Malignant Effusions: Primary versus Metastatic

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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

Objectives

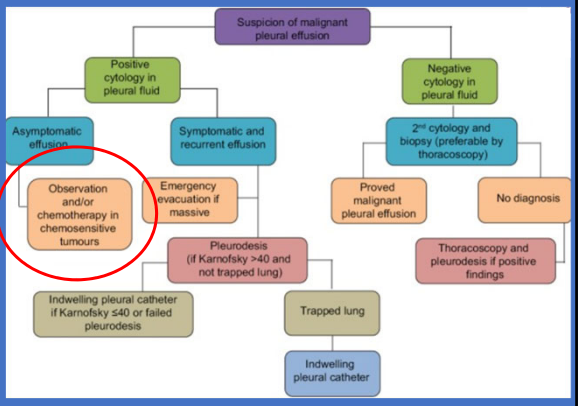
- Review clinical setting and management of serous effusions
- Review the more common metastatic tumors in effusions
- Discuss diagnosis of both common and uncommon metastatic tumors in fluids with comparison to mesothelioma
- Discuss challenges in the cytologic diagnosis of mesothelioma

Clinical Characteristics of Effusions

- Benign diseases are more common causes of effusions (~75%)
  - **Heart failure**
  - **Infection**
  - **Pulmonary embolism**
  - Autoimmune disease/vasculitis
  - Iatrogenic
    - Post-surgical
    - Medicaiton
- Malignant disease
  - Metastatic disease more common
  - Mesothelioma <10%
- Unilateral vs. Bilateral
  - Malignant effusions are more likely to be unilateral (~90%)
  - 18% of bilateral effusions are associated with malignancy

Management of Effusions

- Diagnosis
  - Light criteria
  - Cytology
  - Biopsy
- Management
  - Therapeutic drainage
  - Pleurodesis
  - Treatment of underlying cause
    - Chemotherapy
    - Targeted therapy
    - ICI



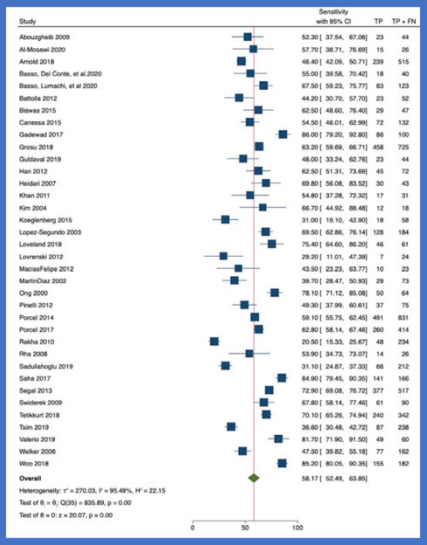
Source: Ferreiro L, Suarez-Antelo J, Valdes, L. *Ann Thorac Med*. 2017;12(1):3-10

Prognosis in Patients With Effusions

- Increased morbidity/mortality even in benign effusions
  - Increased risk of death in inpatients with pneumonia (13.3% at 30 days)
  - 50% 1-year mortality in CHF
  - 46% 1-year mortality in liver failure
- Malignancy
  - Usually recur
    - Guidelines advise against intervention in asymptomatic individuals
  - Indicates advanced disease, with median survival 3-12 months

Historical Accuracy of Effusion Cytology

- Overall sensitivity 58%
  - Varies by tumor type
    - **Mesothelioma (32%)**
    - **Lung adenocarcinoma (84%)**
  - Use of cell blocks and ancillary studies increases sensitivity
- Overall specificity = 97-99%
- Accuracy in tumor typing 94%



Kassirian S, Hinton SN, Cuninghame, et al. *Thorax*. 2022;78(1):32-40.

The International System for Reporting Effusion Cytology

- Developed in 2018 by IAC and ASC to improve diagnostic agreement and accuracy, currently undergoing updates

Category	Examples
I. Nondiagnostic	<50-75 mL, acellular specimen, obscuring elements, poor preservation
II. Negative for malignancy	Adequate, normal elements only
III. Atypia of undetermined significance (AUS)	Insufficient IHC evidence to prove malignancy, lymphocytic effusion without flow, borderline and benign ovarian tumors
IV. Suspicious for malignancy	Insufficient for definitive diagnosis, abundant mucin
V. Malignant	Definitive evidence of malignancy • Divided into primary tumors ("MAL-P") and secondary tumors ("MAL-S")

The International System for Reporting Effusion Cytology

Category	Risk of Malignancy: Pleural Effusions						
	Farahani & Baloch	Zhu et al. 2022	Ahuja & Malviya 2022	Straccia et al. 2022	Jha et al. 2021	Bharti et al. 2022	Pinto et al. 2021
Non-diagnostic	17.4%	40%	0%	18%	87.5%	30.9%	40%
Negative for malignancy	20.7%	29.8%	2.1%	15%	51.61%	12.9%	20.16%
AUS	65.9%	49.3%	33.3%	45.3%	88.23	100%	42.86%
SFM	81.8%	99.3%	94%	93%	87.5%	100%	78.57%
Malignant	98.9%	100%	100%	100%	100%	90.2%	100%

The International System for Reporting Effusion Cytology

Interobserver Agreement

- Highest for negative (76%) and malignant (81%) categories
- Lowest for the suspicious category (22%)
  - 44% of diagnoses varied by two categories

	Size of disagreement			
Category	0 category	1 categories	2 categories	3 categories
2	224/293 (76%)	58/293 (20%)	11/293 (4%)	0
3	30/94 (32%)	61/94 (65%)	3/94 (3%)	0
4	8/36 (22%)	12/36 (33%)	16/36 (44%)	0
5	143/176 (81%)	19/176 (11%)	6/176 (3%)	8/176 (5%)

Comparable to other reporting systems

Body site	Observed agreement	Kappa	Weighted Kappa	Strength of agreement
Breast[8]	68.6%	0.69	0.91	Substantial
Salivary Gland[9]	NR	0.42	NR	Moderate
Lung[10]	49.5%	0.20	NR	Slight
Urine[11]	65%	0.32	NR	Fair
Pancreas[15]	NR	0.45	0.65	Moderate
Pleural fluid	68%	0.51	0.63	Moderate

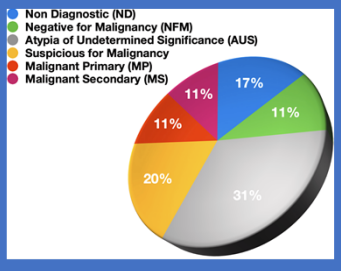
Layfield LJ et al. *Diagn Cytopathol*. 2022;50(1):3-7.

The International System for Reporting Effusion Cytology

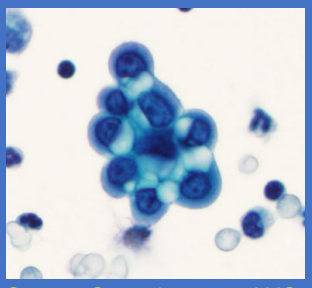
2025 international survey by editors:

- 474 respondents, mostly academic/public health laboratory
- ~60% have adopted the system internationally
  - Most frequently cited reason for not adopting is being unaware of the system/lack of familiarity with the terminology
- ~60% who use the system strictly apply system terminology
  - Users most frequently change criteria for AUS
- Only ~10% respondents use volume as criterion for ND
- Participants want better definition of the AUS and SUS categories

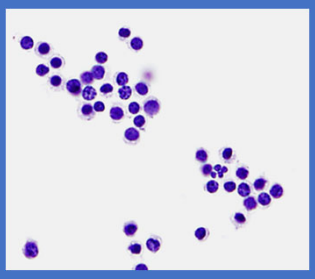
Adoption of TIS for Reporting Effusion Cytology							
	Total	Africa	Australia	Asia	Europe	N. America	S. America
N	471	9	3	277	78	58	46
% Use	61	89	100	62	55	47	72



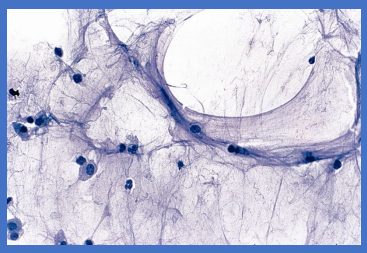
Effusion Cytology Reporting System



Serous Cystadenoma: AUS



Lymphocytic effusion + no flow data: AUS



Pseudomyxoma peritonei: SUS

Pinto D, et al. *J Am Soc Cytopathol.* 2020;9(6):469-77.

Distinction Between Primary and Metastatic Disease

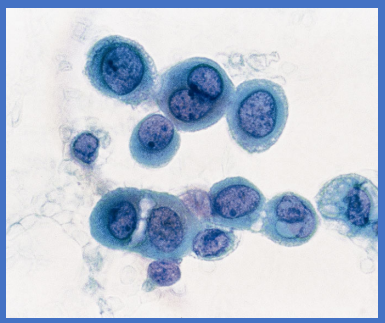
1. Establish malignancy vs. benign disease
2. Differentiate between mesothelioma and metastases
3. If metastatic disease, establish tumor origin
4. If mesothelial, confirm mesothelioma vs. reactive mesothelial proliferations

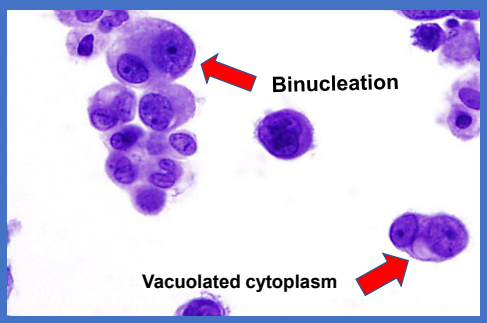
Primary Source in Malignant Effusions

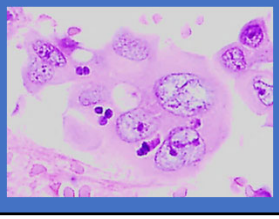
Pleural Effusions		Peritoneal Effusions		Pericardial	
Lung ACA	29-37%	Ovarian ACA	27%	Lung	49-75%
Breast	8-40%*	Gastric	14%	Breast	12-39%±
Ovarian	18-20	Breast	13%	GI tract	6-14%
GI tract	5%	Pancreatic	11%	Hematolymphoid	3%
Lymphoma	3-16%	Colorectal	10%	Ovarian	4-8%
Melanoma	5-6%	Lymphoma	5-12%	Genitourinary	3%
Mesothelioma	1-6%	Melanoma	2%	Melanoma	1%
Sarcoma	1-3%	Mesothelioma	1-8%	Mesothelioma	1%

* Higher figures are in effusions in women only
± Only women in this analysis

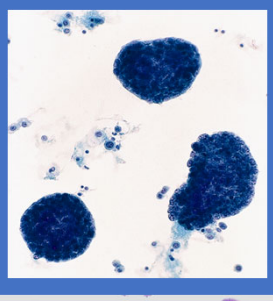
Normal Elements: Mesothelial Cells

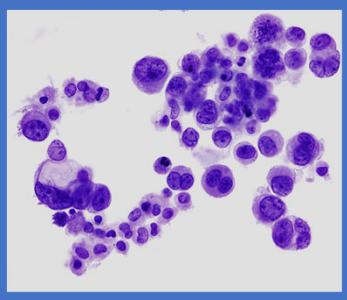






Features of Malignant Effusions





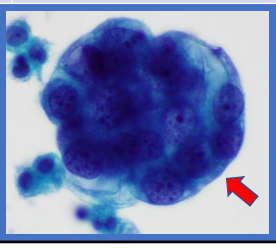
- Increased specimen cellularity
- Morphologically distinct “Second population”
  - May not be apparent in mesothelioma
- Numerous large clusters
  - May be single cells
- +/- cytologic atypia
- Background elements
  - Mucin
  - Psammoma bodies
  - Necrotic debris

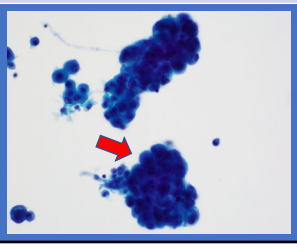
Distinction Between Primary and Metastatic Malignancies

1. Clinical history
   - Prior history of malignancy
   - History of radiation exposure
   - Absence of self-reported asbestos exposure does not exclude risk factors
2. Radiology
   - Parenchymal lesion? Pleural-based lesion?
   - Single lesion vs. multiple pleural-based lesions
     - Localized mesothelioma (one mass) occurs, but is very rare
   - Sites and pattern of metastatic disease
     - Liver, brain, bone, adrenal metastases at presentation are somewhat more common in lung cancer than mesothelioma (~40% vs. 13%)

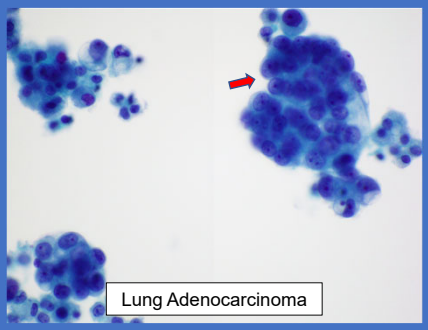
Morphologic Distinction Between Primary and Metastatic Malignancies

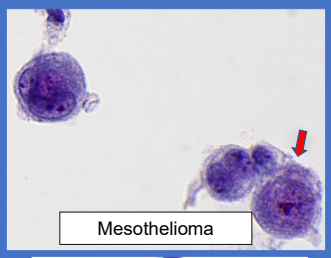
	Adenocarcinoma	Mesothelioma
Clinical History	Smoking history, history of inhaled exposures, family history of lung cancer, radiation exposure	Asbestos exposure, radiation exposure, residence in area with natural fibers (e.g. erionite in the Midwest/West US), radiation exposure, BAP1-Tumor Predisposition syndrome
Radiology	Dominant parenchymal lung mass, multifocal consolidative opacities, spiculated nodule +/- ground-glass component, single mass	Unilateral (usually right) pleural effusion, ascites (peritoneal mesothelioma), recurrent effusions, pleural nodularity/multiple masses; involvement of pleura>peritoneum>pericardium
Morphology	Clusters with smooth borders, vacuolated cytoplasm, +/- high N/C ratio	Large clusters with scalloped borders, "windows," single central nucleolus, low to moderate N/C ratio, comparatively "bland" morphology

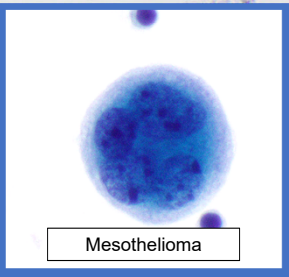


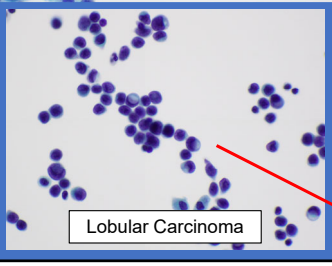


Morphologic Distinction Between Primary and Metastatic Malignancies





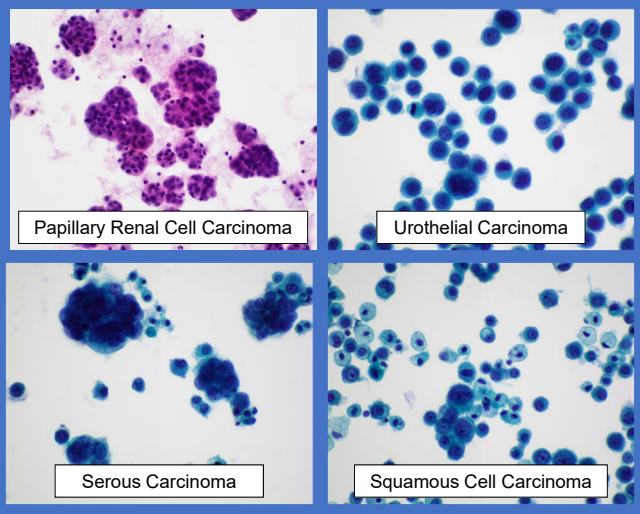




If history of lobular carcinoma, always stain, even if not morphologically detectable

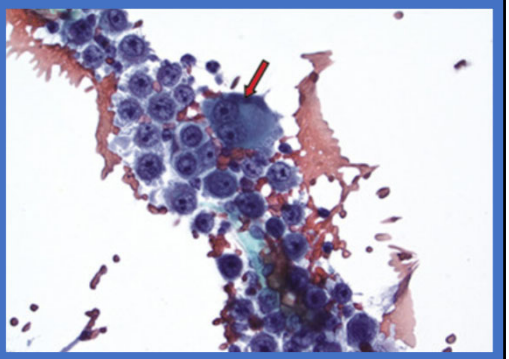
Morphologic Evaluation of Serous Effusions

Morphologic overlap exists between many types of metastatic carcinomas and mesothelioma



Melanoma in Effusions

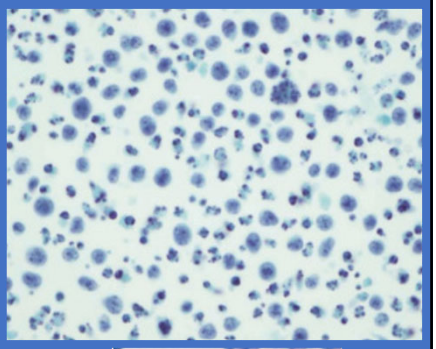
- 1-6% effusions
- Usually single cells, but can be clustered
- Shared features with mesothelioma:
  - Low NC ratio
  - Binucleation
  - Eccentric nuclei
- Melanin in 50-83% of cases
- Can show weak and focal keratin staining in rare cases

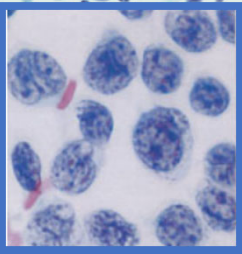


Pantanowitz, Chivukula. *Cytojournal*. 2022;19:15

Lymphoma in Effusions

- 3-16% of effusions
- N/C ratio is typically higher, chromatin coarser than mesothelial proliferation
- Lymphoma in effusions almost always represents involvement by previously-diagnosed disease
- 75% are B-cell lymphomas
- 44-50% are large B-cell lymphomas
  - Cellular samples
  - Often smaller than mesothelial cells
  - Higher N/C ratio than mesothelial cells

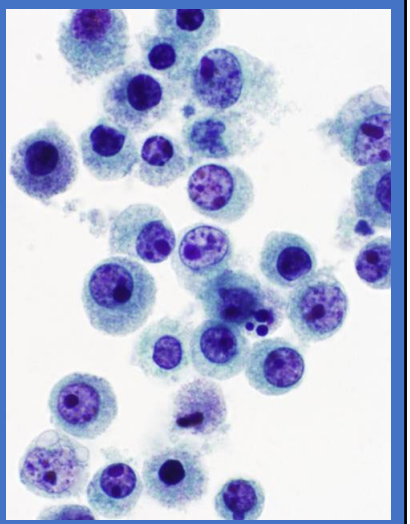




Koh J, et al. *J Pathol Transl Med*. 2022;56(4):173-86.
Das. *Diagn Cytopathol*. 2006;34(5):335-47.

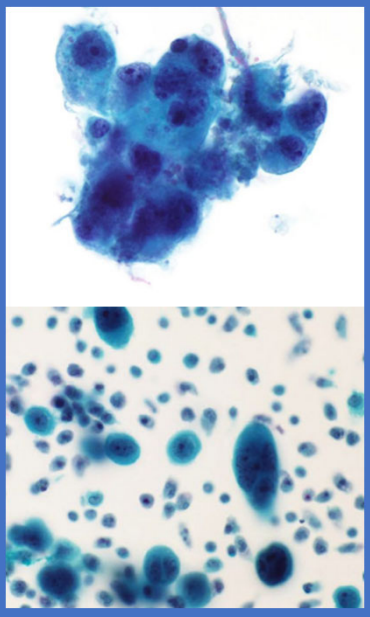
Primary Effusion Lymphoma

- 0.1% effusions
- Immunocompromised patients
- Most (not all) **HHV-8 +**
- B-cell lymphoma
  - **Negative for pan-B markers**
  - LCA, CD138+
  - Clonal Ig gene rearrangements
- Large, dyshesive cells with plasmablastic features
- Ancillary studies (IHC, flow cytometry) required
- Resistant to chemotherapy and fatal within 6 months



Mesothelioma vs. Sarcoma

- 1-6% effusions
- Usually patients have established history
- Cells may be rounded or oval in liquid-based preparations even if spindled on histology
- Can be singly-dispersed cells, multinucleated
  - Ewing sarcoma
  - Vascular tumors (EHE, angiosarcoma)
  - Undifferentiated pleomorphic sarcoma



Adapted from: Chen AL, et al. *Cancer Cytopathol*. 2019;127(12):778-84.

Metastatic Carcinoma vs. Mesothelioma: Immunohistochemistry

Epithelial/Carcinoma Markers			Mesothelioma Markers		
Marker	Sens.	Spec.	Marker	Sens.	Spec.
CEA	63-78%	98%	Calretinin	85-96%	87-100%
BerEP4	74-89%	95-98%	WT-1	78%	62%
MOC31	86-92%	87-97%	D2-40	79%	100%
Claudin-4	91-100%	99-100%	Mesothelin	75%	71%

Recommended: 2 epithelial markers
2 mesothelial markers

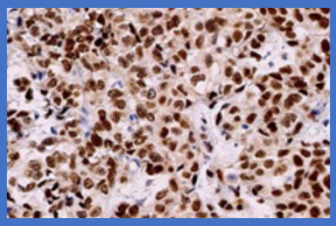
Mesothelioma vs. Metastatic Lung Adenocarcinoma: SOX6 Immunohistochemistry

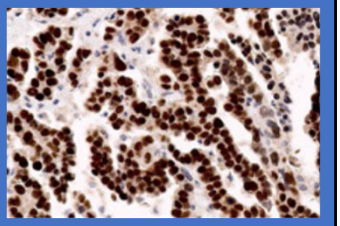
Meso vs. LUAD

98% sensitivity
93% specificity

Epithelioid Mesothelioma (54 Cases)						Lung Adenocarcinoma (69 Cases)					
		Immunohistochemical Score*						Immunohistochemical Score*			
Marker	No. Positive Cases, n (%)	0	1+	2+	3+	Marker	No. Positive Cases, n (%)	0	1+	2+	3+
SOX6	53 (98)	1	0	5	48	SOX6	5 (7)	64	2	3	0
Calretinin	53 (98)	1	4	0	49	Calretinin	15 (22)	54	9	6	0
D2-40	53 (98)	1	2	6	45	D2-40	7 (10)	62	4	3	0
WT1	42 (78)	12	10	3	29	WT1	0	69	0	0	0

*0, negative; 1+, <10%; 2+, 10% to 50%; 3+, <50% of tumor cells with immunoreactivity.

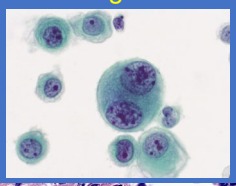


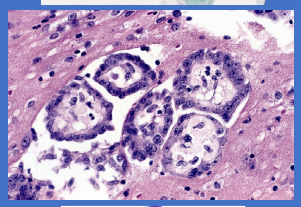


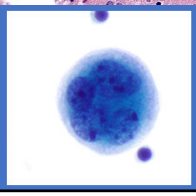
Adapted from: Kambara T, et al. *Am J Surg Pathol*. 2020;44(9):1259-1265.

Malignant Mesothelioma: High Power

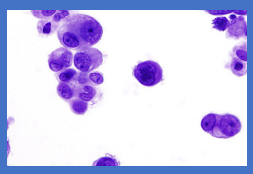
Malignant

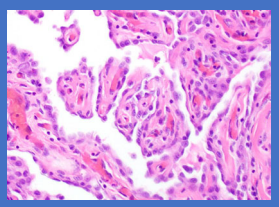


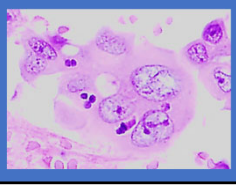




Benign

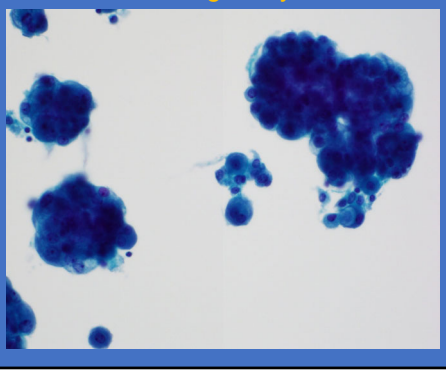






Morphologic Features Favoring Malignant Mesothelioma Over Reactive

- High cellularity
- Numerous large "mulberry" clusters
  - Reactive mesothelial cells do not form large groups
  - Clusters of >20-40 cells are indicative of malignancy
- Marked cytomegaly
- Severe cytologic atypia



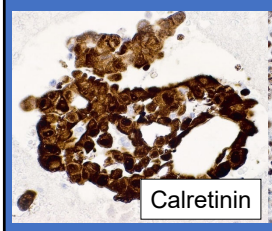
Diagnostic Immunohistochemistry for Malignant Mesothelioma

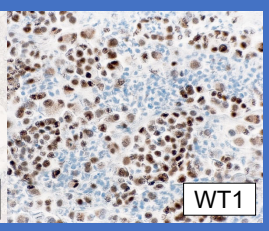
Sensitivity of effusion cytology historically only ~32%

4-stain panel

Keratin	Claudin-4
Calretinin	TTF-1
WT1	MOC31, CEA, etc.
D2-40	Other lineage markers

Only confirms mesothelial differentiation, not malignancy

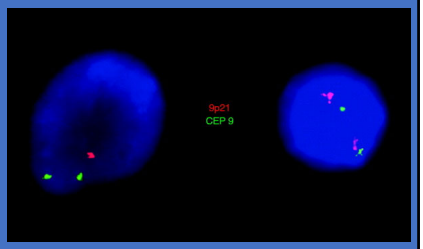




What ancillary studies distinguish between benign and malignant mesothelial cells?

Malignant Mesothelioma: Cytogenetics

- Karyotype characterized by multiple chromosome and arm-level losses
- FISH has sensitivity and specificity, can be performed on FFPE
  - Deletion of 9p21 (CDKN2A)
    - 70% pleural epithelioid mesotheliomas
    - >95% sarcomatoid mesotheliomas
  - Deletion of 22q (NF2)
    - 60% mesotheliomas (epithelioid>sarcomatoid)
  - Deletion 3p21 (BAP1)
    - 20% mesotheliomas
- Homozygous 9p21 deletion has 100% specificity
  - ~35% have homozygous deletion; another 3-35% heterozygous
- However: time-consuming and requires expertise for interpretation



Factor RE et al. Cancer Cytopathol .2009;117(4) 247-53

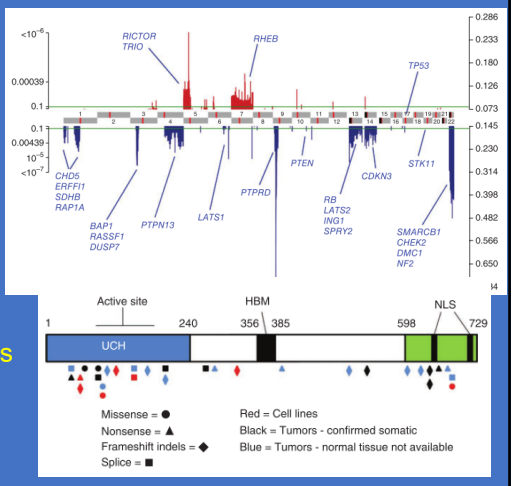
Immunohistochemistry for Distinction Between Benign and Malignant Mesothelial Proliferations

Marker	Reactive %	Mesothelioma %	Sens. (%)	Spec. (%)
Desmin	84-86	0-10	48	97
EMA	4-6	71-100	68-99	74-97
GLUT-1	0-37	40-100	40-99	80-100
P53	0-14	16-86	41-61	91
IMP3	0-27	36-91	36-77	73-100
BAP1	0	57-80	57-67	100
MTAP	0	45	45	100
NF2	0	35-65	35-65	100

- Many markers proposed based on preferential expression
- Either alone or in combination, not proven to reliably distinguish between benign and malignant mesothelial cells
  - Benign mesos may express any of these markers

Immunohistochemistry Surrogates for Genetic Alterations in Mesothelioma

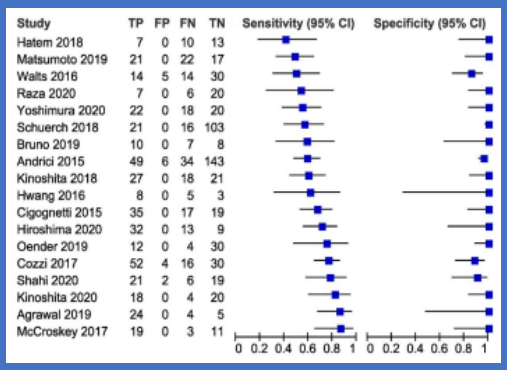
- At least single copy loss of *BAP1* locus at 3p21 in 30%
- 18-63% have mutations or translocations involving *BAP1*
- In total, approximately **60-79%** malignant mesotheliomas have *BAP1* alterations
- Loss of nuclear BAP1 expression reflects underlying *BAP1* alterations



Bott et al. Nat Genet. 2011;43(7):668-72.

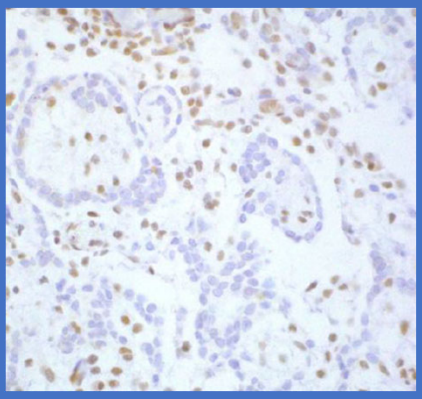
Immunohistochemistry Surrogates for Genetic Alterations in Mesothelioma

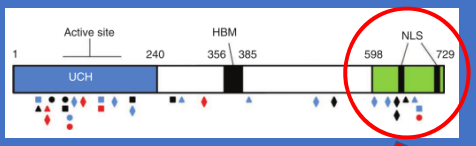
- Up to 70% of mesotheliomas show loss of nuclear BAP1 expression
  - 70% epithelioid mesotheliomas
  - 15-25% sarcomatoid mesotheliomas
- Sensitivity +/-, specificity high
  - Loss of BAP1 is NOT seen in benign mesothelial cells
- Most studies require loss in 100% of tumor cells



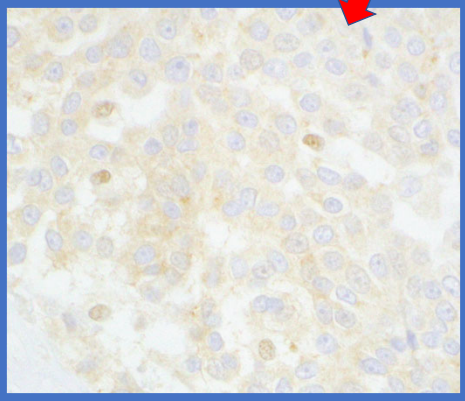
Adapted from Girolami I, et al. Cancer Cytopathol. 2021. doi:10.1002/cncy.22509 [online ahead of print]

BAP1 Immunohistochemistry





Cytoplasmic staining counts!



Diagnostic MTAP Immunohistochemistry

- *CDKN2A* deleted in 60-70% mesotheliomas
  - Sarcomatoid > epithelioid
  - Traditionally queried only by FISH
- *MTAP* gene co-deleted in 75% of cases with *CDKN2A* deletions
- MTAP immunohistochemistry is ~75% sensitive for *MTAP* deletion
- 100% of cases with *MTAP* deletions have *CDKN2A* deletions
- MTAP itself may be a target of therapy

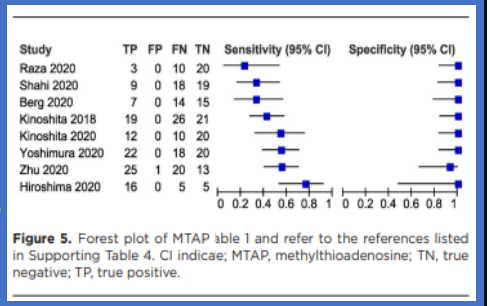
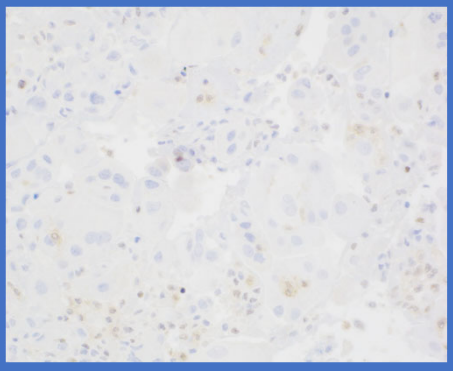


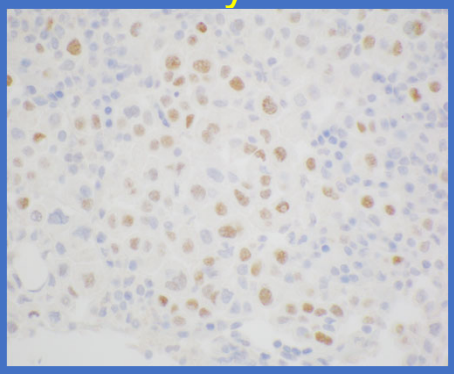
Figure 5. Forest plot of MTAP able 1 and refer to the references listed in Supporting Table 4. CI indicae; MTAP, methylthioadenosine; TN, true negative; TP, true positive.

Adapted from Girolami I, et al. Cancer Cytopathol. 2021;129(7):506-16.

Diagnostic MTAP Immunohistochemistry

Complete loss OR cytoplasmic loss only





Status of nuclear expression not reliable correlate of gene status

BAP1/MTAP Immunohistochemistry for Mesothelioma

	MPM N=45		RMH N=21			
	Positive[a]	Negative[a]	Positive[a]	Negative[a]	Sensitivity, %	Specificity, %
MTAP IHC	19	26	0	21	42.2	100
BAP1 IHC	27	18	0	21	60.0	100
9p21 FISH	28	17	0	21	62.2	100
BAP1/MTAP IHC	35	10	0	21	77.8	100
BAP1 IHC/9p21 FISH	38	7	0	21	84.4	100

Kinoshita Y, et al. Cancer Cytopathol. 2018;126(1):54-63.

TABLE 1. Correlation Between MTAP and BAP1 Immunohistochemistry Results on the Cytology and Surgical Specimens in Cases for Which Paired Specimens Were Available

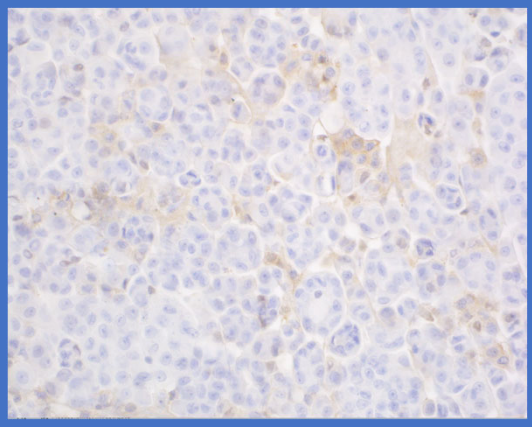
	MTAP			BAP1			
Case No.	Cytology Specimen	Surgical Specimen	Agreement	Cytology Specimen	Surgical Specimen	Agreement	MTAP or BAP1 Loss on Cytology
1	Partial[a]	Intact	Agree[b]	Intact	Intact	Agree	No
2	Lost	Lost	Agree	Lost	Lost	Agree	Yes
3	Partial[a]	Intact	Agree[b]	Lost	Lost	Agree	Yes
4	Partial[a]	Intact	Agree[b]	Lost	Lost	Agree	Yes
5	Lost	Lost	Agree	–	–	–	Yes
6	Intact	Intact	Agree	Intact	Intact	Agree	No
7	Lost	Lost	Agree	Lost	Lost	Agree	Yes
8	Lost	Lost	Agree	Intact	Intact	Agree	Yes
9	Lost	Lost	Agree	Lost	Lost	Agree	Yes
10	Intact	Intact	Agree	Lost	Lost	Agree	Yes
11	Intact	Intact	Agree	Lost	Lost	Agree	Yes
12	Intact	Intact	Agree	Lost	Lost	Agree	Yes
13	Intact	Intact	Agree	Lost	Lost	Agree	Yes
14	Lost	Lost	Agree	Lost	Lost	Agree	Yes
15	Intact	–	–	Intact	–	–	No
16	Intact	–	–	Intact	–	–	No
17	Intact	–	–	Intact	–	–	No
18	Intact	–	–	–	–	–	No
19	Intact	–	–	Lost	–	–	Yes
20	Intact	–	–	Lost	–	–	Yes
21	Lost	–	–	Lost	–	–	Yes
Total	33%	43%	100%	63%	77%	100%	71%

Abbreviations: BAP1, BRCA-associated protein 1; MTAP, methylthioadenosine phosphorylase.
[a]Case 1 demonstrated 80% intact MTAP staining and cases 2 and 3 demonstrated 40% intact MTAP staining.
[b]Threshold for loss was set at 25% staining.

Kinoshita Y, et al. Cancer Cytopathol. 2018;126(1):54-63.

Diagnostic NF2 Immunohistochemistry

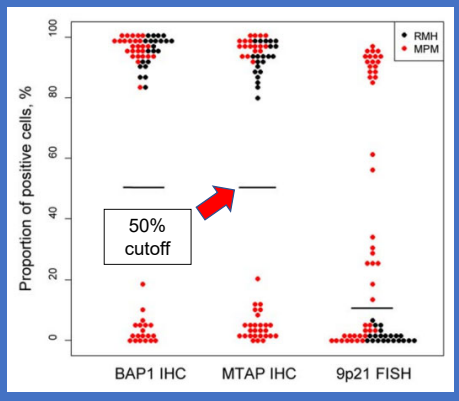
- *NF2* mutations or deletions in 60% mesotheliomas
  - Sarcomatoid>epithelioid
- NF2/Merlin loss in 77% tumors with underlying *NF2* alterations
  - 96% in cases with homozygous deletion, structural variants or mutations
- IHC: loss of membranous/cytoplasmic staining



Diagnostic MTAP Immunohistochemistry

No established standard threshold (number of cells) to confirm malignancy

- Kinoshita et al. propose a 50% cutoff due to bimodal distribution of staining
- Berg et al. suggest using a 75% cutoff based on cutoff in surgical specimens



Kinoshita Y, et al. Cancer Cytopathol. 2018;126(1):54-63.

Heterogeneous Loss of Marker Expression

Tumors can show heterogeneous MTAP expression/subclonal loss

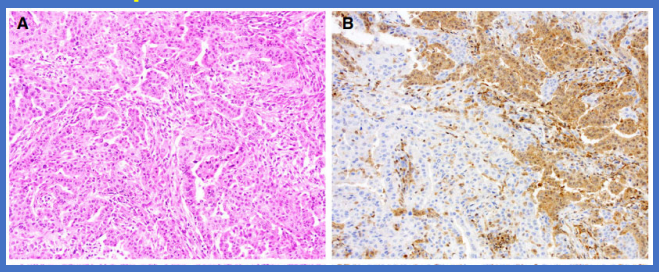


Table 6. *MTAP* and *CDKN2A* copy numbers and MTAP immunohistochemistry findings in nine mesotheliomas with heterogeneous MTAP expression

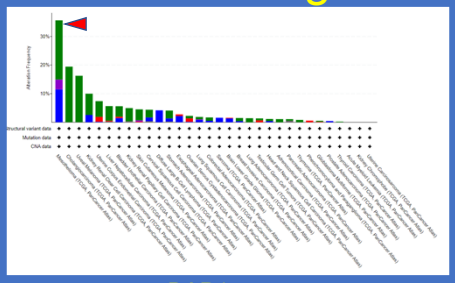
				MTAP immunostaining pattern		
Case	Histotype	*MTAP* copy number	*CDKN2A* copy number	Epithelioid component	Sarcomatoid component	Spatial distribution of foci with MTAP loss and retention
6	Biphasic	1D	2D	Loss in 30% of cells	Loss in 30% of cells	Admixed
8	Epithelioid	1D	2D	Loss in 10% of cells	NA	Admixed
15	Biphasic	1D	1D	Loss in 50% of cells	Loss in 100% of cells	Admixed
16	Epithelioid	1D	1D	Loss in 80% of cells	NA	Spatially discrete
24	Epithelioid	Neutral	1D	Loss in 50% of cells	NA	Spatially discrete
26	Biphasic	Neutral	1D	Loss in 5% of cells	Loss in 100% of cells	Spatially discrete
30	Biphasic	Neutral	Neutral	Loss in 5% of cells	Not stained	Spatially discrete
33	Epithelioid	Neutral	Neutral	Loss in 5% of cells	NA	Spatially discrete
39	Epithelioid	Neutral	Neutral	Loss in 1% of cells	NA	Admixed

1D, Single-copy (heterozygous) deletion; 2D, Two-copy (homozygous) gene deletion; MTAP, Methylthioadenosine phosphorylase; NA, Not applicable; Neutral, NO copy number alteration detected.

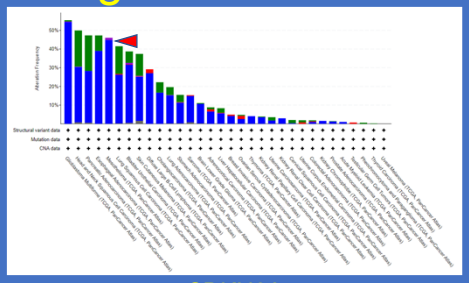
Loss in as few as 5% of cells can be seen in tumors with genetic alterations

Chapel D, et al. Histopathology. 2021;78(7):1032-42.

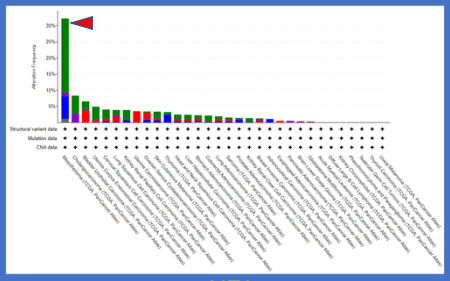
BAP1, CDKN2A, and NF2 Mutations Among Solid Malignancies



BAP1



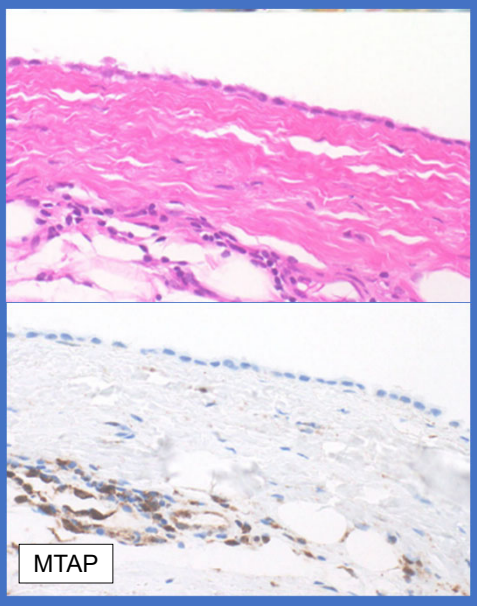
CDKN2A



NF2

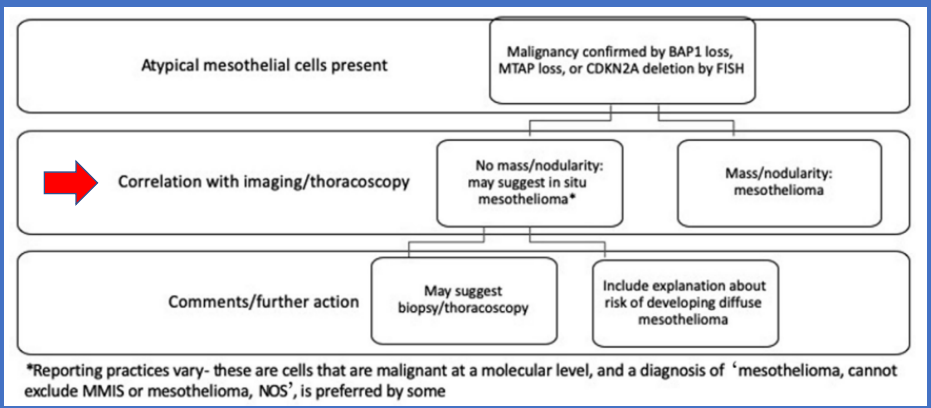
Mesothelioma In-Situ

- Pre-invasive lesion
- Entire specimen submitted
- Evidence of oncogenic genetic abnormalities
- Absence of radiologic evidence for disease



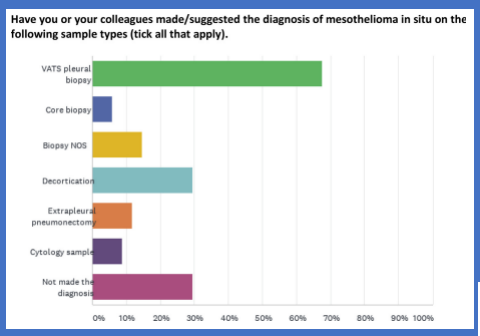
Adapted from: Michael CW, et al. *Diagn Cytopathol*. 2023;51(6):374-88.

Mesothelioma In-Situ in Cytology Specimens?



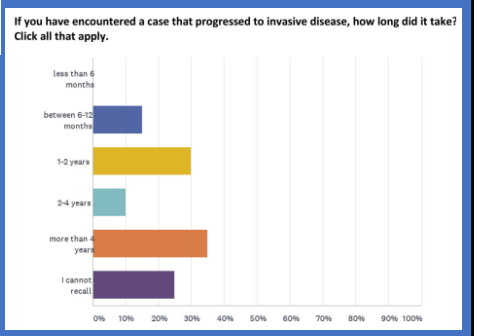
Klebe S, et al. Cancer Cytopathol. Pathology. 2021;53(4):446-53.

Mesothelioma In-Situ



Survey of 34 (heavily selected) thoracic pathologists: ~70% have made the diagnosis

Some evidence that some cases progress to invasive disease



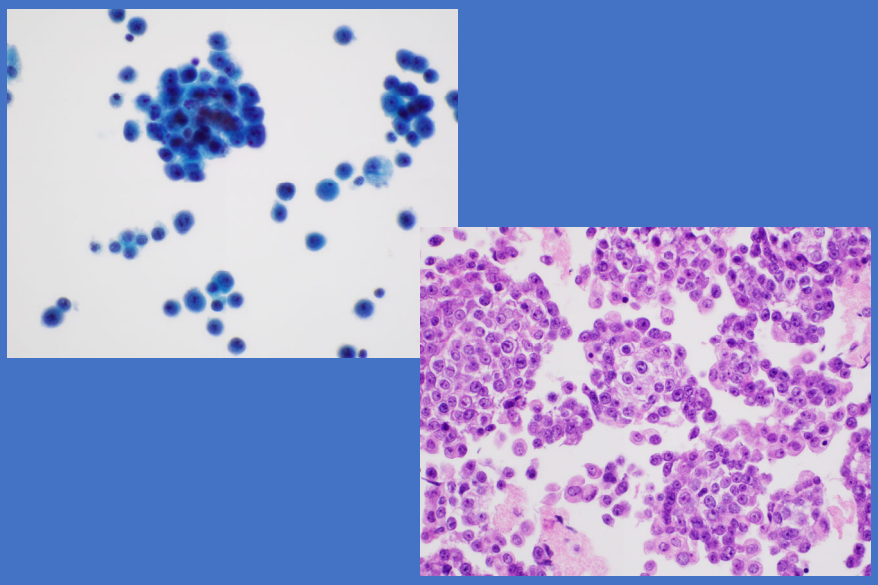
Klebe S, et al. Cancer Cytopathol. Pathology. 2021;53(4):446-53.

Is it possible to make a definitive diagnosis of malignant mesothelioma on effusion cytology?

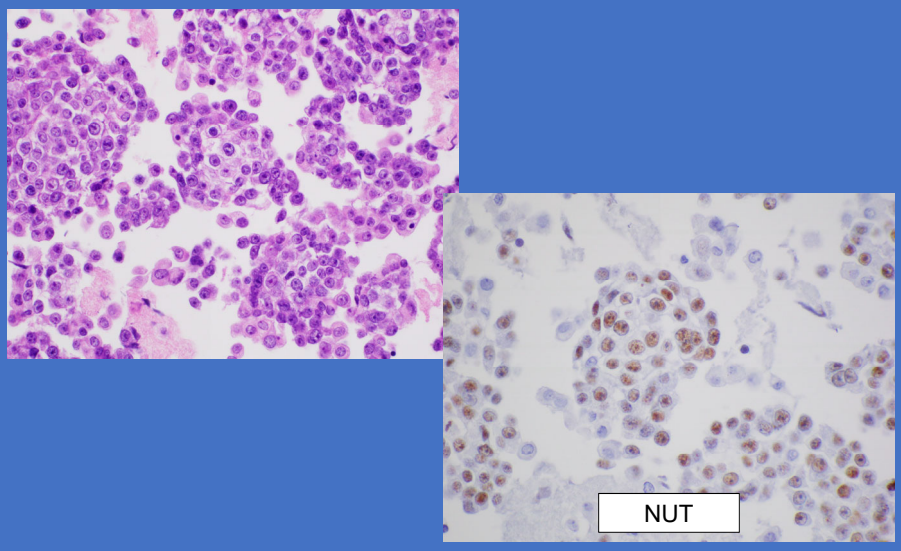
Yes, if:

- Appropriate clinical and radiologic context, and:
  - Numerous large groups of cells with proven mesothelial differentiation (IHC)
  - Presence of one or more of the following:
    - FISH (9p, 22q) shows typical chromosomal deletions
    - Nuclear BAP1 loss by immunohistochemistry
    - Cytoplasmic MTAP loss by immunohistochemistry
    - Loss of Merlin expression by immunohistochemistry
- Without all supporting evidence, can interpret as"Suspicious for malignant mesothelioma"
  - Prompts **pleural biopsy** or planned **pleurectomy/decortication with frozen section**
  - If surrogate markers show loss of expression, can raise possibility of MIS/low-volume disease

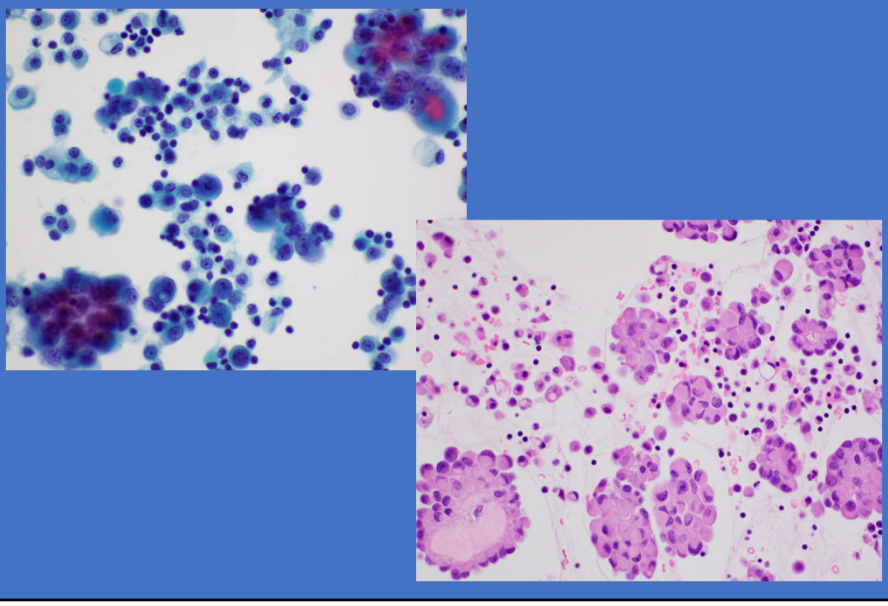
Mesothelioma?



NUT Carcinoma



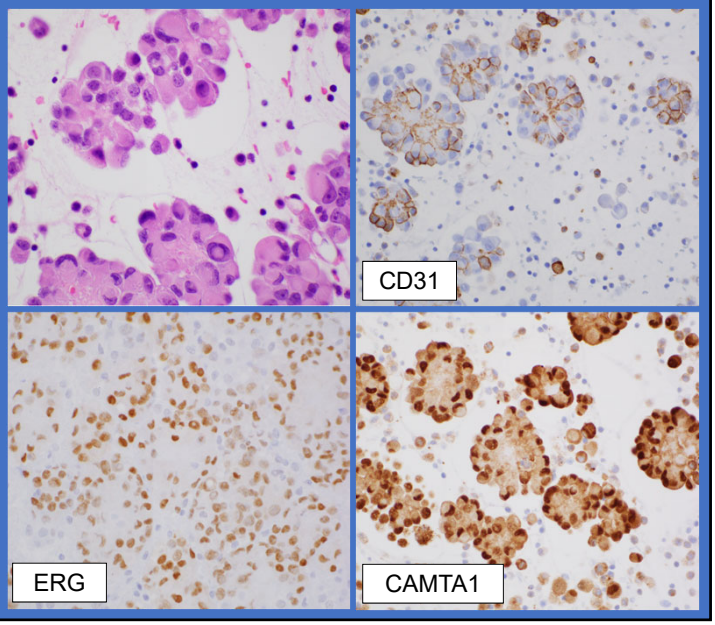
Mesothelioma?



Epithelioid Hemangioendothelioma

90% WWTR-CAMTA1

<5% YAP1-TFE3



Malignant Effusions: Summary

- Current reporting system
  - ROM for each category is variable between studies
  - Interobserver agreement is greatest for negative and malignant categories
  - AUS and SUS categories most challenging to practitioners
- Most malignant effusions represent metastatic adenocarcinoma
  - Significant overlap in morphology between mesothelioma and metastatic lesions
  - Carcinoma > lymphoma > melanoma > sarcoma, mesothelioma
  - Take morphologic and immunophenotypic findings in clinical/radiologic context
- Judicious use of ancillary testing clarifies most diagnostic issues
  - IHC panel of 4 stains suggested
  - Cytogenetics, molecular testing, flow cytometry in select circumstances
- Diagnosis of mesothelioma vs. reactive mesothelial proliferation
  - Requires appropriate clinical and radiographic context
  - Confirm mesothelial differentiation and exclude metastasis
  - Immunohistochemical surrogates for genetic alterations facilitate diagnosis
    - BAP1
    - MTAP
    - NF2
- Consider mesothelioma in-situ/low-volume disease if convincing evidence in effusion but no radiologic correlate
  - Lag time to development of mesothelioma and treatment implications need further study

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