

PATHOLOGY OF MALIGNANT MESOTHELIOMA**PPS San Francisco, 2015**

Richard Attanoos
Cardiff
UK

Disclosures

None

DIFFUSE PLEURAL MESOTHELIOMA AND ASBESTOS EXPOSURE IN THE NORTH WESTERN CAPE PROVINCE

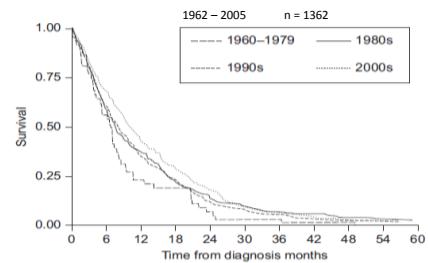
J. C. WAGNER, C. A. SLEGGS, and PAUL MARCHAND
Brit. J. Ind. Med., 1960, 17, 260.



Breast Cancer Res Treat 2011; 130: 1429–1434
 doi: 10.1007/s10601-010-00008-1
 published online: 20/01/2011

Predicting survival in malignant mesothelioma

A.W. Musk*,^a N. Olsen^{a,*}, H. Alfonso^a, A. Reid^b, R. Mina^a, P. Franklin^a, J. Sleath^a, N. Hammond^a, T. Threlfall^a, K.B. Shilkin^{c,d} and N.H. de Klerk^{e,f,g}

**Predictors of Survival****Predictors of Malignancy**

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(1):32–39
 doi:10.1089/jcl.2010.0159
 Advance Access Publication 26 August 2010

Survival and Prognostic Factors in Malignant Pleural Mesothelioma: A Retrospective Study of 314 patients in the West Part of Japan

Shuko Nojiri¹, Kenichi Gemba², Keisuke Aoe³, Katsuya Kato⁴, Takahiro Yamaguchi⁵, Tsugumichi Saito⁶, Kiyoshi Kubota^{1*} and Takanori Kishimoto²

International Archives of Occupational and Environmental Health
 April 2004, Volume 77, Issue 3, pp 191-199
 Date: 27 Feb 2004

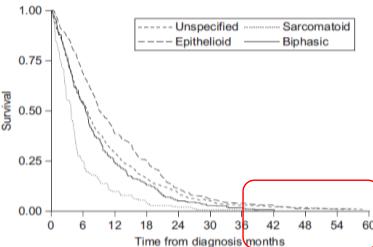
Factors influencing long-term survival in mesothelioma patients—results of the German mesothelioma register

V. Neumann, A. Rüttel, M. Schärnach, K.-M. Müller, M. Fischer

Predicting Survival in Mesothelioma

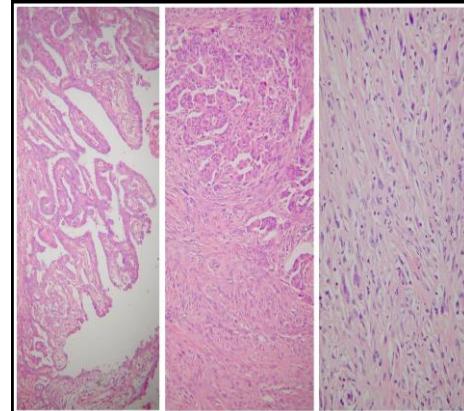
Favourable

- Young Age
- Female Gender
- Low stage
- Performance status
- Pathology – Epithelioid type



WHO - Mesothelial Tumours 4th Ed. 2015

- Diffuse Malignant Mesothelioma
 - Epithelioid mesothelioma
 - Sarcomatoid mesothelioma
 - Desmoplastic mesothelioma
 - Biphasic mesothelioma
- Localised Malignant mesothelioma
 - Epithelioid mesothelioma
 - Sarcomatoid mesothelioma
 - Biphasic mesothelioma
- Well-differentiated papillary mesothelioma
- Adenomatoid tumour

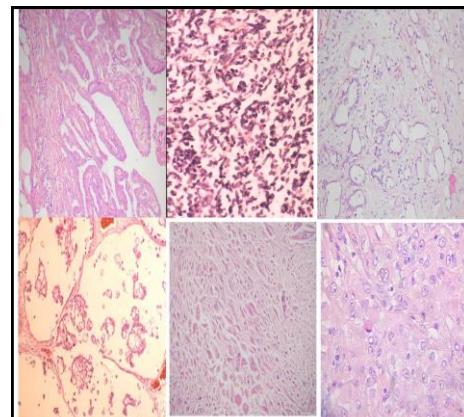


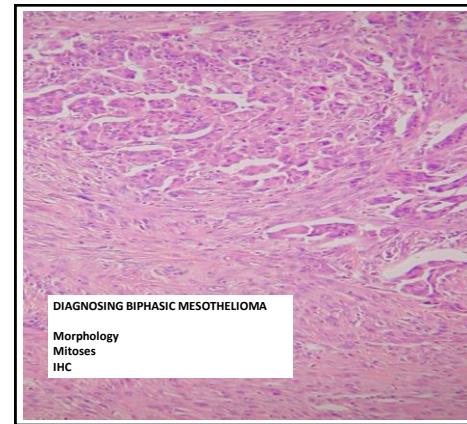
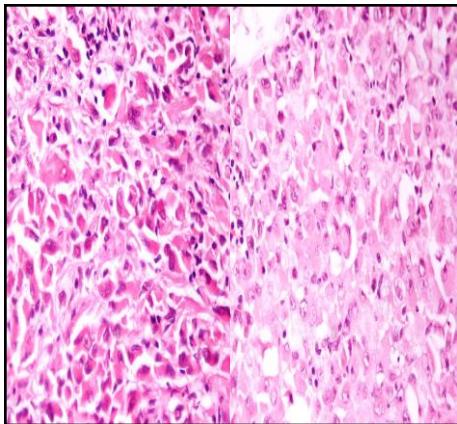
Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

2012 Update of the Consensus Statement from the International Mesothelioma Interest Group

Aliza N. Hasain, MD; Thomas Colby, MD; Nelson Chidgzoy, MD; Thomas Krausz, MD; Richard Attanoos, MB, BS; Mary Beth Becker, MD; Alan C. Bercuck, MD; Kelly Butry, MD; Philip T. Cagle, MD; Lucian R. Chiosea, MD; Andrew Chung, MD; Sanja Dacic, MD; PhD; Armando Frain, MD; Françoise Galateau-Salle, MD; Allen Gibbs, MD; Allen Gown, MD; Samuel Hammer, MD; Leslie Itzky, MD; Alberto M. Marchevsky, MD; Andrew G. Nicholson, DM; Victor Roggli, MD; William D. Travis, MD; Mark Wick, MD

Epithelioid mesothelioma
Tubulopapillary
Micropapillary
Trabecular
Acinar
Adenomatoid
Solid
Clear cell
Decidualoid
Adenoid cystic
Signet ring cell
Small cell
Rhabdoid
Pleiomorphic
Sarcomatoid mesothelioma
Conventional, spindle cell
Desmoplastic
Heterologous differentiation (osteosarcomatous, chondrosarcomatous, etc.)
Lymphohistiocytoid (may also be classified as epithelioid)
Biphasic/mixed





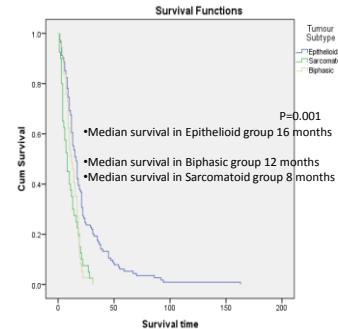
UK Mesothelioma 1967 – 2012

PLEURAL

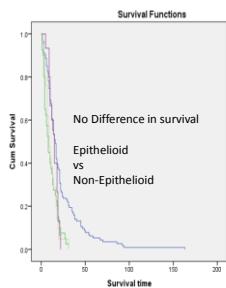
- 191
- 78% MALES
- 59.7% Epithelioid
- 19.4% Biphasic
- 20.9% Sarcomatoid
- 112
- 58% MALES
- 58% Epithelioid
- 31.3% Biphasic
- 10.8% Sarcomatoid

Survival –Mesothelioma subtype
Survival –Biphasics (Predominant pattern)
Survival –Morphology pattern
Survival –Nuclear grade

Pleural-Survival by tumour type

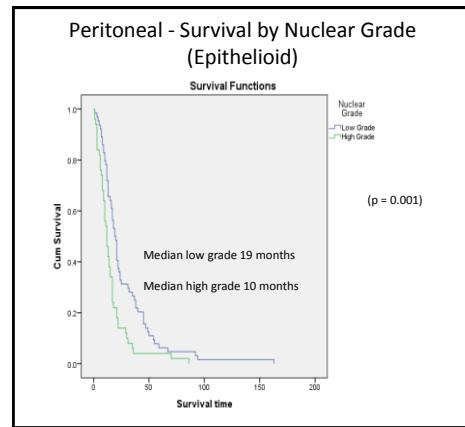
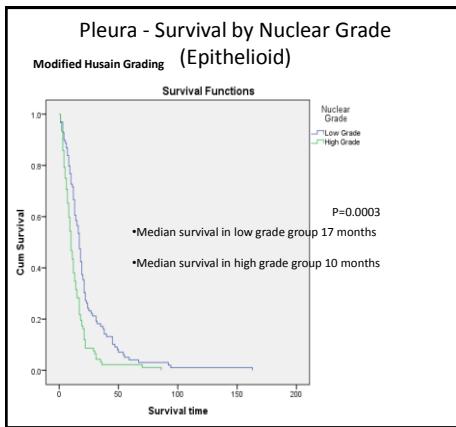
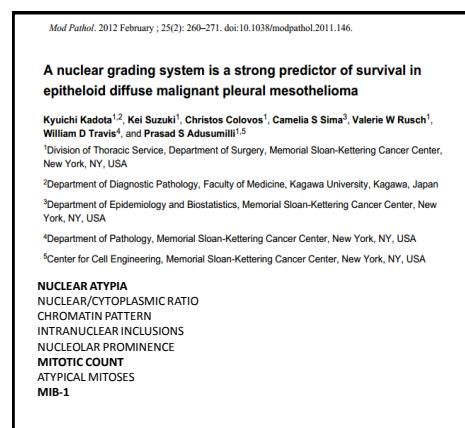
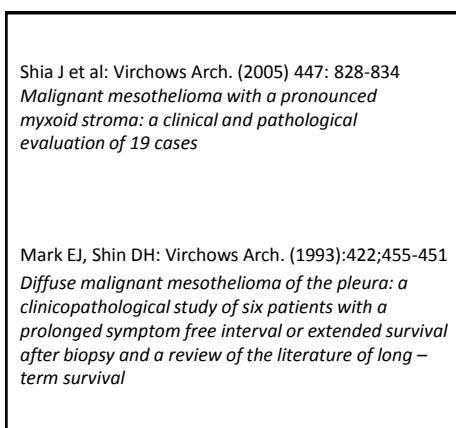
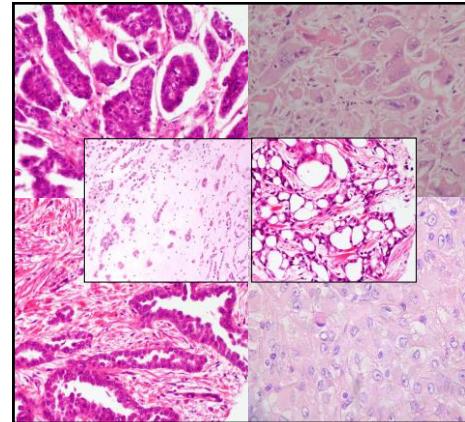
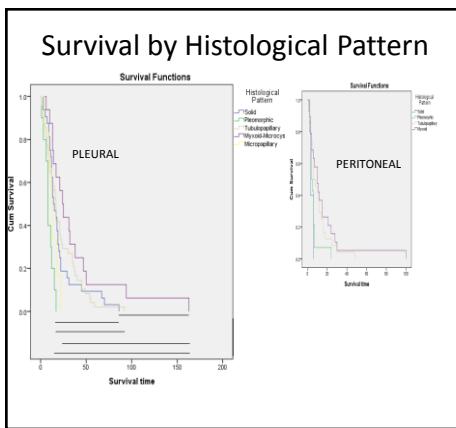


BIPHASIC – EPITHELIOID V SARCOMATOID PREDOMINANT NEOPLASMS



Survival by Histological Pattern

	Myxoid-Microcystic 24 months	Tubulopapillary 17 months	Solid 14 months	Micropapillary 12 months	Pleomorphic 8 months
Myxoid-Microcystic 24 months	-	NS	0.040	0.008	0.000080
Tubulopapillary 17 months	NS	-	NS	NS	0.003
Solid 14 months	0.040	NS	-	NS	0.001
Micropapillary 12 months	0.008	NS		-	NS
Pleomorphic 8 months	0.000080	0.003	0.001	NS	-



Pathological predictors

- **Host Response**

- **Cell membrane molecules**
 - c-MET (Levallet G, Mesopath, 2012)
 - Axl (Pinato DJ, 2013)
 - PDGFR-B – FISH (Tsao AS, 2014)
 - Aquaporin 1 (Kao SC, 2012)
 - CD9 (Amatya VJ, 2013)
 - CD10 (Kadota K, 2015)
 - **Proliferation and cell cycle**
 - MIB-1 index (Kadota K, 2012)
 - p16 deletion (Dacic S, 2008)-FISH

Virchows Arch (2008) 453:627–635
DOI 10.1007/s00428-008-0689-3

Prognostic significance of p16/cdkn2a loss in pleural malignant mesotheliomas

Sanja Dacic · Hannelore Kothmaier · Stephanie Land
Yongli Shuai · Iris Halbwedi · Patrizia Morbini ·
Bruno Murer · Camilla Comin ·
Françoise Galateau-Salle · Funda Demirag ·
Handan Zeren · Richard Attanoos · Alan Gibbs ·
Philip Cagle · Helmut Popper

- Long term (3yrs) - lack of p16 deletion
IHC + FISH

Adverse factor p16 deletion

p16 deletion

Inactivation of tumor suppressor genes

Recent studies showed the usefulness of P16 deletion in separating benign versus malignant lesions

Diagnostic importance of 9p21 homozygous deletion in malignant mesotheliomas

Simone Chiessa¹, Alyssa Krasinskas¹, Philip T Cagle¹, Kisha A Mitchell¹, Dani S Zander¹
and Sanja Djeric¹

²Division of Anatomic Pathology, Department of Pathology, University of Pittsburgh Medical Center.
These authors contributed equally to this work.

Presbyterian University Hospital, Pittsburgh, PA, USA; ^bThe Department of Pathology, The Methodist Hospital, Houston, TX, USA and ^cDepartment of Pathology, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA

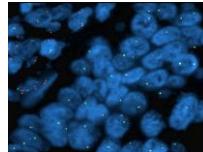
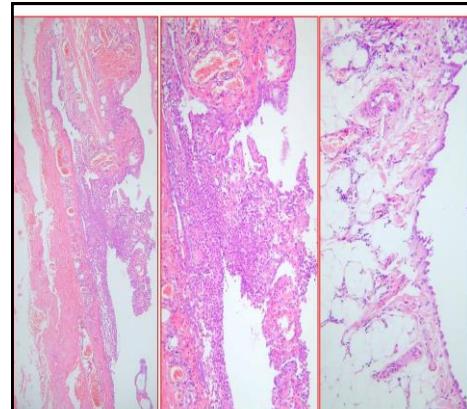
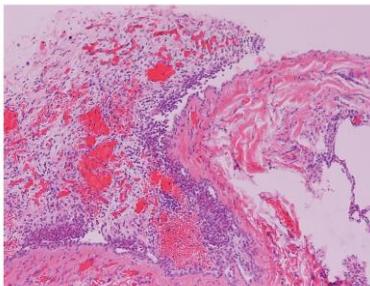


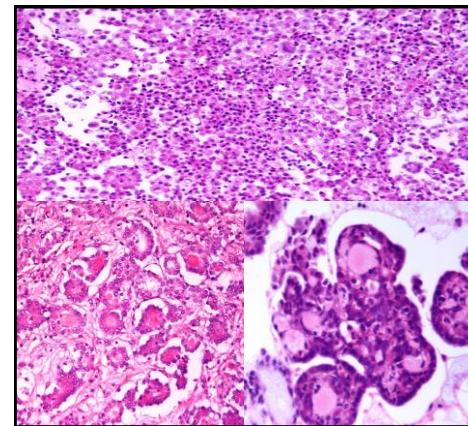
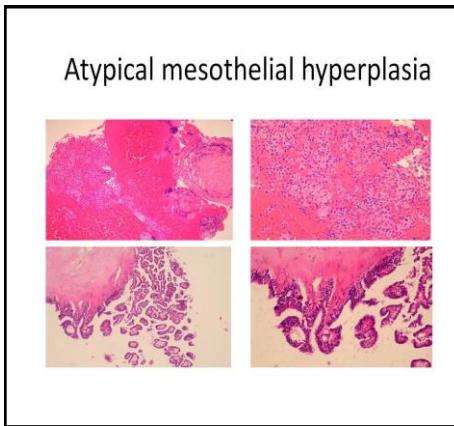
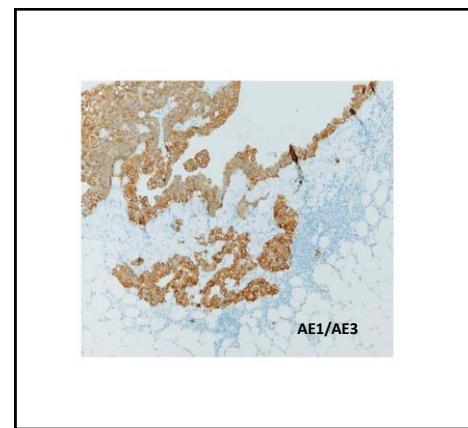
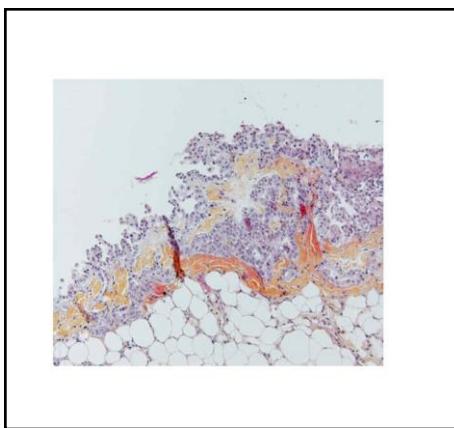
Table 1. Summary of p16 immunohistochemical and FISH analysis		
Study group	Immunohistochemistry (IHC) p16 deletion per site positive (%)	FISH per deletion per site (%)
Florid methotrexate	32/32 (100%)	35/35 (100%)
Foot-and-mouth disease vaccination	6/21 (29%)	5/20 (25%)
Fluracil	34/40 (87%)	0/40 (0%)

Category	IgE	IgE+
PLM	~70%	~68%
PM	~30%	~28%
BM	~90%	~92%

Predicting Malignancy

Benign v Malignant





Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

2012 Update of the Consensus Statement from the International Mesothelioma Interest Group

Aliya N. Hussain, MD; Thomas Colby, MD; Nelson Onderdon, MD; Thomas Krausz, MD; Richard Attanoos, MB, BS; Mary Beth Bradley, MD; Alair C. Burzzich, MD; Kelly Butler, MD; Philip T. Cagle, MD; Lucian R. Chiorescu, MD; Andrew Chang, MD; Sanja Dacic, MD, PhD; Amanda Fraire, MD; Françoise Calataeu-Salle, MD; Allen Gibbs, MD; Allen Gown, MD; Samuel Hammar, MD; Leslie Litzky, MD; Alberto M. Marchevsky, MD; Andrew G. Nicholson, DM; Victor Roggli, MD; William D. Travis, MD; Mark Wick, MD

Review
Am J Clin Pathol 2013;139(2):16
DOI 10.1309/AJCP2012071700001

Received: December 21, 2011
Accepted: January 10, 2012
Published online: March 24, 2012

Guidelines for the Cytopathologic Diagnosis of Epithelioid and Mixed-Type Malignant Mesothelioma

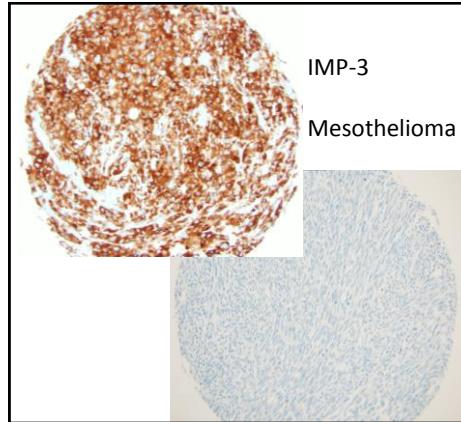
Complementary Statement from the International Mesothelioma Interest Group. Also Endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology

Andrea Hjørne^a; Valeria Ascoli^b; Carlos W.M. Bedrossian^c; Matthilde E. Boon^d; Jenette Creaney^e; Ben Davidson^f; Annika Dejmek^g; Katalin Dobrá^h; Andrea Fassinaⁱ; Andrew Field^j; Pınar Firat^k; Toshiaki Kamei^l; Tadeo Kobayashi^m; Claire W. Michaelⁿ; Sevgen Onder^o; Amanda Segal^p; Philippe Vuille^r

MARKER	AUTHOR	MESOTHELIOMA	REACTIVE
EMA	Wolanski,1998 Cury,1999 Casalots,1999 Roberts,2001 Attanoos,2003	75%	15%
p53	Kafri,1992 Mayall,1992 Ramael,1992 Cagle,1994 Esposito,1997 Casalots,1999 Cury,1999 Roberts,2001 Manganaro,1998 Attanoos,2003	59%	9%
Desmin	Mayall,1992 Hurlmann,1994 Scoone,1993 Attanoos,2003 Garcia-Prats,1998 Gonzalez-Lois,2001	28%	83%

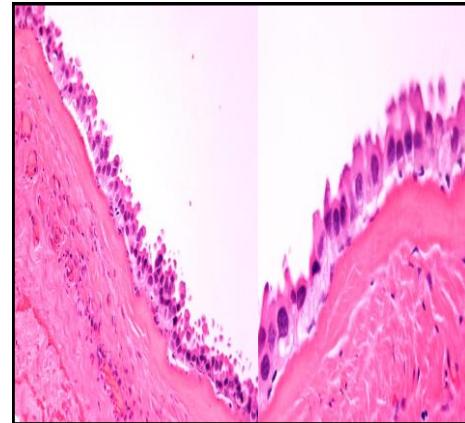
Markers: Reactive v Neoplastic

MARKER	AUTHOR	MESOTHELIOMA	REACTIVE
GLUT-1	Kato,2007	100%	0%
	Hasteh,2010	47%	12%
	Husain 2014	58%	0%
	Lagana 2012	53%	0%
	Wei,2013	81%	14%
	Ucer,2013	80%	7%
	Lee 2013	60%	13%
CD 146	Sato,2010	94%	0%
CD 147	Pinheiro,2012	80%	0%
IMP-3/L5235	Ikeda 2011	36%	5%
	Lee 2013	53%	27%
	Hanley, 2008	91%	0%
	Shi 2011	82%	0%
XIAP	Lyons 2008	80%	11%



Markers: Reactive v Neoplastic

MARKER	AUTHOR	MESOTHELIOMA	REACTIVE
p16 deletion ICC	Chiosea 2008	-	15%
	Takeda 2010	82%	
	Kobayashi 2008	54%	
	Monaco 2011	100%	
	Krasinskas 2010	58%	
p16 deletion FISH	Chung 2010	45%	
	Kobayashi 2008	69% (EPI); 100% (SARC)	
	Takeda 2010	86% (EPI); 67% (SARC)	
	Ille 2003	69% (EPI); 100% (SARC)	
	Krasinskas 2010	32% (EPI); 100% (SARC)	
	Wu 2013	56% (EPI); 100% (SARC)	



p16 FISH Deletion in Surface Epithelial Mesothelial Proliferations Is Predictive of Underlying Invasive Mesothelioma
Hwang, Harry MD*; Tse, Christopher MBBs*; Rodriguez, Stephanie HT, ASCP*; Gown, Allen MD*; Churg, Andrew MD*

American Journal of Surgical Pathology:
May 2014 – Volume 38 – Issue 5 – p681 - 688

- Surface & Deep mesothelial proliferations show same p16 deletions (5/11 pleural +1/7 peritoneal)
- Surface p16 deletions may allow for a diagnosis of mesothelioma in appropriate clinical /radiologic setting
- Absence of p16 deletion *cannot* rule out mesothelioma

BAP1 Immunohistochemistry and p16 FISH to Separate Benign From Malignant Mesothelial Proliferations

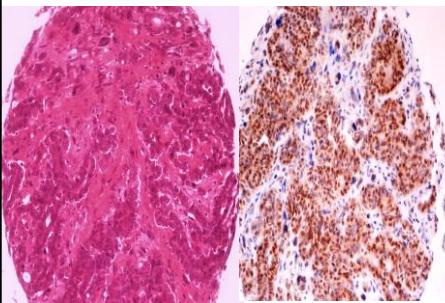
Brandon S. Sheffield, MD,* Harry C. Hwang, MD,† Anna F. Lee, MD,‡
Kim Thompson, HT, ASCP, QIHC,‡ Stephanie Rodriguez, HT, MB, ASCP,‡
Christopher H. Tse, MBBs,‡ Allen M. Gown, MD,‡ and Andrew Churg, MD*

Am J Surg Pathol, 2015 epub ahead of print

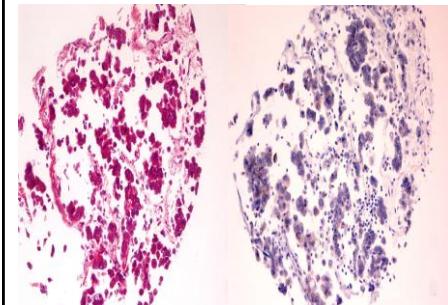
Loss of BAP-1 IHC + p16⁻ FISH – highly specific
Combined - 58% sensitivity - detecting MM
Superior to Glut – 1, IMP-3, EMA and p53

Negative results do not rule out Mesothelioma

Mesothelioma – BAP-1



Mesothelioma Loss of BAP-1
 Mutated Bap-1
 No staining



BAP-1

- Loss of BAP-1 – Germline mutations 20% MM
- BAP-1 – Hereditary mesothelioma
- BAP-1 – *COMMON* syndrome
 - Cutaneous/Ocular Melanoma**
 - Mesothelioma**
 - Other Neoplasms**
- BAP-1 – Good prognostic factor in MM

Conclusion

- Pathological factors- predictive of prognosis
 - Pleura/Peritoneum
 - Epithelioid vs Non-Epithelioid
 - Myxoid /Microcystic rich morphology
 - Nuclear grade
- Pathological factors-predictors of malignancy
 - Invasion
 - P16 deletion by FISH
 - BAP-1 mutation

Guidelines for Pathologic Diagnosis of Malignant Mesothelioma

2012 Update of the Consensus Statement from the International Mesothelioma Interest Group

Alyya N. Hascak, MD; Thomas Colby, MD; Nikolay Ondrejov, MD; Thomas Krausz, MD; Richard Altevogt, MB, BS;
Mary Beth B. Gershenson, MD; Michael J. Koss, MD; Daniel L. Laskin, MD; Daniel L. Laskin, MD;
Andrew Churg, MD; Allen Cates, MD; Mark E. Crowley, MD; Mark E. Crowley, MD; Mark E. Crowley, MD;
Allen Gibbs, MD; Mark J. Holden, MD; Mark J. Holden, MD; Mark J. Holden, MD; Mark J. Holden, MD;

TIME FOR A UNIFIED DOCUMENT?

CYTOLOGIC

Auto Cytopathology 2013;89(2-10): DOI: 10.1002/ACCP.201200274

Received December 22, 2012
Accepted January 10, 2013
Published online March 24, 2013

Guidelines for the Cytopathologic Diagnosis of Epithelioid and Mixed-Type Malignant Mesothelioma

Complementary Statement from the International Mesothelioma Interest Group. Also Endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology

Andrea Hjeloe^a; Valeria Ascoli^b; Carlos W.M. Bedrossian^c; Mathilde E. Boon^d
Jennette Creasman^e; Ben Davidson^f; Annika Dejmek^g; Katalin Dobra^h
Andrea Di Fassinaⁱ; Andrew Field^j; Pinar Firat^k; Toshiaki Kamei^l
Tadeusz Kobylanski^m; Claire W. Michaelⁿ; Sevgen Onder^o; Amanda Segal^p
Philippe Vuille^r

Thank you

Sanja Dacic
Francoise Galateau-Salle
Lucian Chiriac
Cristian Ortiz-Villalon

And
Allen Gibbs, I guess!