatment and follow up data were retrieved from the MESOBANK.

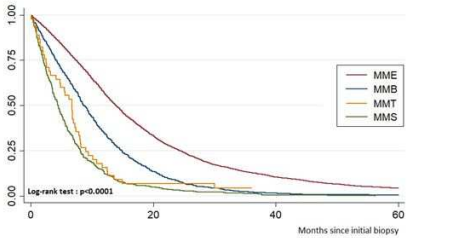
Inter-observer agreement : Transitional, Y/N?

Simple Kappa coefficient	Obs 1	Obs 2	Obs 3	Obs 4	Obs 5	Obs 6	Obs 7	Obs 8	Obs 9	Obs 10	Obs 11	Obs 12	Obs 13	Obs 14
Obs1		0.41	0.55	0.49	0.22	0.10	0.25	0.60	0.46	0.47	0.17	0.15	0.26	0.18
Obs2			0.58	0.58	**0.71**	0.22	0.53	0.23	**0.70**	0.36	0.52	0.51	**0.67**	0.40
Obs3				0.48	0.39	0.12	0.44	0.17	0.42	0.39	0.17	0.31	0.39	0.45
Obs4					0.19	0.28	0.26	0.21	**0.75**	0.25	0.33	0.27	0.50	0.41
Obs5						0.52	0.47	0.16	0.53	0.45	0.56	0.46	0.54	0.32
Obs6							0.33	0.07	0.30	0.32	0.50	0.45	0.55	**0.64**
Obs7								0.11	0.43	0.37	0.50	**0.65**	**0.69**	0.58
Obs8									0.34	0.46	0.16	0.27	0.20	0.15
Obs9										0.42	0.48	0.47	**0.62**	0.36
Obs10											0.36	0.38	0.44	0.22
Obs11												0.60	0.45	0.29
Obs12													**0.67**	**0.65**
Obs13														**0.67**
Obs14														

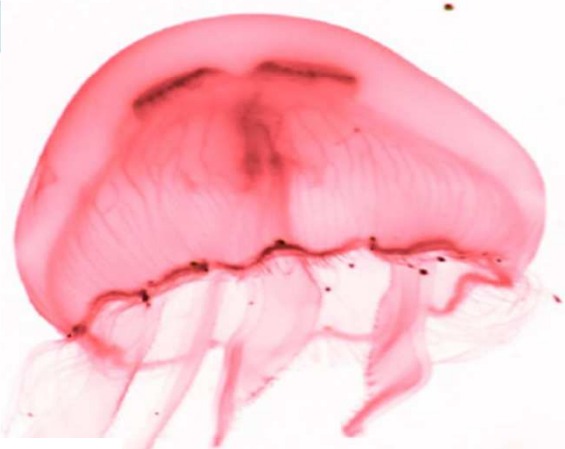
Strength of agreement	Value of wk
Excellent	>0.8
Good	0.61 - 0.80
Moderate	0.41 - 0.60
Fair	0.21 - 0.40

Transitional, Y/N? Panel

Overall kappa (2017) = 0.41



	N	Median	1 yr-survival [CI95%]	2 yrs-survival [CI95%]	5 yrs-survival [CI95%]
EMM	5219	14 mos	55% [53%; 57%]	24% [23%; 26%]	4% [3%; 5%]
BMM	787	9 mos	32% [28%; 35%]	7% [5%; 9%]	0% [0%; 1%]
Transitional MM	20	6 mos	16% [7%; 28%]	7% [1%; 16%]	0%
SMM	465	4 mos	12% [9%; 15%]	3% [1%; 5%]	0%



Galateau Salle et al, JTO 2019

How AI can help the pathologist

Prérequis

Depuis 1998 -2018

Plateforme de lames numérisées

Aperio AT2

CENTRE LEON BERARD

CALOPIX
CHANGING DIGITAL IMAGING

>40 000 lames numérisées archivées sur à partir de la platefoorme sur un serveur au CLB

Base clinico biologique

mesoBANK

Cohorte de + de 23000 patients
>200 annotations/pts systématique
1500 pts/an

Réseau d'experts
France:20 experts
International: 25 experts

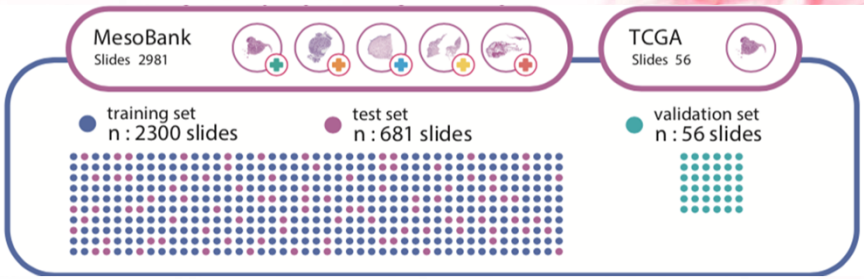
Procédure de certification diagnostique standardisée pour chaque cas enregistré

GOLD STANDARD

Procédure de validation croisée entre les équipes internationales

Data

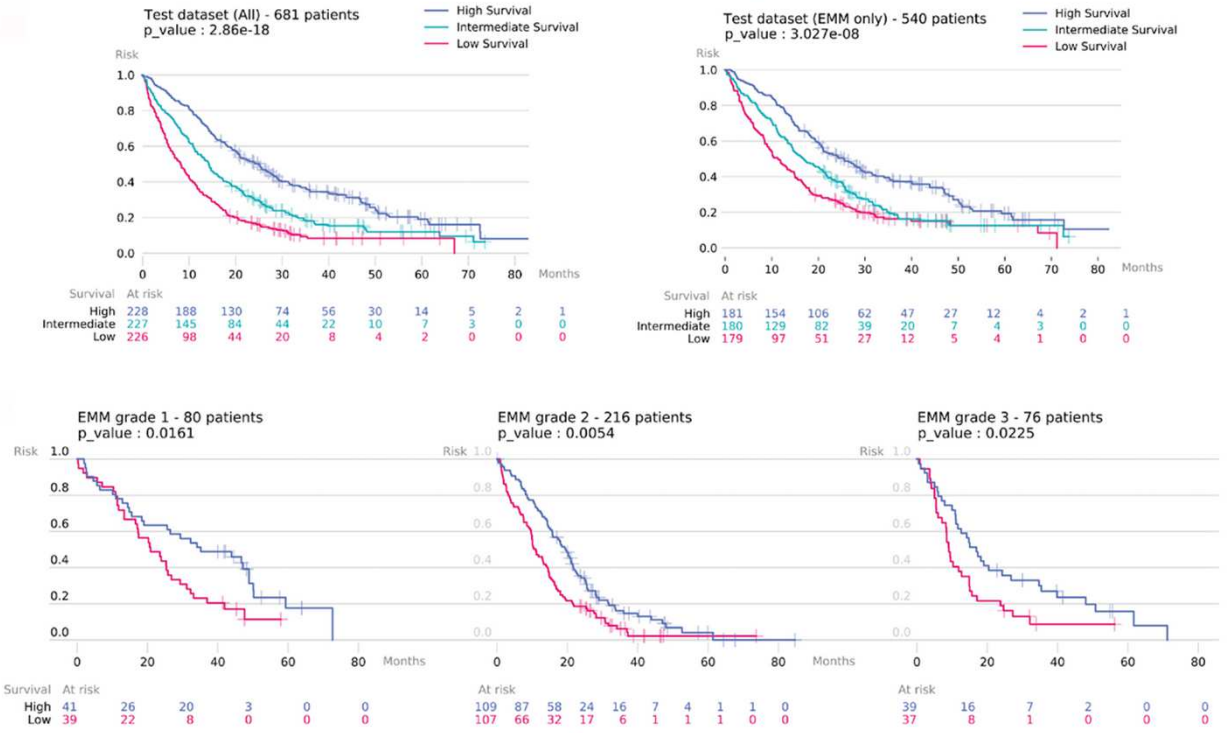
- The MESOPATH / MESOBANK database is an exhaustive repository of French clinical data and HES histological samples pertaining to mesothelioma.
- This dataset was randomly divided into a training set (2,300 slides) and an entirely separate test set (681 slides).
- On the training set, a five-fold cross-validation strategy was applied. The model was then trained on the entire 2,300 training slides and evaluated on the test set of 681 slides.
- Moreover, a validation set of 56 H&E WSIs from 56 MM patients from an independent dataset was obtained from TCGA in order to test MesoNet robustness.



P.Courtiol OWKIN et al,

Results

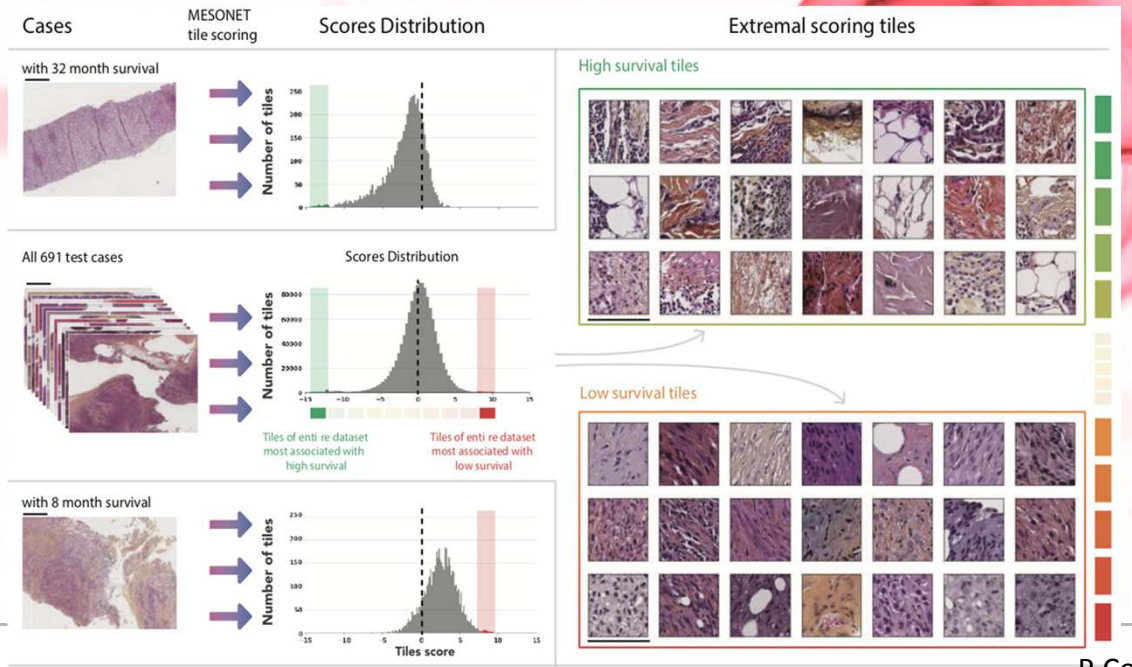
- The model **is able to stratify patients** even within established histological classification



P.Courtiol OWKIN et al,

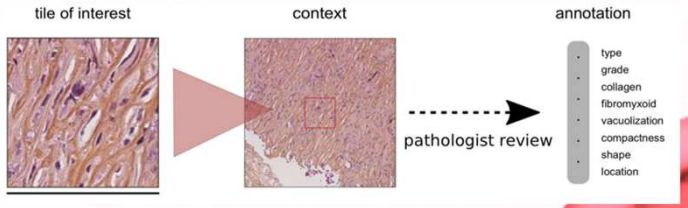
Interpretability

- One can extract the **most predictive tiles** for the algorithm so they can be **analyzed by an expert pathologist**
- The most predictive tiles associated with low survival (n= 50) were located primarily in **stromal regions.**



P.Courtiol OWKIN et al,

Interpretability



- Two independent expert pathologists analyzed the specific histological features differentiating predictive and non-predictive tiles for low and high survival tiles, separately.
- Predictive high survival tiles were of lower-grade tumors, less pleomorphic and showed a greater inflammatory response
- Low survival tiles were of higher-grade tumors, more pleomorphic, atypical and showing a lower inflammatory response

High pleomorphism, atypia and a lower inflammatory response are consistently associated with a lower survival and should be taken into account by pathologists for MM diagnosis and staging.

Well-differentiated Papillary Mesothelioma of the Pleura: A Series of 24 Cases.

American Journal of Surgical Pathology. 28(4):534-540, April 2004.
*Galateau-Salle, Francoise *+++[//]; Vignaud, Jean Michel +; Burke, Louise [S]; Gibbs, Allen [P]; Brambilla, Elisabeth +; Attanoos, Richard [P]; Goldberg, Marcel ++; Launoy, Guy ++[//]*

F>M
Median age : 60 years old

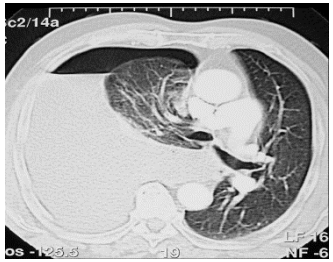
Code ICD0-9052/1

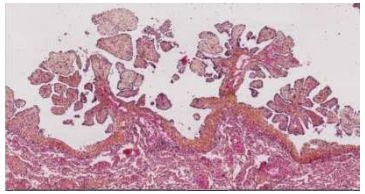
TABLE 1. Clinical Features in Well-Differentiated Papillary Mesothelioma of the Pleura (*continued*)

Case No.	Age (yr)	Sex	Presentation	CT Scan	Asbestos Exposure	Previous History	Treatment
16	71	F	Pleural effusion	ND	No		Unknown
17	69	F	Pleural effusion	ND	Yes		ND
18	59	F	Pleural effusion	Pleural-based thickening	HHC Yes		Chemotherapy
19	72	M	Left pleural effusion and pneumothoraces	Absence of tumor	No		No treatment
20	73	F	Pleural effusion	Multiples small nodules	No		No treatment pleurectomy
21	31	F	Pleural effusion	Pleural thickening and multiple small nodules	No		No treatment
22	61	M	Pleural effusion	Multiple small nodules	No		No treatment
23	60	F	Pleural effusion	No thickening	Possible HHC		No follow-up
24	50	F	Pleural effusion	Multiple nodules	No		No follow-up

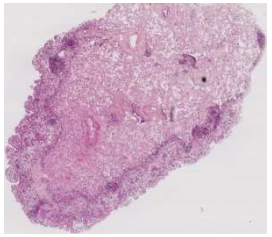
CT, computed tomography; ND, not determined; HHC, household contact; HAE, heavy asbestos exposure; HFP, hyaline fibrous plaque.

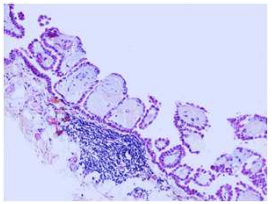
WDPM





EMM mimicking WDPM





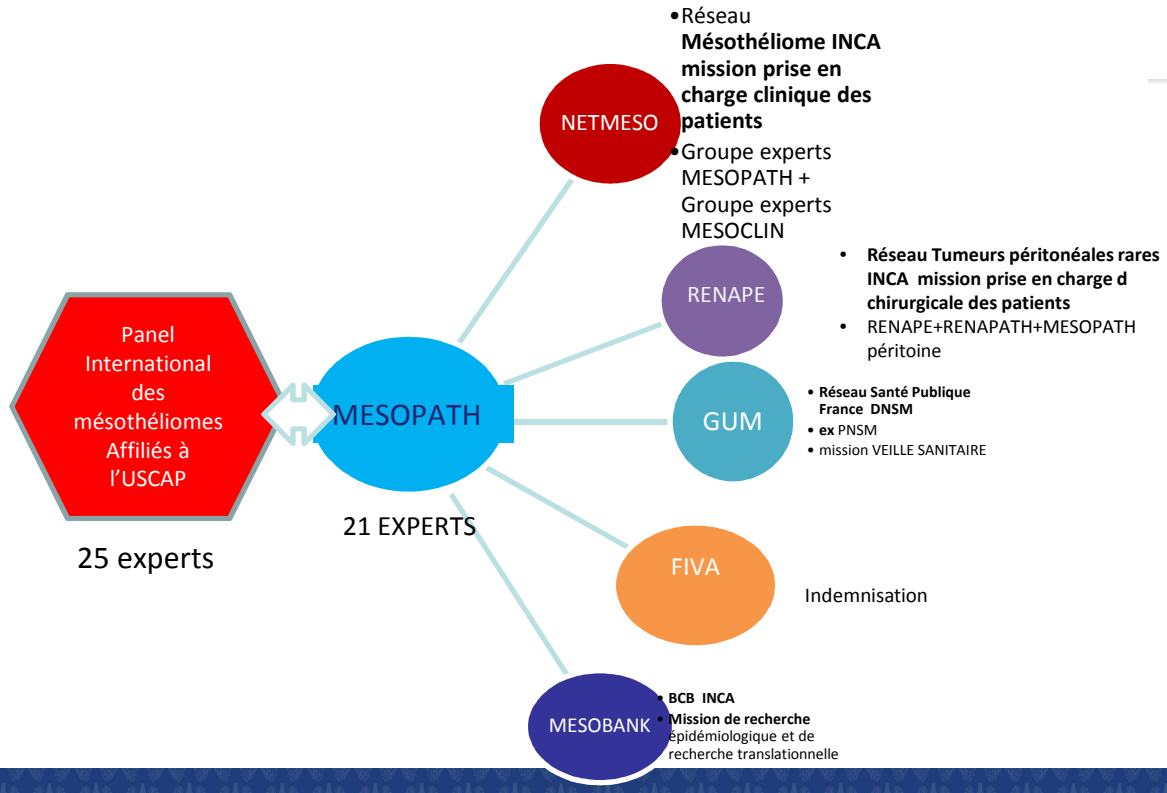
Male 69 yrs old
Asbestos exposed
Unilateral pleural effusion
Disseminated micronodules

BAP1 loss
Survival 17 months

	Median survival	2-year survival
WDPM	26 months	61% $CI_{95\%}$ = [30% ; 92%]
Epithelioid	12 months	18% $CI_{95\%}$ = [14% ; 21%]

BAP1 100% retained
HD p16 0% homozygous deletion
Stevers et al, genetically defined by mutually exclusive mutations in TRAF7 and CDC42. Mod Pathol. 2019 Jan;32(1):88-99

MESOPATH prise en charge multidisciplinaire



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MISE AU POINT

Mésothéliome : les dispositifs en place en France « le réseau mésothéliome » 1998–2013

The French mesothelioma network from 1998 to 2013

Françoise Galateau-Sallé[a,*,c], A. Gilg Soit Ilg[b], N. Le Stang[c], P. Brochard[d], J.C. Pairon[e], P. Astoul[f], C. Frenay[f], G. Blaizot[a], S. Chamming's[e], S. Ducamp[b], T. Rousvoal[a], A. de Quillacq[a], V. Abonnet[a], I. Abdalsamad[a], H. Begueret[a], E. Brambilla[a], F. Capron[a], M.C. Copin[a], C. Danel[a], A.Y. de Lajartre[a], A. Foulet-Roge[a], L. Garbe[a], O. Groussard[a], S. Giusiano[a], V. Hofman[a], S. Lantuejoul[a], J.M. Piquenot[a], I. Rouquette[a], C. Sagan[a], F. Thivolet-Bejui[a], J.M. Vignaud[a], A. Scherpereel[g,h], M.C. Jaurand[i], D. Jean[i], P. Hainaut[j], L. Chérié-Challine[b], M. Goldberg[b], D. Luce[b], E. Imbernon[b]

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[i] Inserm, UMR-674, IUH, 75010 Paris, France
[j] International Prevention Research Institute, 69000 Lyon, France

Accepté pour publication le 13 janvier 2014

French standardized procedure of certification

for each case submitted

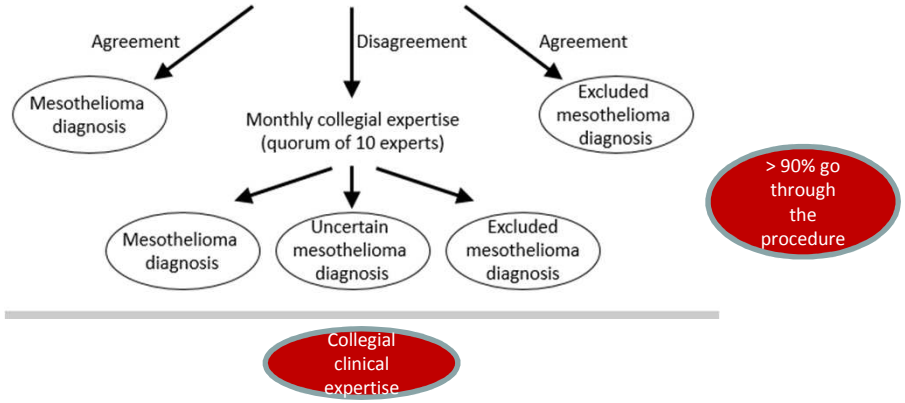
using a digitilized platform TELESLIDE-TRIBVN (MESOPATH-Pleura and MESOPAH –Peritoneum)

ing

Initial pathologist diagnosis

↓

3 experts blindly reviewed the slides (WHO classification 2015)
Additional IHC (CKs +2 +ve and 2 - ve markers) + specific organ markers (10markers/per case)
since 2012 additional molecular markers BAP1 and FISH CDKNp16 and RNASeq when necessary



Mis and underdiagnosis of MPM is still a problem today need ancillary techniques and knowledge of new entities

An awareness of the clinical settings and diverse morphological, cytological features and stromal characteristics of mesothelioma is important to avoid misdiagnosis.

Immunohistochemistry is still mandatory in the identification of misleading patterns

Molecular markers are crucial tools for the separation of benign versus malignant mesothelial proliferations and RNAseq for a more accurate classification and avoid misdiagnosis.

Thanks

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Franck Tirode
Leader molecular group

Thoracic Cancers Worldwide

JP Michot &The lab

Elise & Cyril

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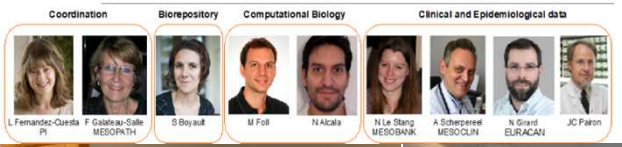
InVS Institut de veille sanitaire

Nolwenn Le Stang & Gaetane Blaizot
Marie Claude Jaurand & Didier Jean
Jean Claude Pairon & Patrick Brochard
The International Mesothelioma panel
The french Mesopanel

Experts	International Meso panel	Year of entry	Experts	Site	Year of entry
T. Allen	Texas AM university USA	2008	P. Hasleton	Manchestr UK	1998
R. Attanoos	Cardiff UK	2008			
E. Brambilla	Grenoble F	1995	D.Henderson S. Klebe	Adelaide Flinder University AU	1998
A. Borszczuck	Columbia University USA	2008	A. Husain	Chicago University USA	2008
P. Cagle	Baylor College of Medicine USA	1998	K.Hiroshima	Tokyo University	2009
L. Chirieac	Women and Brigham hospital	2008	K. Kerr	Aberdeen University	
A. Churg	Vancouver	1998	K.Kouki	Hiroshima University JP	1998
			S. Lantuejoul	University Grenoble	2011
T. Colby	Mayo Clinic Scootsdale USA	1998	H. Popper	Graz University A	2008
S. Dacic	University pittsburg USA	2008	M.Praet	Gent University	1998
J. Fukuoka	University Nagasaki JP	2011	V.Roggli	Durham University	1998
A. Gibbs	Cardiff, UK	1998	B.Travis	Memorial Sloane Kettering USA	1998
S. Hammar	Seattle USA	1998	JM. Vignaud	Lorraine	1995

MESOMICS
Multi-omics characterization of Malignant Pleural Mesothelioma



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

Nicholson A et al, JTO sept 2019