Assessing the lung and mediastinum in cancer-is tissue the issue?

- George Santis

Optimal management of Cancer

- Histological diagnosis & accurate staging at presentation
- Molecular analysis of primary tumour and increasingly, of recurrent/progressive disease
- Correct diagnosis of recurrent or metastatic disease

Pulmonary involvement in extrathoracic cancers

- Lung nodule/s
- Mediastinal lymphadenopathy
- Pleural effusions

Pulmonary metastases in Urological Cancers

Primary tumour	Frequency of lung metastases (%)	Frequency at autopsy (%)
Testis	12	70-80
Kidney	20	50-75
Bladder	7	25-30
Prostate	5	15-50

What is the alternative to tissue?

PET-CT in cancer diagnosis and staging

- FDG taken up in conditions with increased glucose metabolism
- Not dependent on size or shape of lymph nodes/mass
- High uptake occurs in cancer

FDG-PET IN THE ASSESSMENT OF ISOLATED PULMONARY NODULES

SUV > 2.5

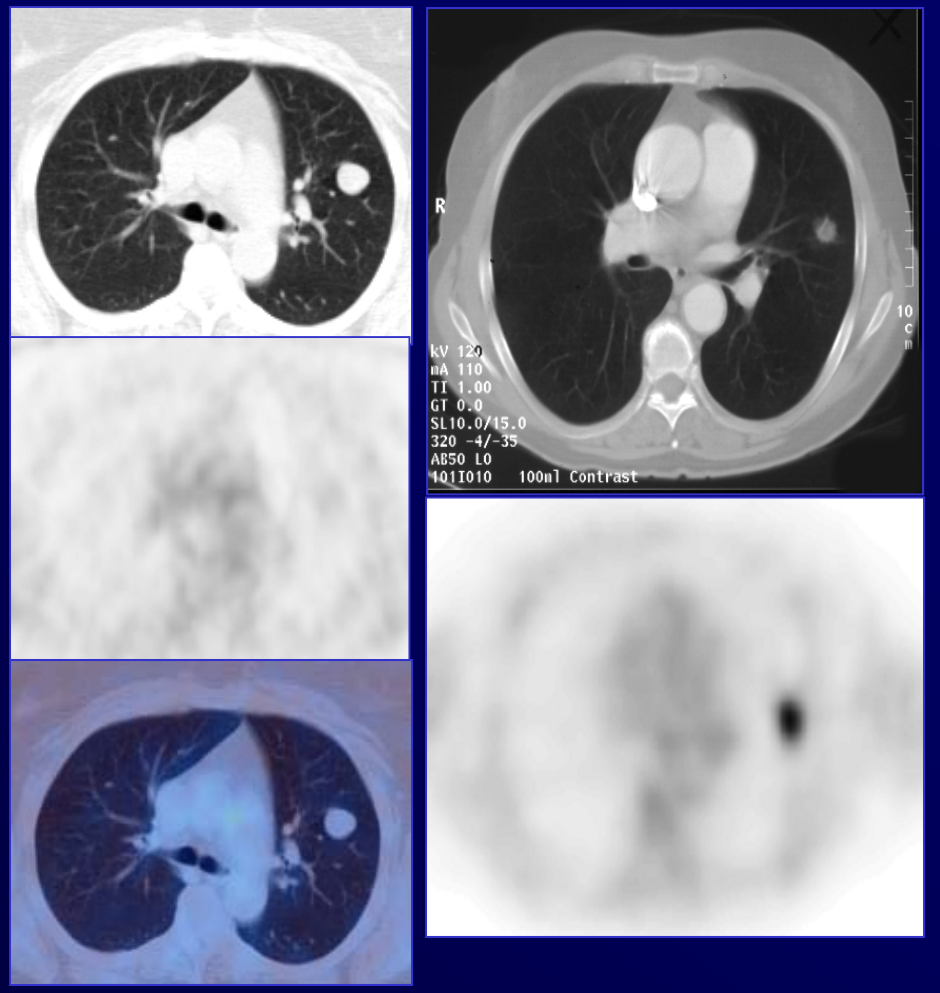
Sensitivity 94%

Specificity 71%

Accuracy 86%

PPV 90%

NPV 85%



Any visual uptake probability of malignancy 60%

Pulmonary Nodules-False Positive PET-CT

False positives

Granulomas

Abscess

Sarcoid

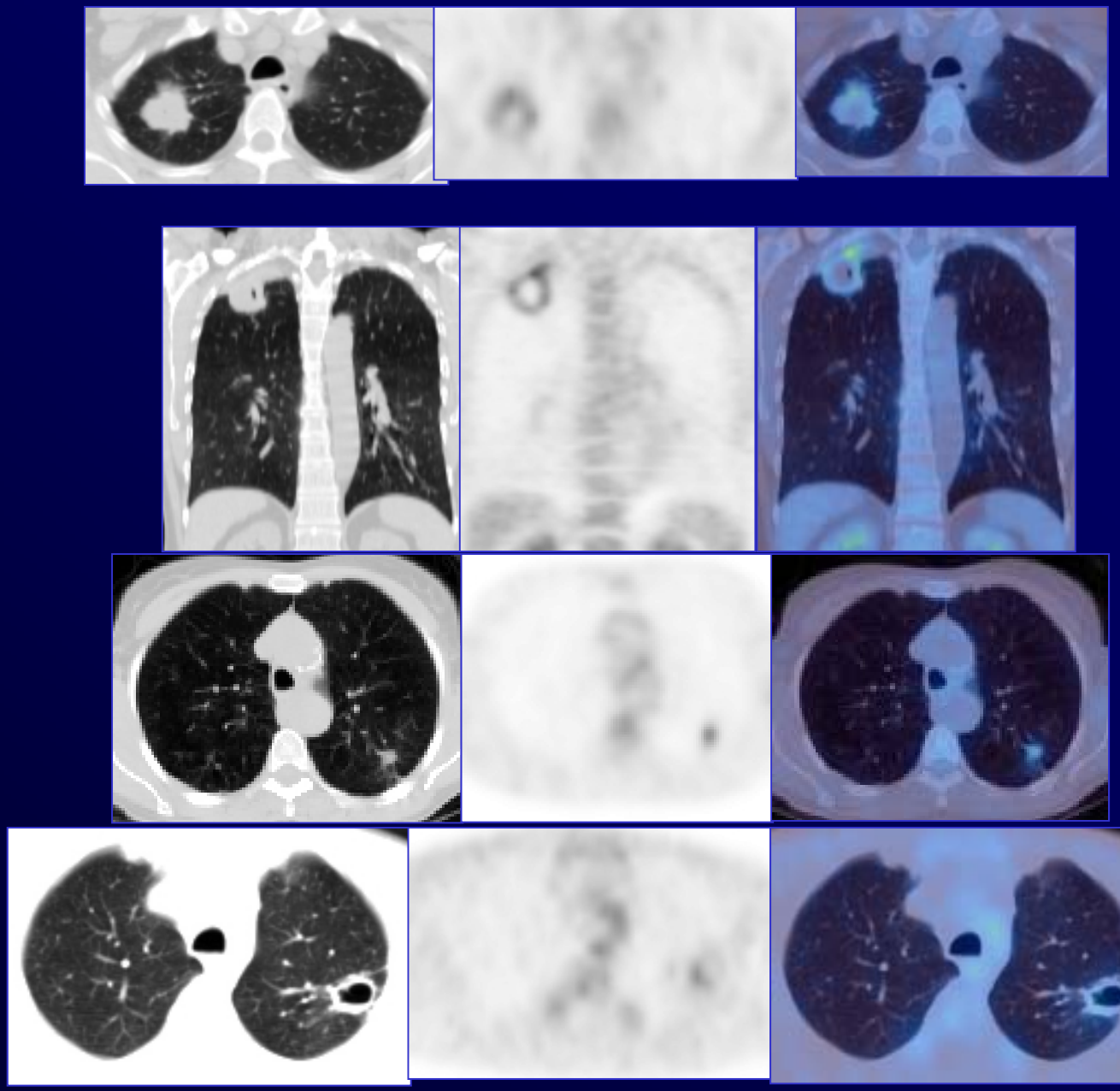
Amyloid

Wegener's

Rheumatoid

Histoplasmosis

Aspergillosis



N Stage - accuracy

Author	No:	CT	PET	PET/CT
Cerfolio 2003	400	68%	76%	
Cerfolio 2004	129		56%	78%
Malek 2008	170	78%	74%	
Yang 2008	122	70%		85%
de wever 2007	50	60%	70%	80%

Nodal Stage

Patients	Sens %	Spec %	PPV %	NPV %	Prev-alence %
CT n = 3438	57	82	56	83	28
PET n = 1045	84	89	79	93	32

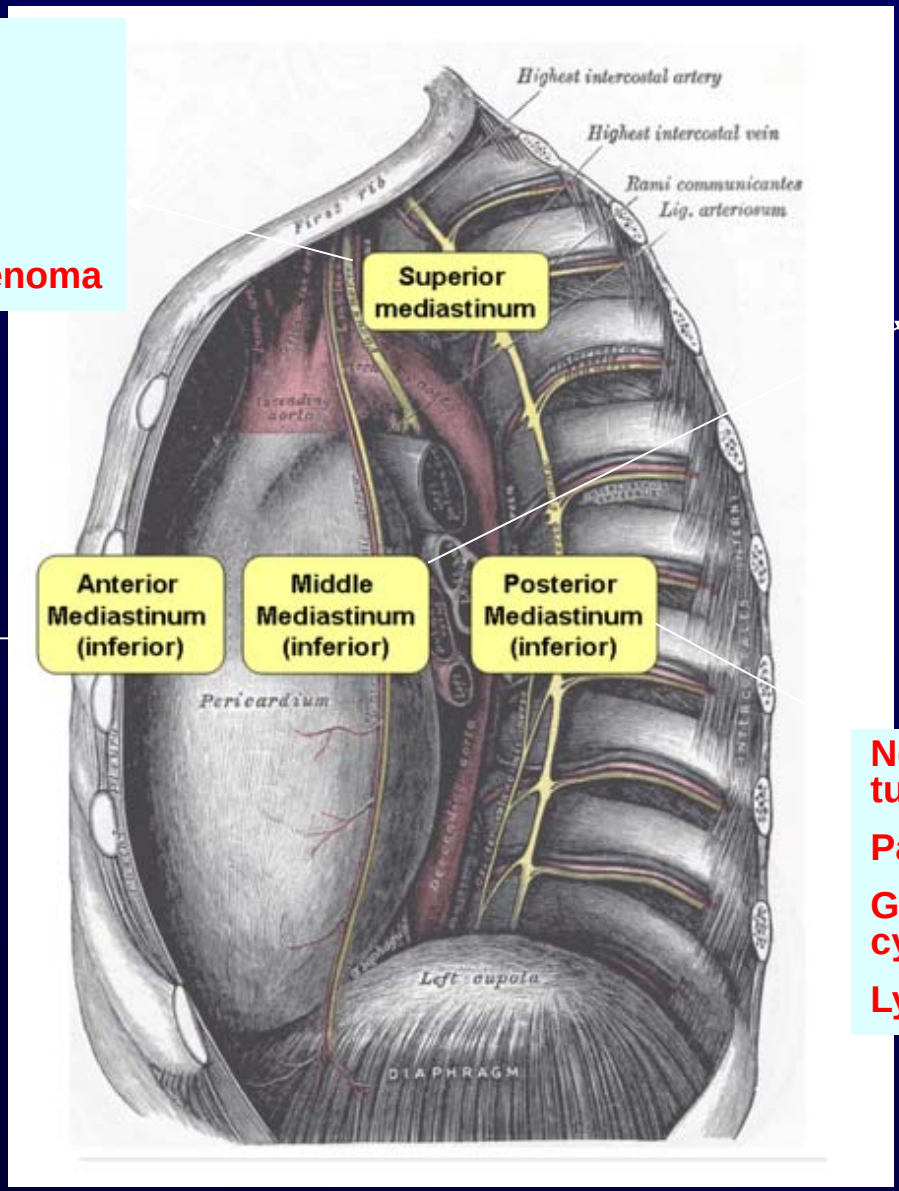
Toloza et al Chest 2003

Sampling pulmonary nodules for pathological diagnosis-what are the options?

- Ultrasound or CT-guided transthoracic biopsy/FNA
- Bronchoscopy and endobronchial radial probe + FNA
- Surgery

Localization of pathology

Thymoma
Thymic cysts
Lymphoma
Thyroid lesions
Parathyroid adenoma



Pericardial cyst
Bronchial cyst
Lymphoma

Thymoma
Thymic cysts
Germ cell tumours
Thyroid & parathyroid lesions
Lymphoma
Paraganglioma
Soft tissue tumours

Neurogenic tumours
Paraganglioma
Gastroenteric cysts
Lymphoma

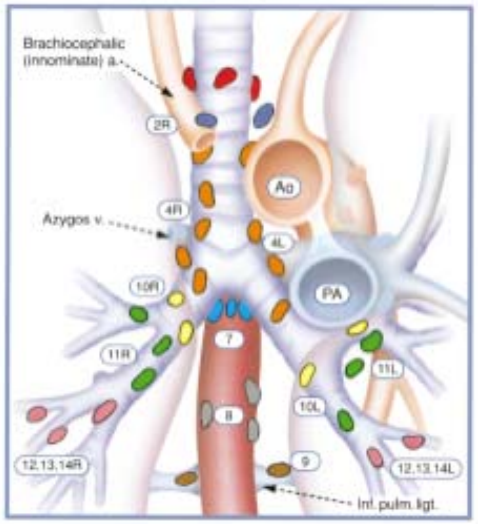
Pathological diagnosis of abnormal mediastinum

Mediastinoscopy is the gold standard, or is it??

Endobronchial Ultrasound (EBUS)

- Ultrasonic ‘hybrid’ bronchoscope with linear scanning ultrasound capability
- Dedicated aspiration needle with echogenic tip
- Balloon Port
- Doppler

EBUS at KHP



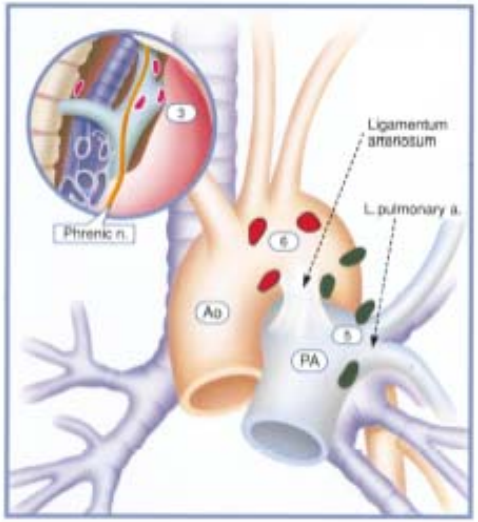
Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N_1 = single digit, ipsilateral
N_2 = single digit, contralateral or supraclavicular

Aortic Nodes

- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)



Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N_1 Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

(Mountain/Dresler modifications from Naruke/ATS-LCSG Map)

TABLE 3
Procedures Used to Sample Lymph Nodes, by Lymph Node Level

Lymph node level	Mediastinoscopy	Thoracotomy	Chamberlain/VATS	Esophageal sonography
2L, 2R	✓	✓		
4L, 4R	✓	✓		✓
5, 6		✓	✓	✓
7	✓	✓		✓
8, 9		✓		✓
10L, 10R		✓	✓	
11–14		✓		

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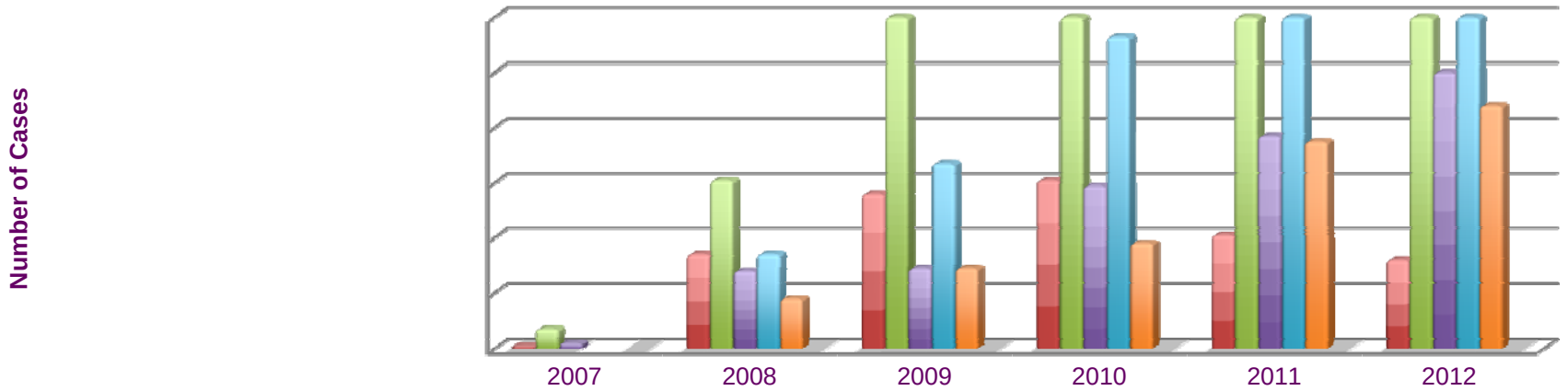
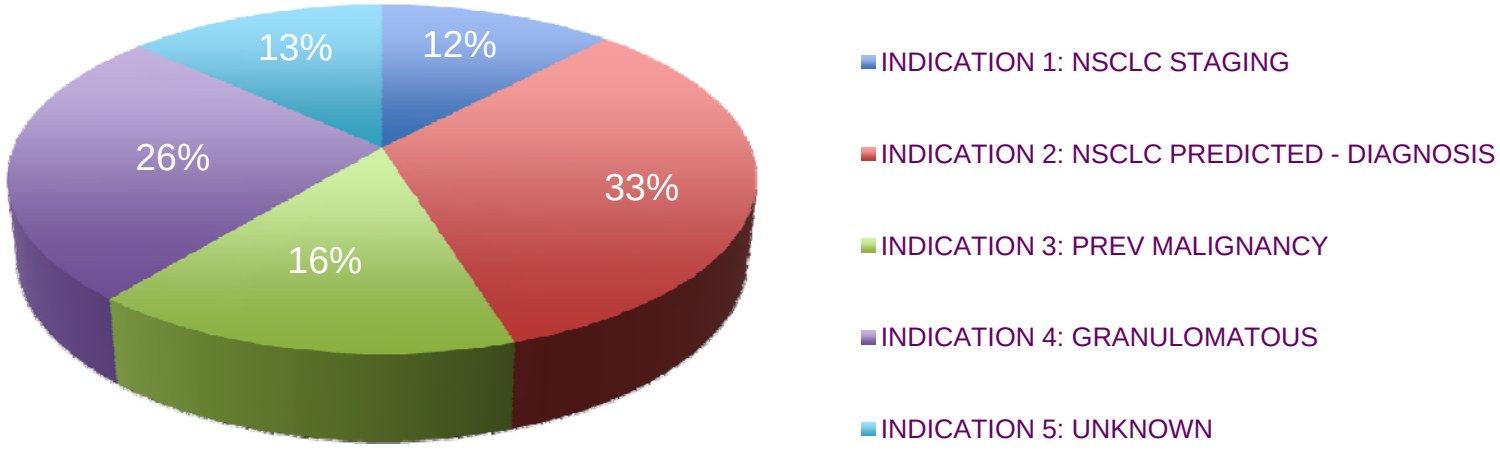
Bunyarovich T et al JNM 2006

Indication for referral / year

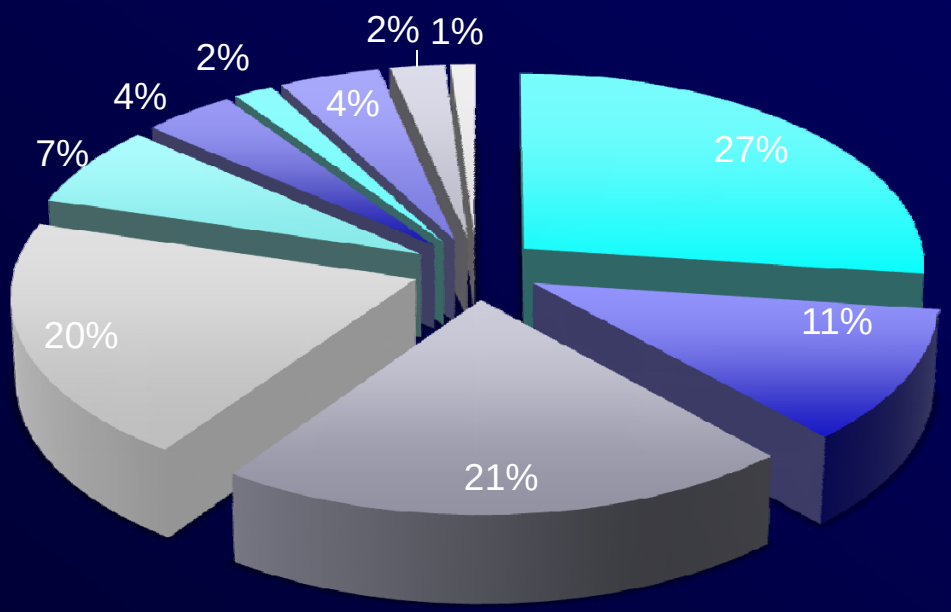


	2007	2008	2009	2010	2011	2012
INDICATION 1: NSCLC STAGING	1	34	56	61	41	32
INDICATION 2: NSCLC PREDICTED - DIAGNOSIS	7	61	132	130	134	156
INDICATION 3: PREV MALIGNANCY	2	28	29	59	77	100
INDICATION 4: GRANULOMATOUS		34	67	113	129	139
INDICATION 5: UNKNOWN		18	29	38	75	88
GRAND TOTAL	10	175	313	401	456	515

EBUS Referrals (2008-12)

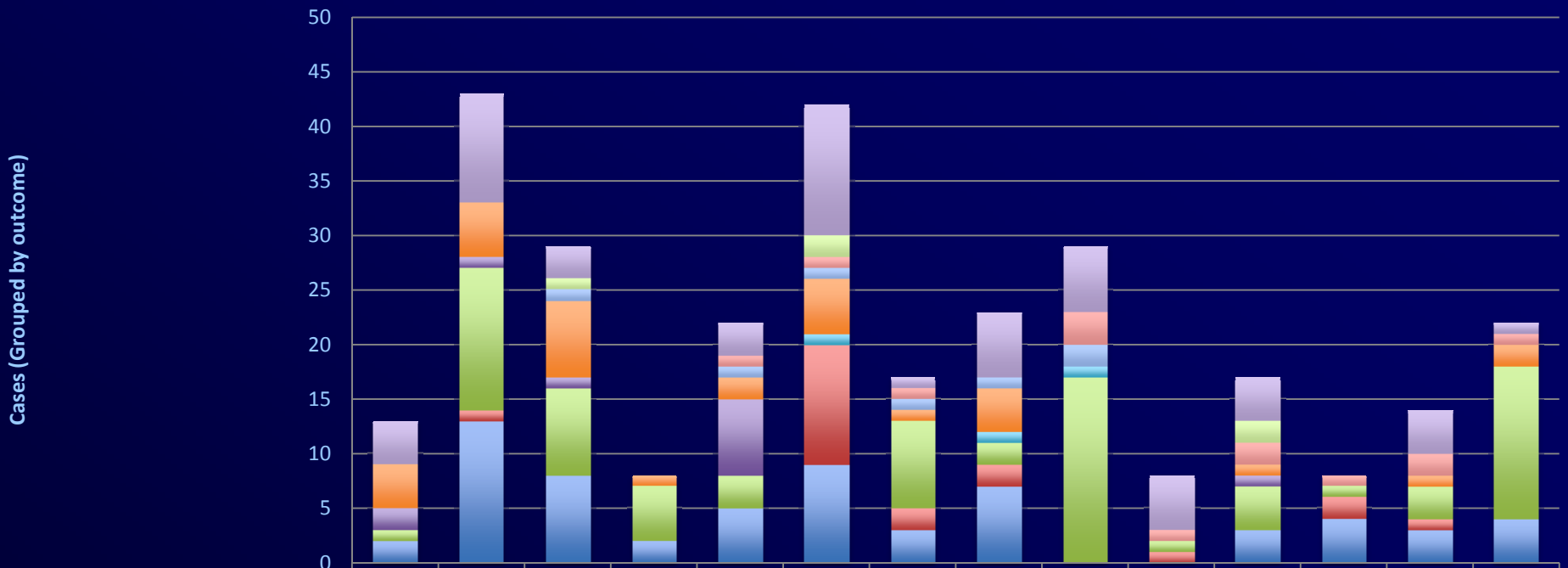


Diagnostic outcome of EBUS-TBNA in patients with pre-existing malignancy



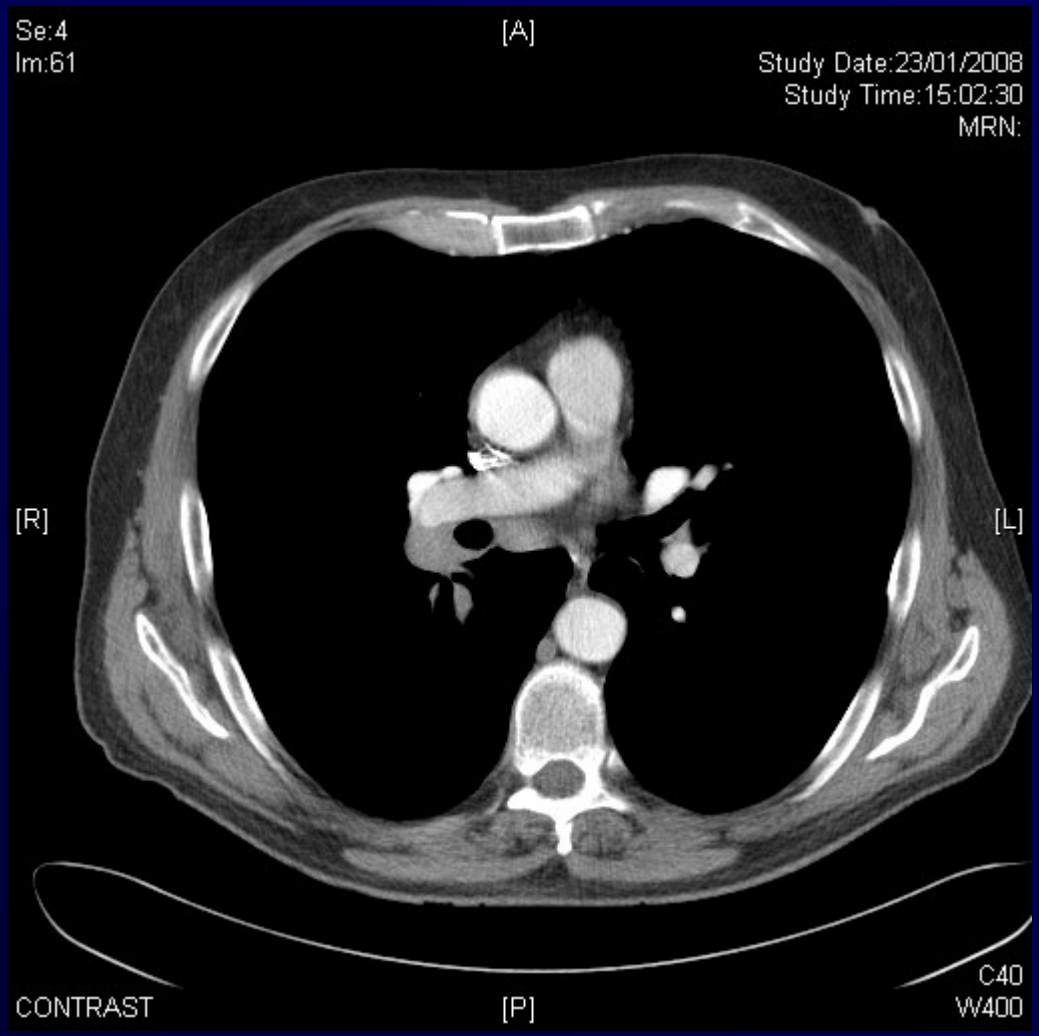
- METASTASIS OF KNOWN CANCER
- NEW CANCER
- GRANULOMATOUS
- REACTIVE
- LYMPHOPROLIFERATIVE
- METASTASIS UNCERTAIN 1ARY
- OTHER
- NON-DIAGNOSTIC
- NIL TO SAMPLE
- MISSED

Indication 3: Previous cancer vs Outcome



	BLADDER CA	BREAST CANCER	COLORECTAL CA	GYNAE TUMOURS	HNCC	LYMPHOMA	MULTIPLE	NOT AVAILABLE	NSCLC	OESOPHAGEAL CANCER	OTHER MALIGNANCY	OTHER UROLOGICAL	PROSTATE CA	RENAL CANCER
REACTIVE	4	10	3		3	12	1	6	6	5	4		4	1
OTHER			1			2					2			
NON-DIAGNOSTIC					1	1	1		3	1	2	1	2	1
NIL TO SAMPLE			1		1	1	1	1	2					
NEW CANCER	4	5	7	1	2	5	1	4			1		1	2
MISSED						1		1	1					
METASTASIS UNCERTAIN 1ARY	2	1	1		7						1			
METASTASIS OF KNOWN CANCER	1	13	8	5	3		8	2	17	1	4	1	3	14
LYMPHOPROLIFERATIVE		1				11	2	2		1		2	1	
GRANULOMATOUS	2	13	8	2	5	9	3	7			3	4	3	4

Total:	13	43	29	8	22	42	17	23	29	8	17	8	14	22
	4%	15%	10%	3%	7%	14%	6%	8%	10%	3%	6%	3%	5%	7%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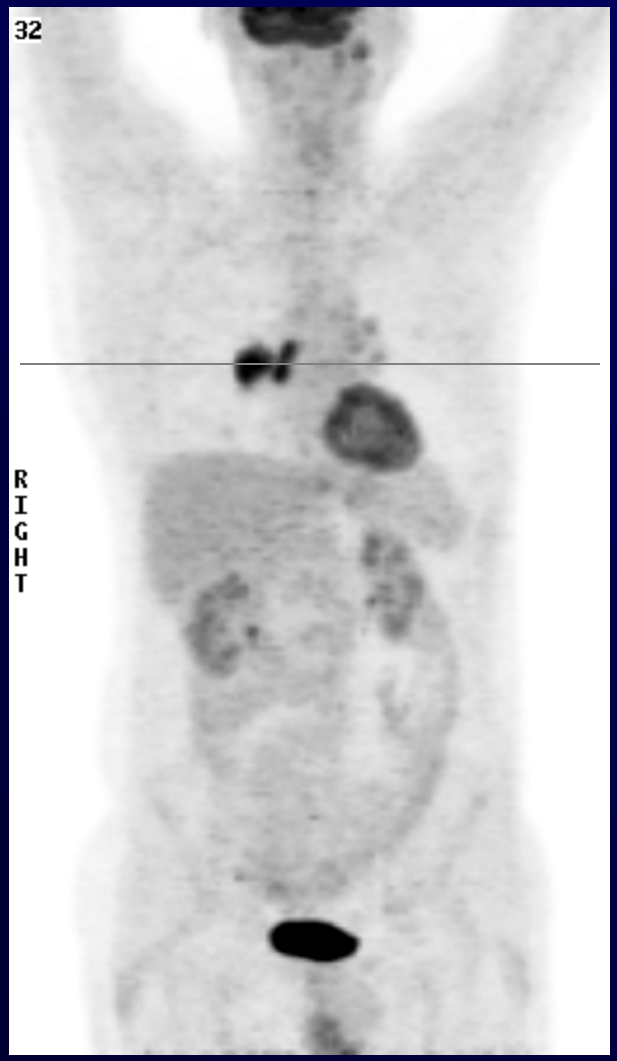
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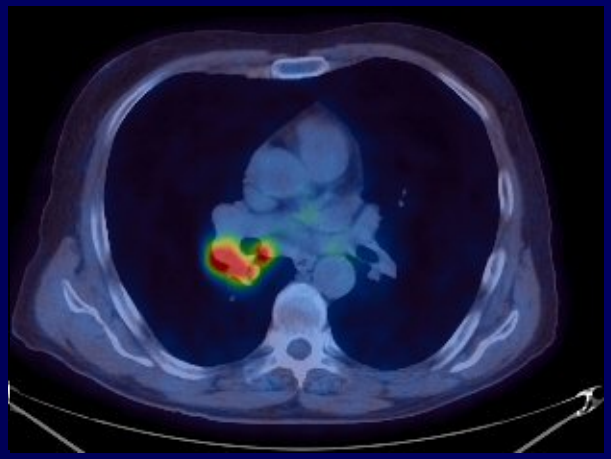
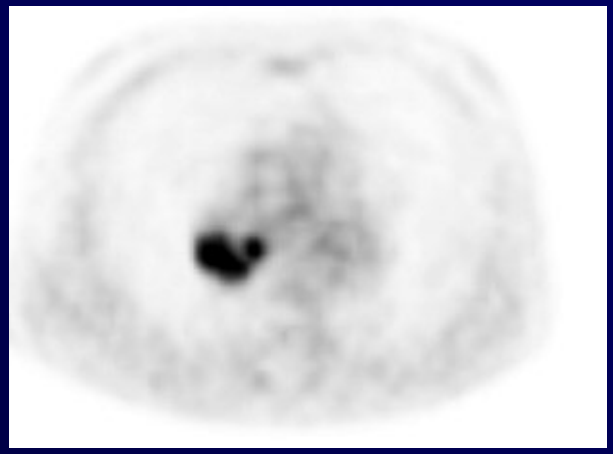
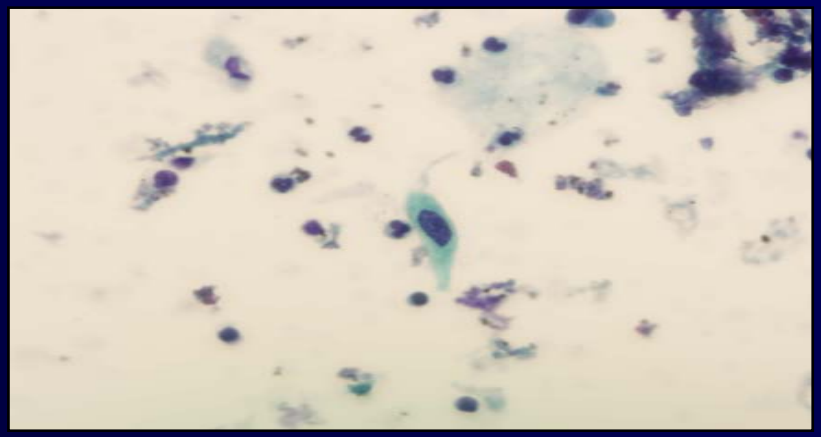
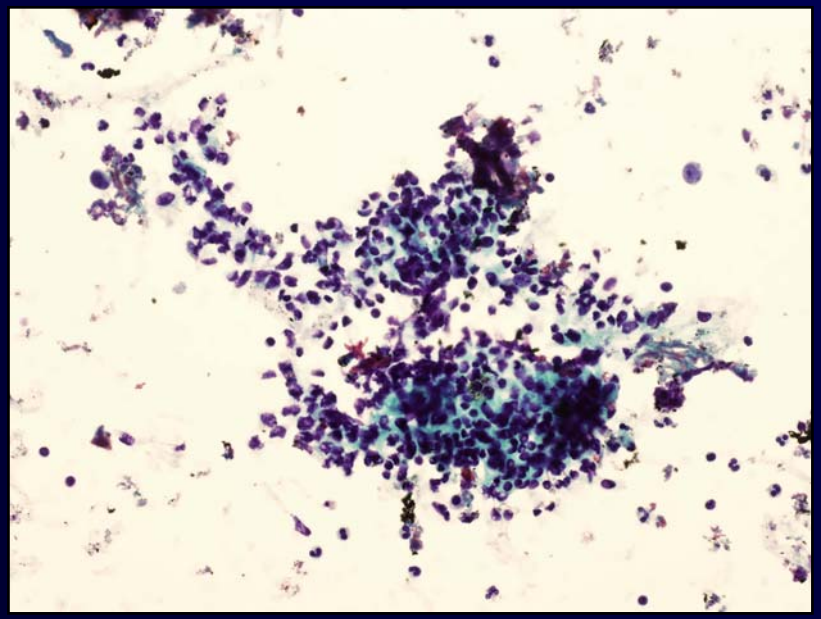




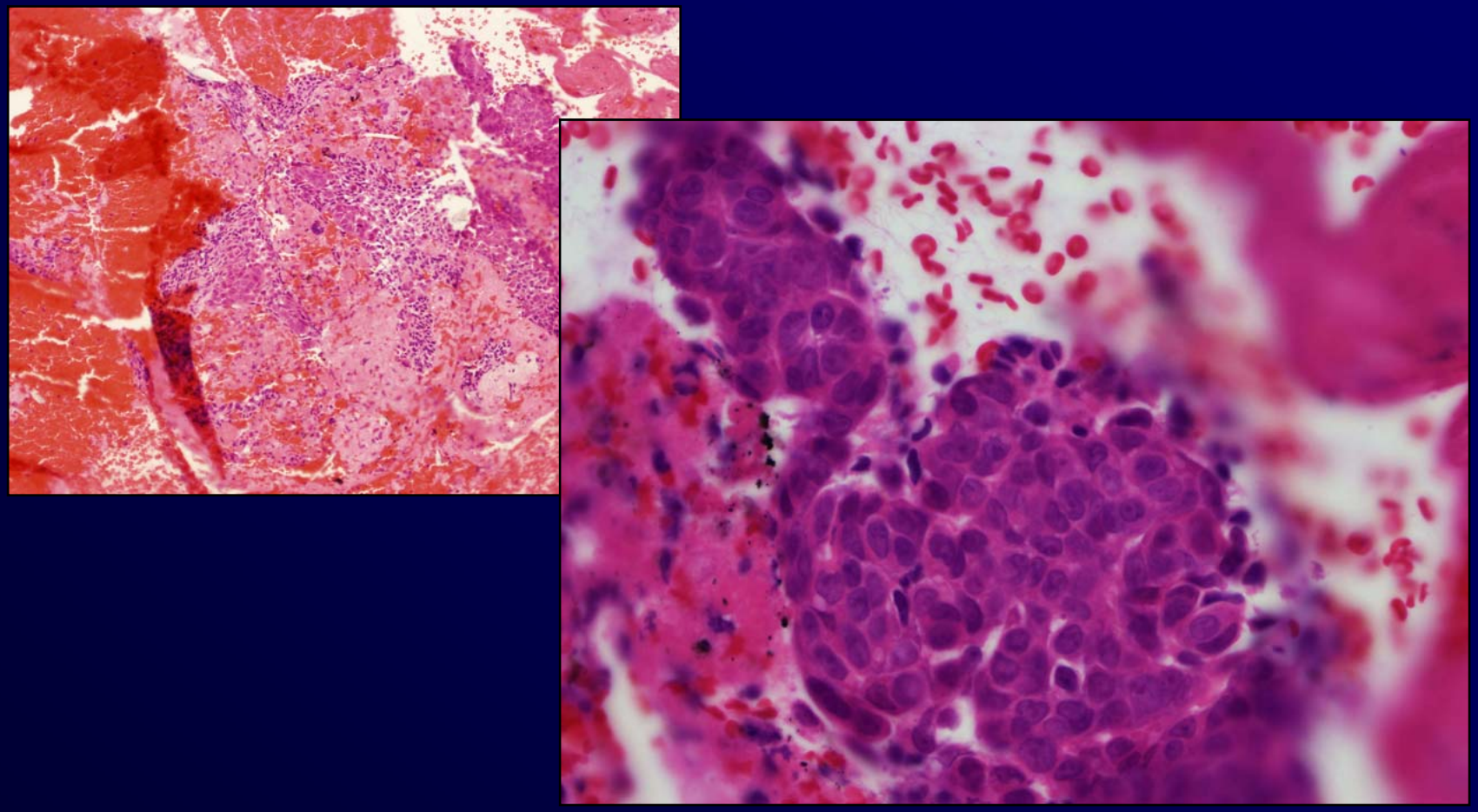
DC Right Hilar Mass EBUS-FNA





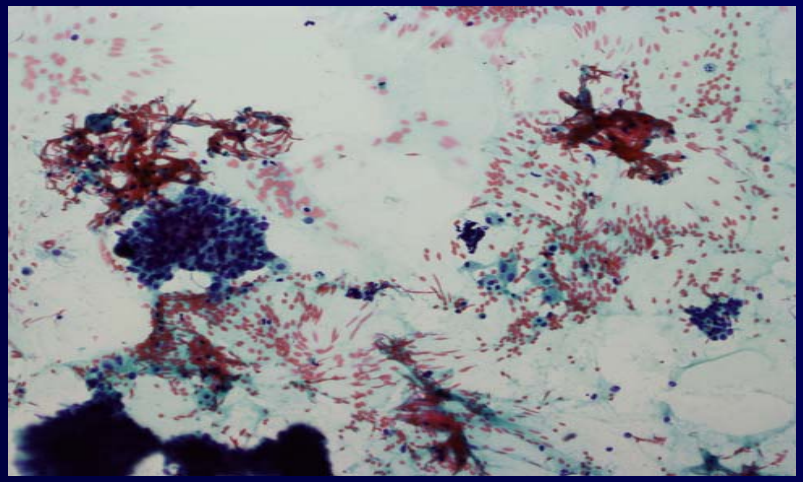
- Cellular aspirate
- Malignant cells present
- High nuclear to cytoplasmic ratio
- Pleomorphic nuclei
- Prominent nucleoli
- Turquoise cytoplasm
- No lymphocytes

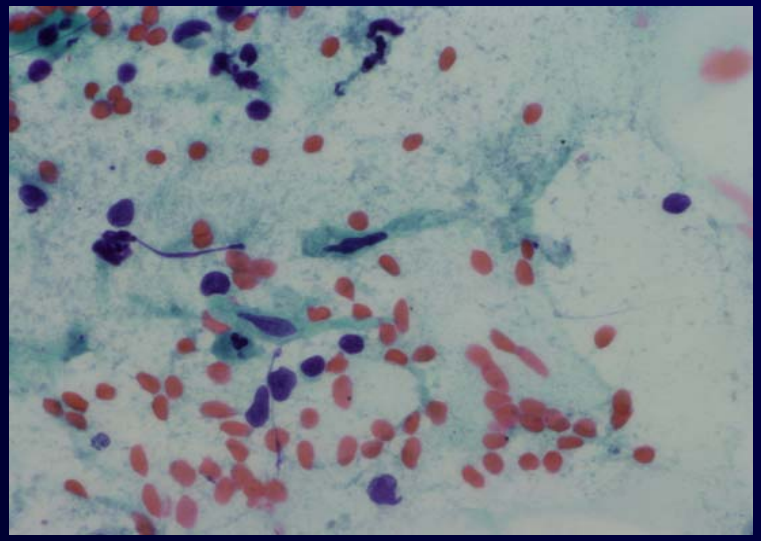
Cell Block



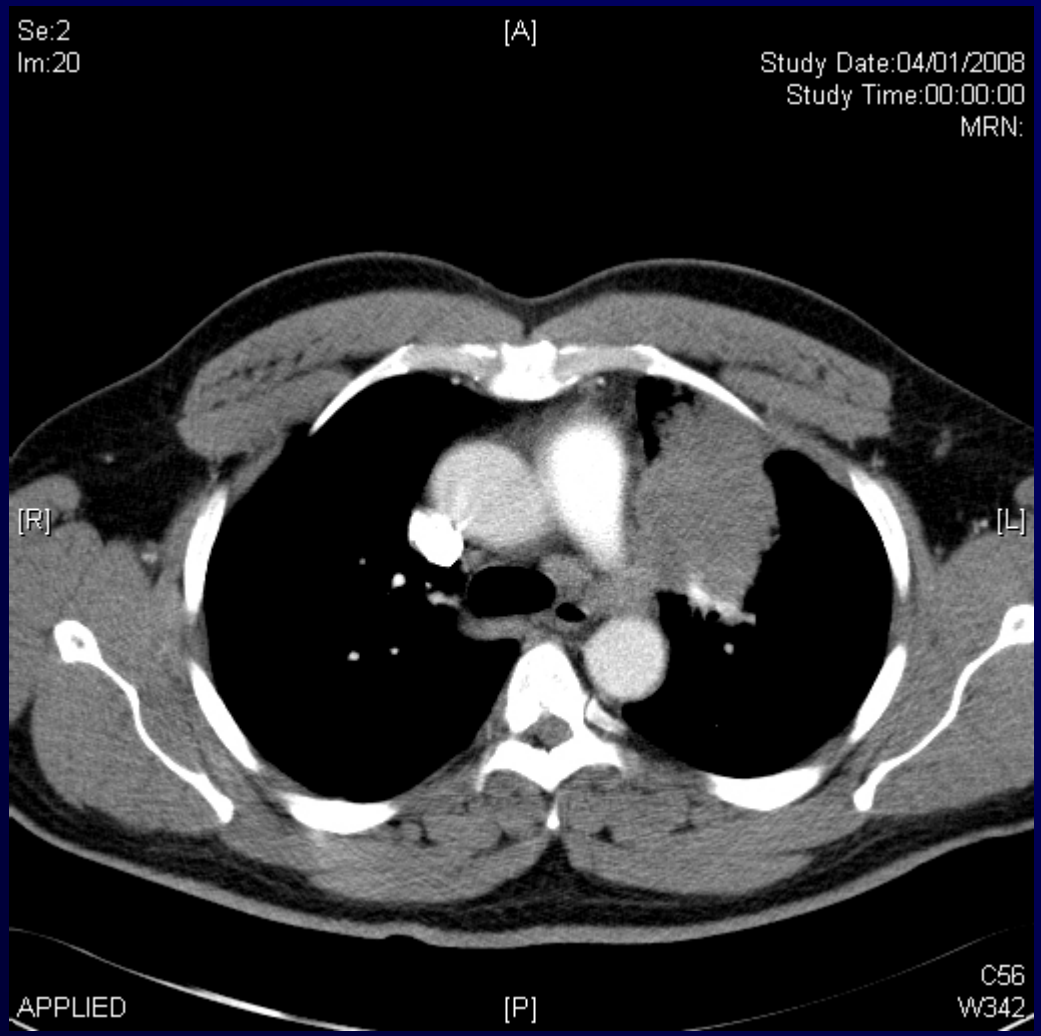
Diagnosis: NON-SMALL CELL CARCINOMA
- PROBABLY SQUAMOUS

DC subcarinal node





- Cellular aspirate
- Mixed population of lymphocytes
- Malignant cells also present
- High nuclear to cytoplasmic ratio
- Angulated nuclei
- Prominent nucleoli
- Turquoise cytoplasm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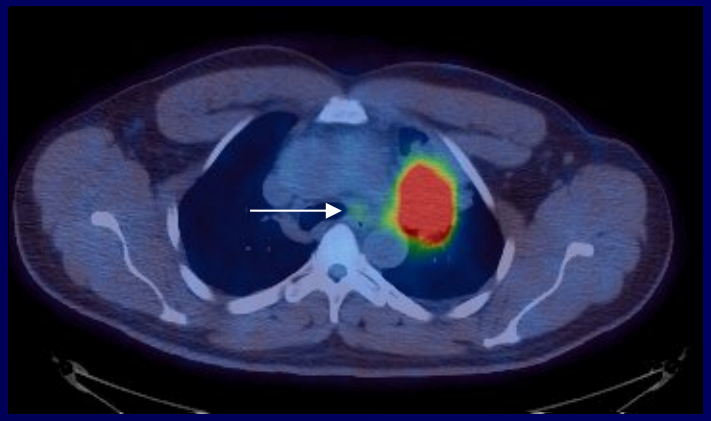
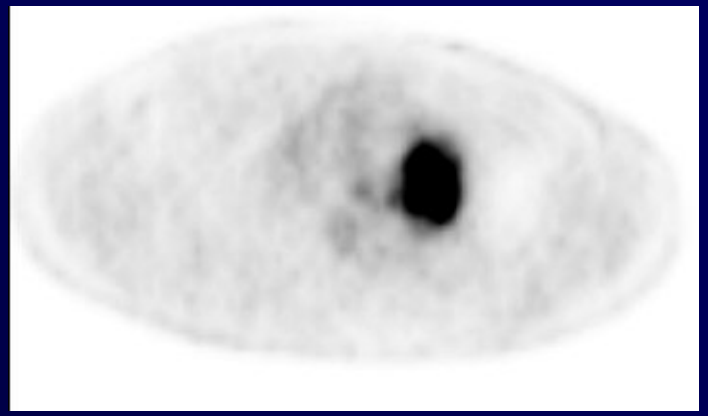
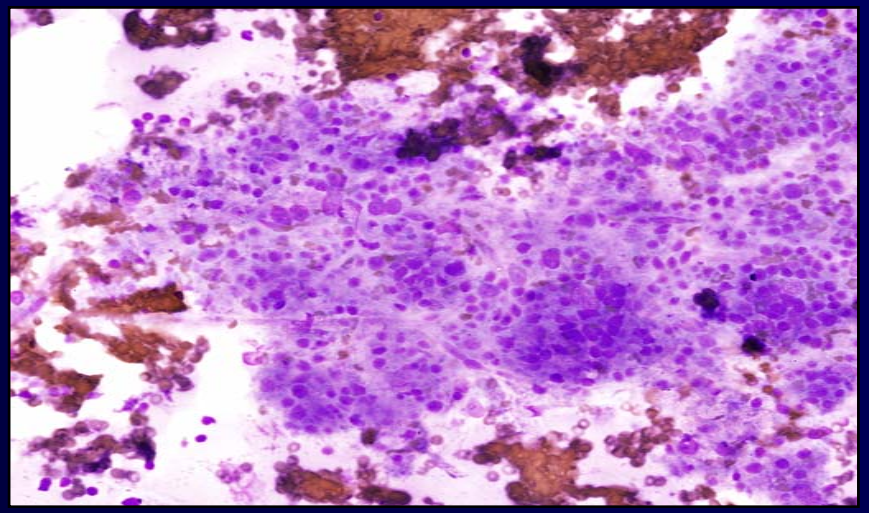
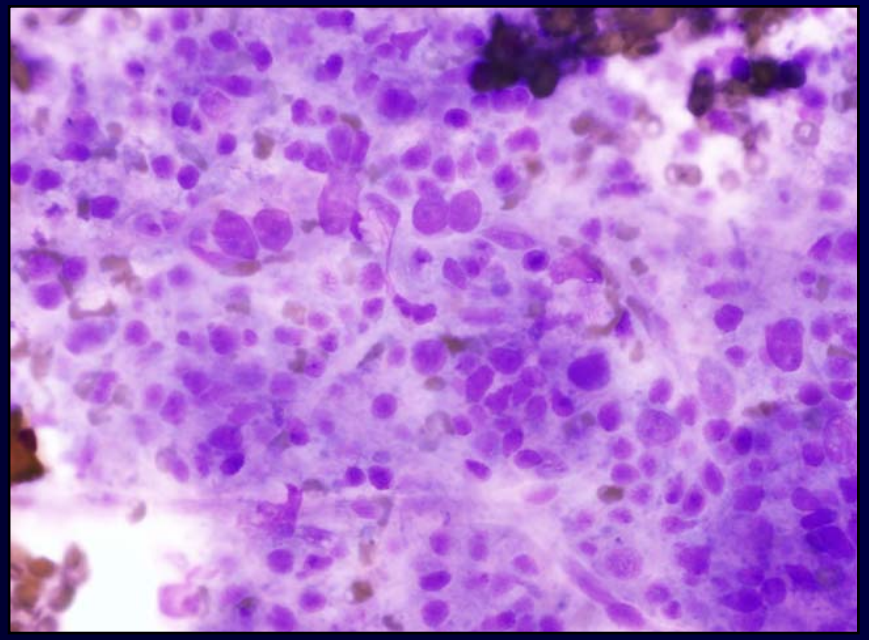


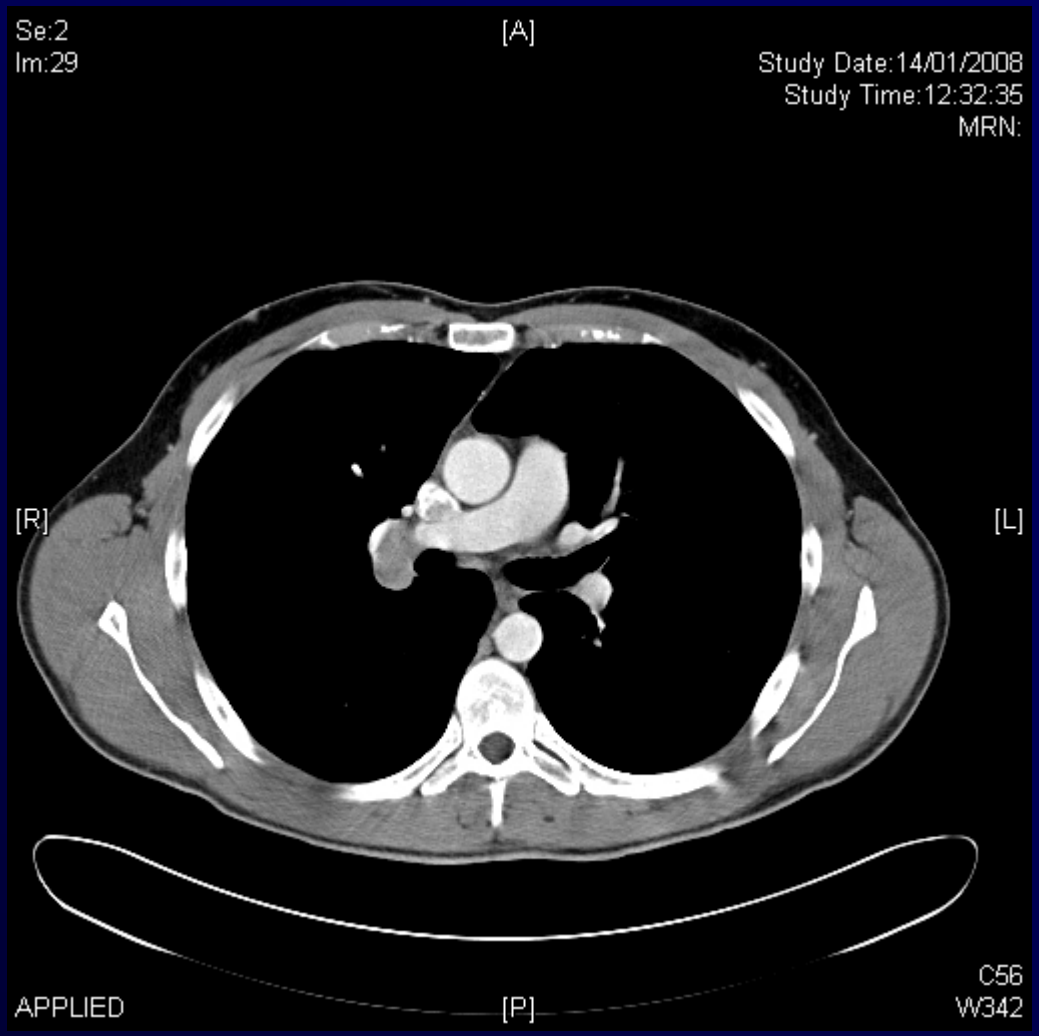


Patient BK: EBUS-FNA from station 4L lymph node





- Mixed population of lymphocytes
- Few groups of atypical cells also present
- High nuclear to cytoplasmic ratio
- Angulated nuclei
- Prominent nucleoli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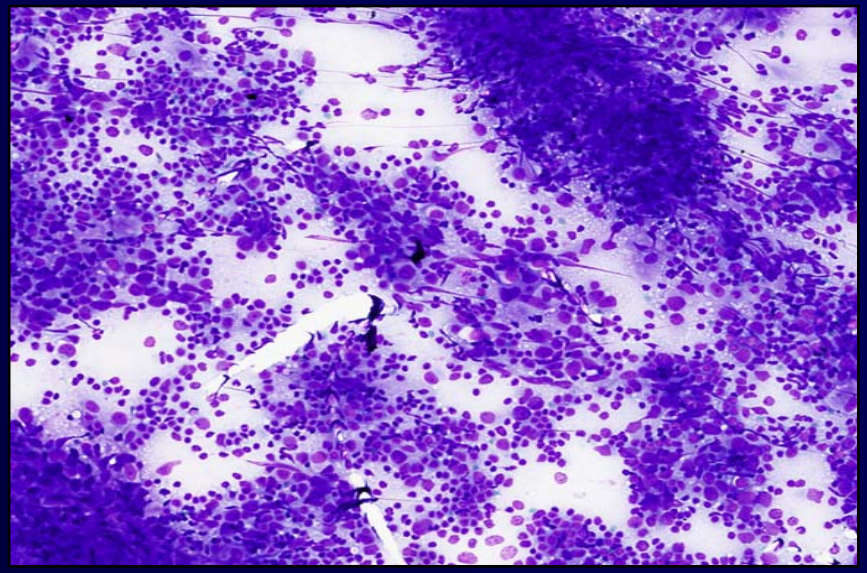
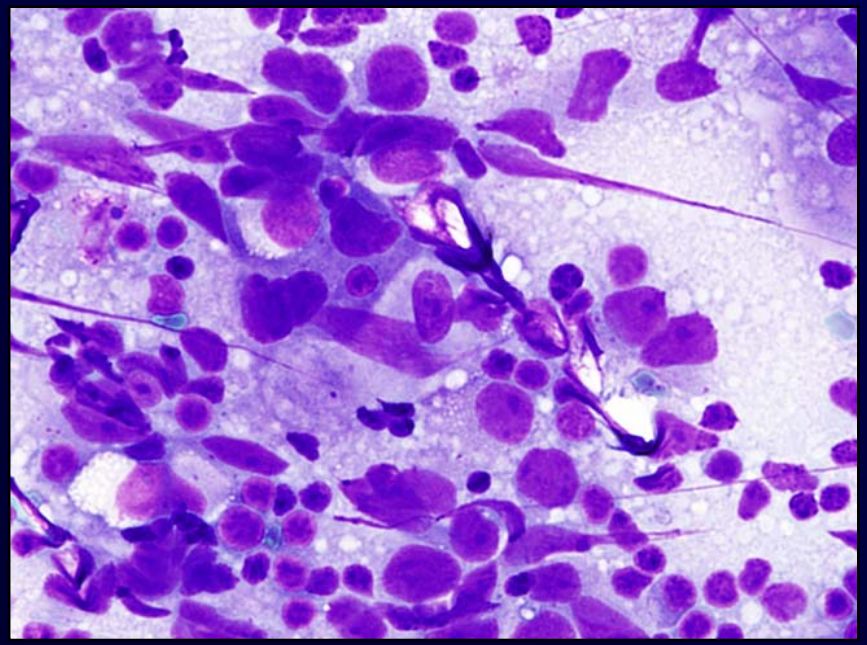
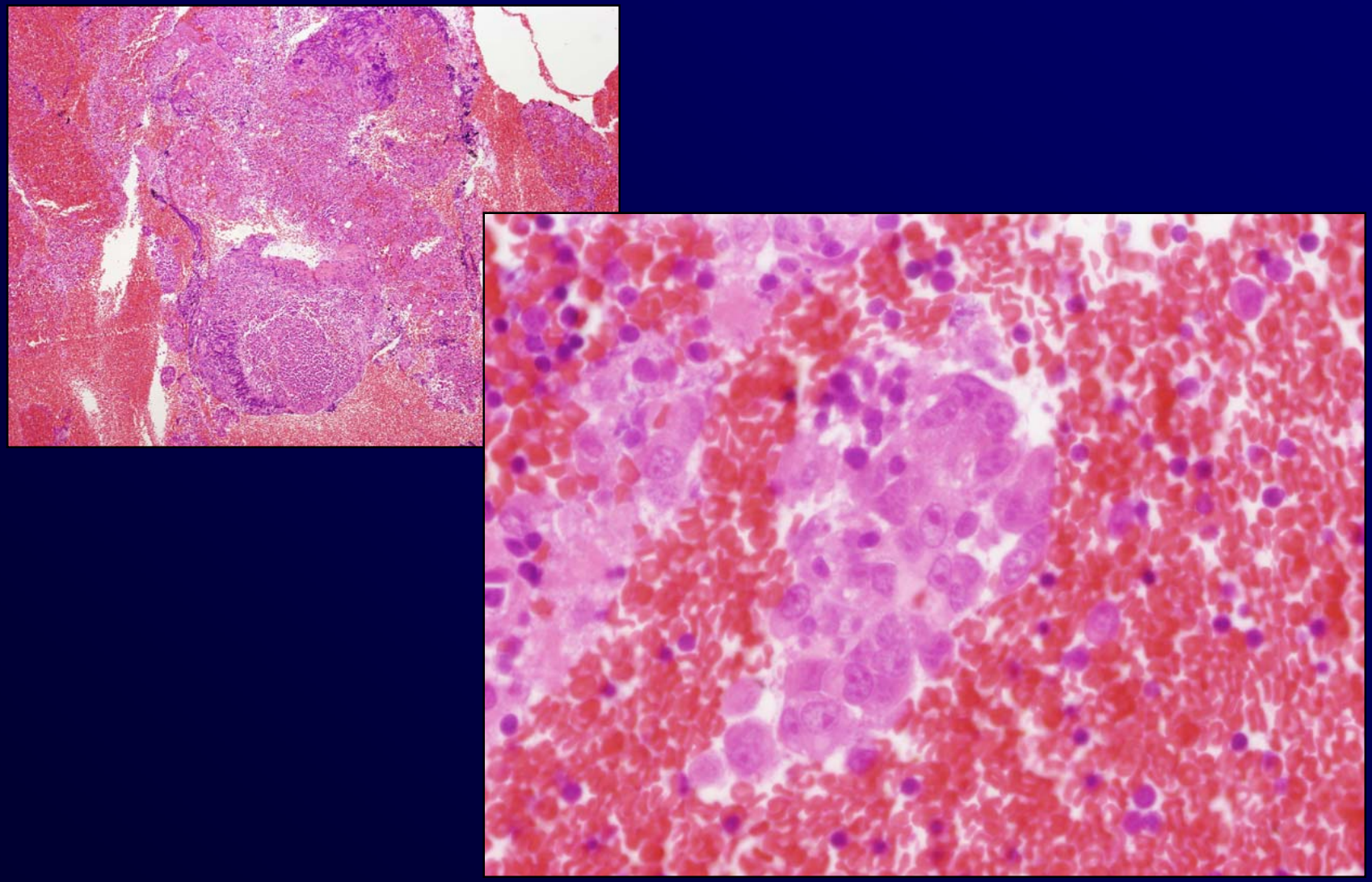


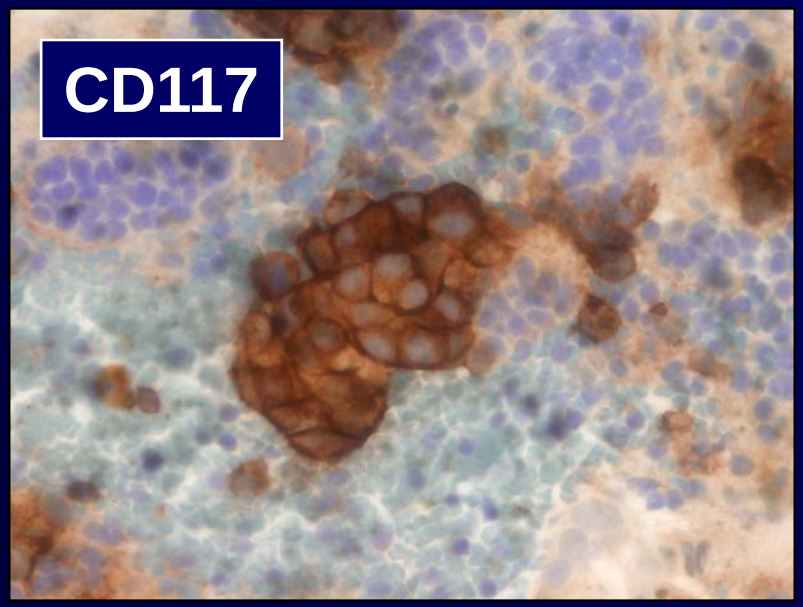


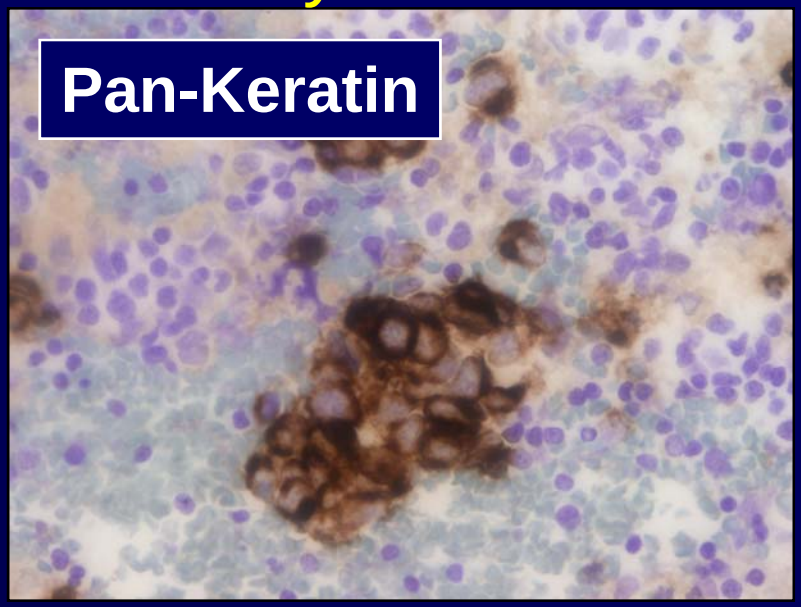
- Mixed population of lymphocytes
- Malignant cells also present
- High nuclear to cytoplasmic ratio
- Pleomorphic nuclei
- Prominent nucleoli
- Delicate cytoplasm

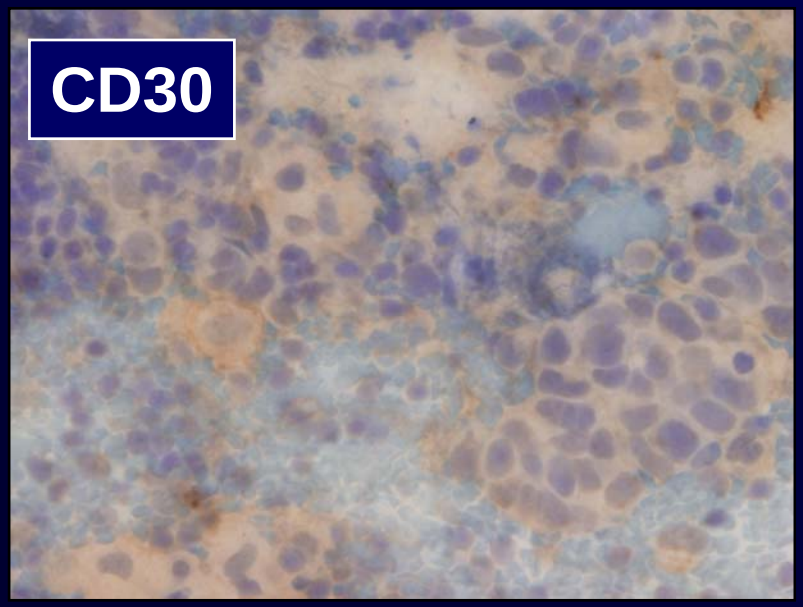
Cell Block

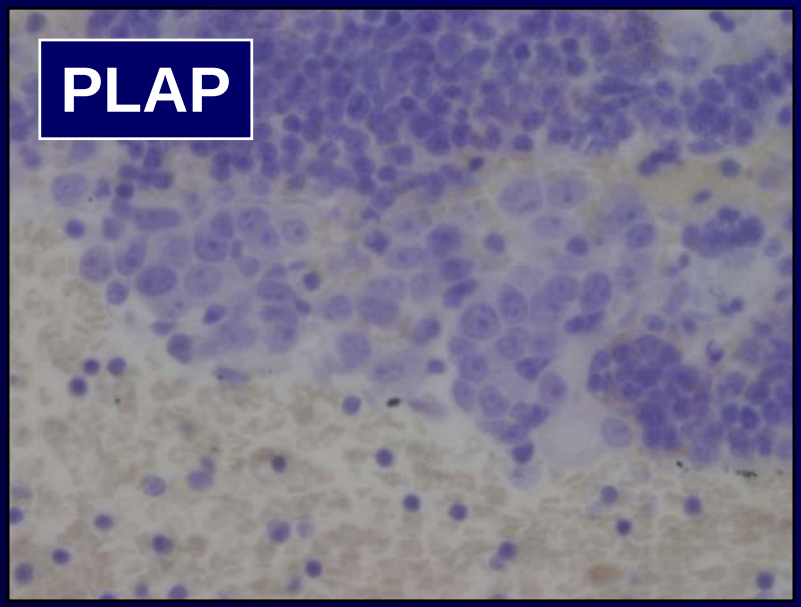


Immunohistochemistry









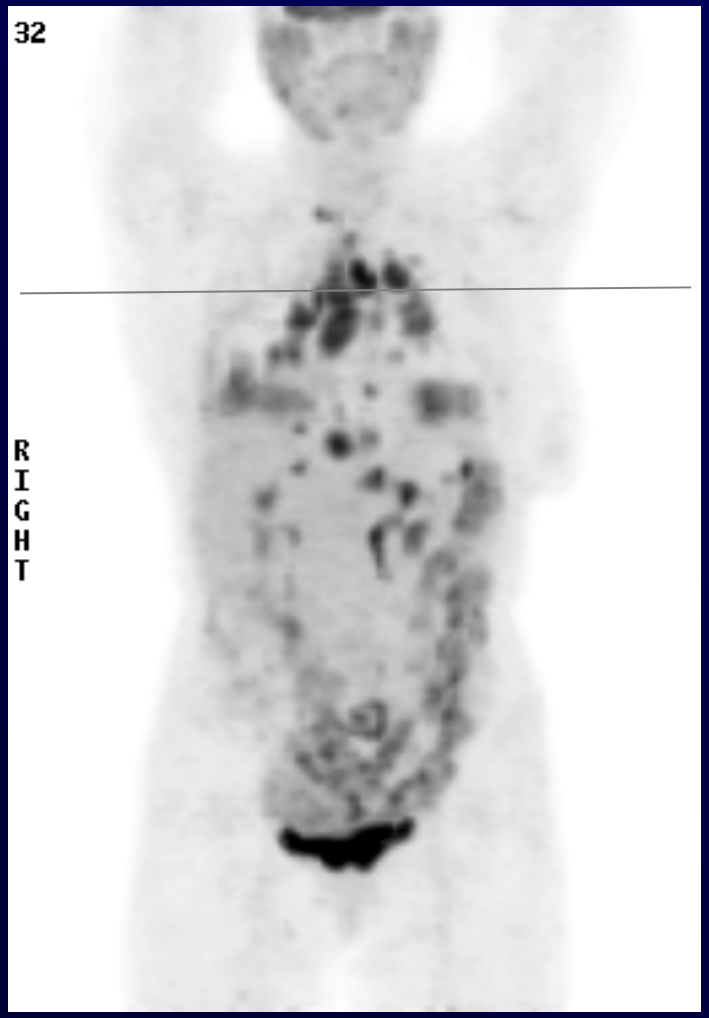
?METASTATIC NON-SEMINOMATOUS GERM CEL TUMOUR

Primary reviewed:

- *CD117 positive*
- *Pan-keratin positive*
- *PLAP negative*
- *CD30 negative*

Final Diagnosis:

- METASTASES FROM PRIMARY TESTICULAR TUMOUR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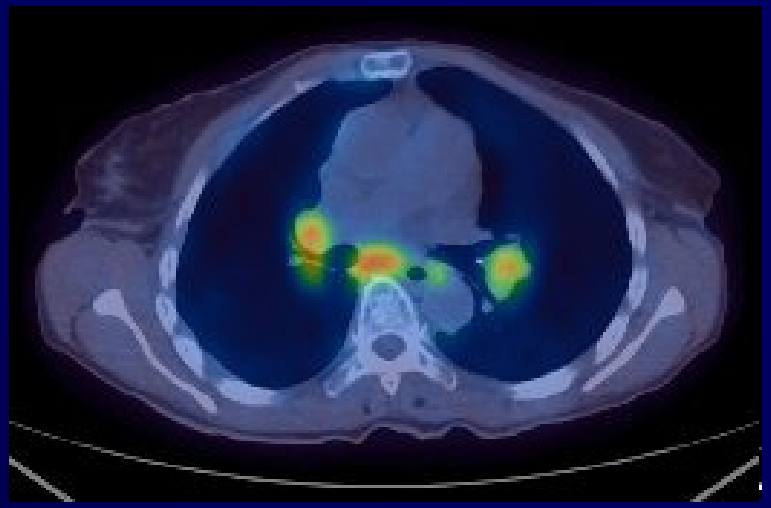

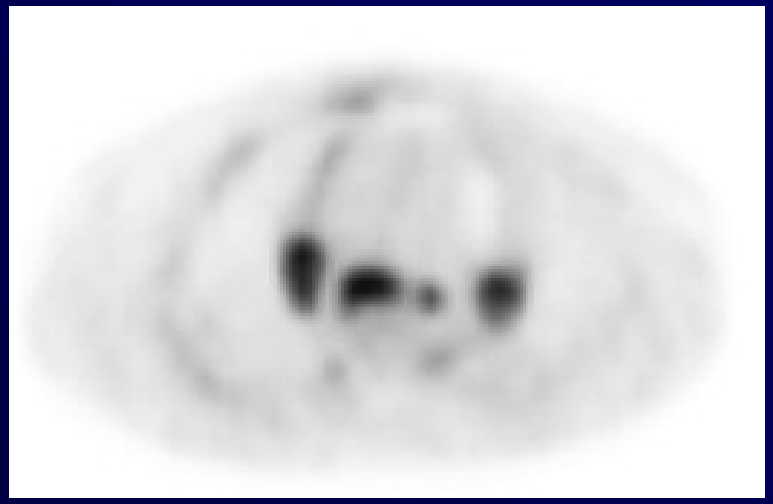

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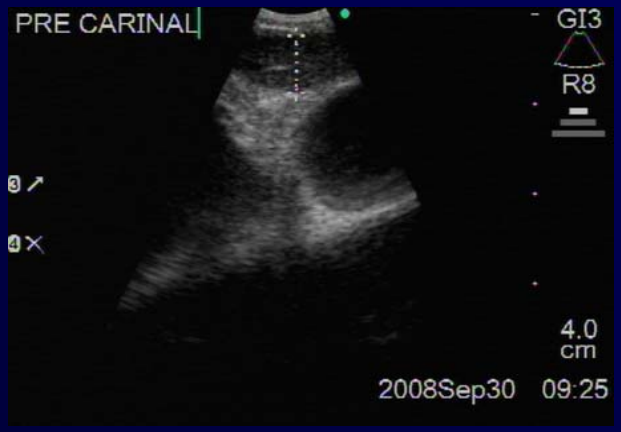
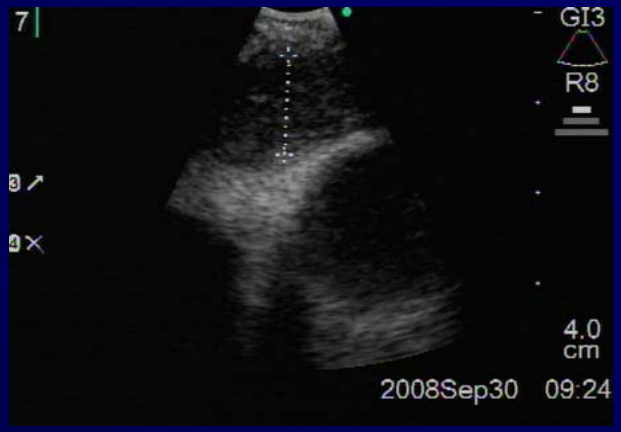
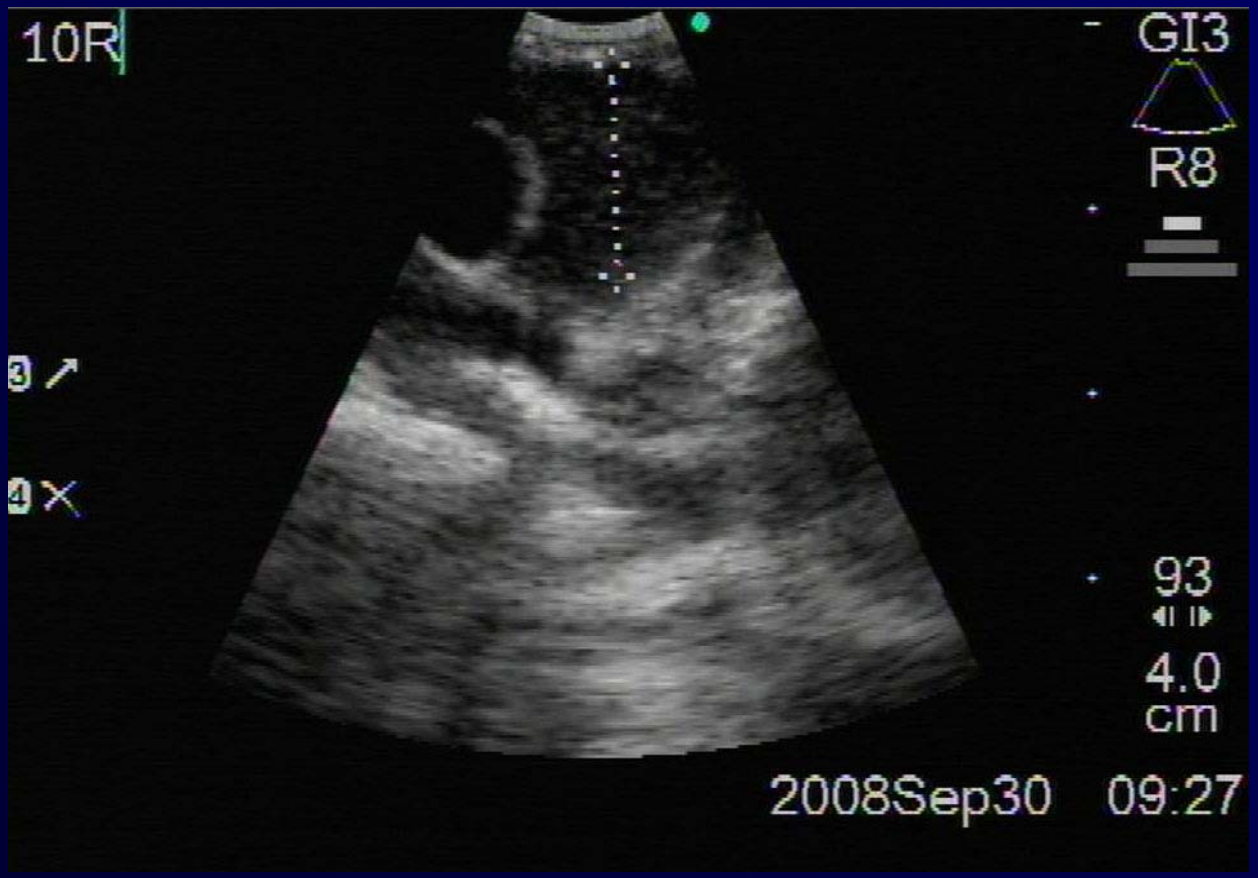
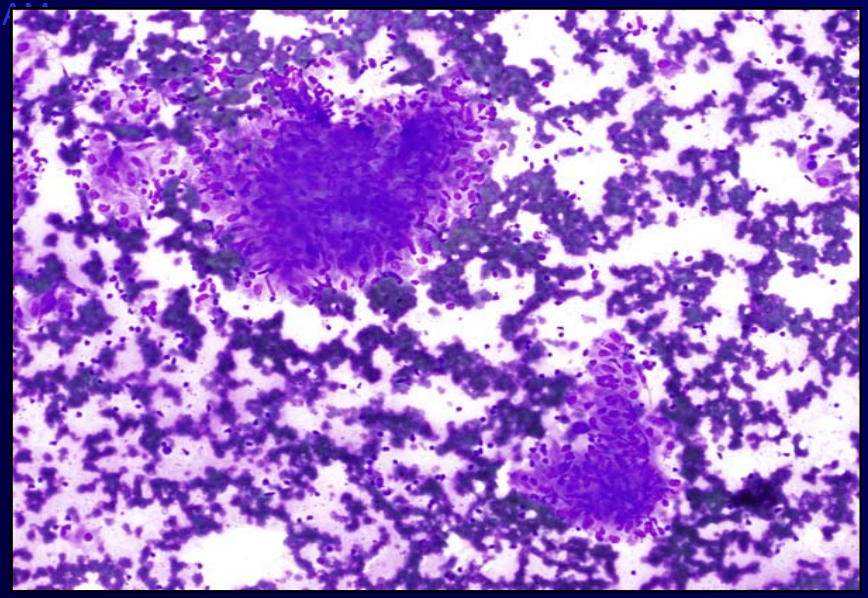


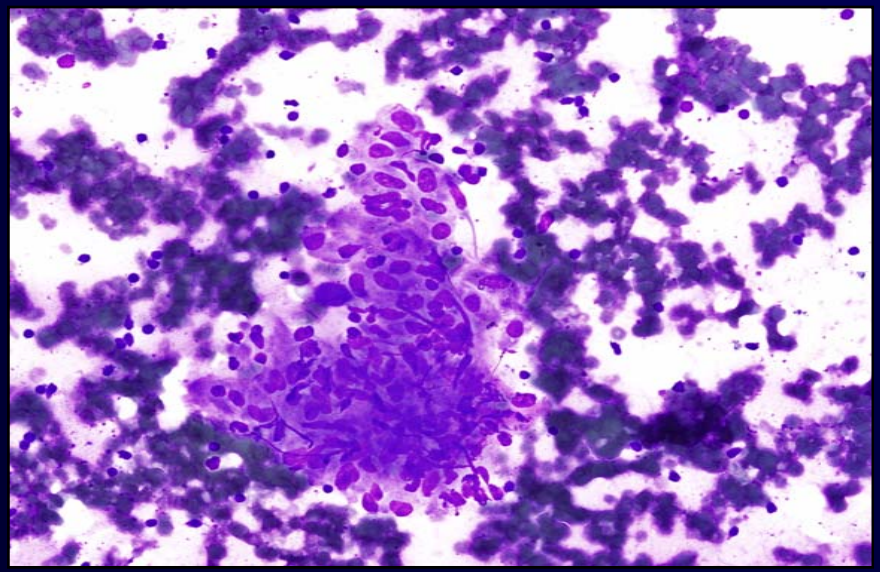


FDG avid mediastinal/hilar nodes.
RCC L kidney

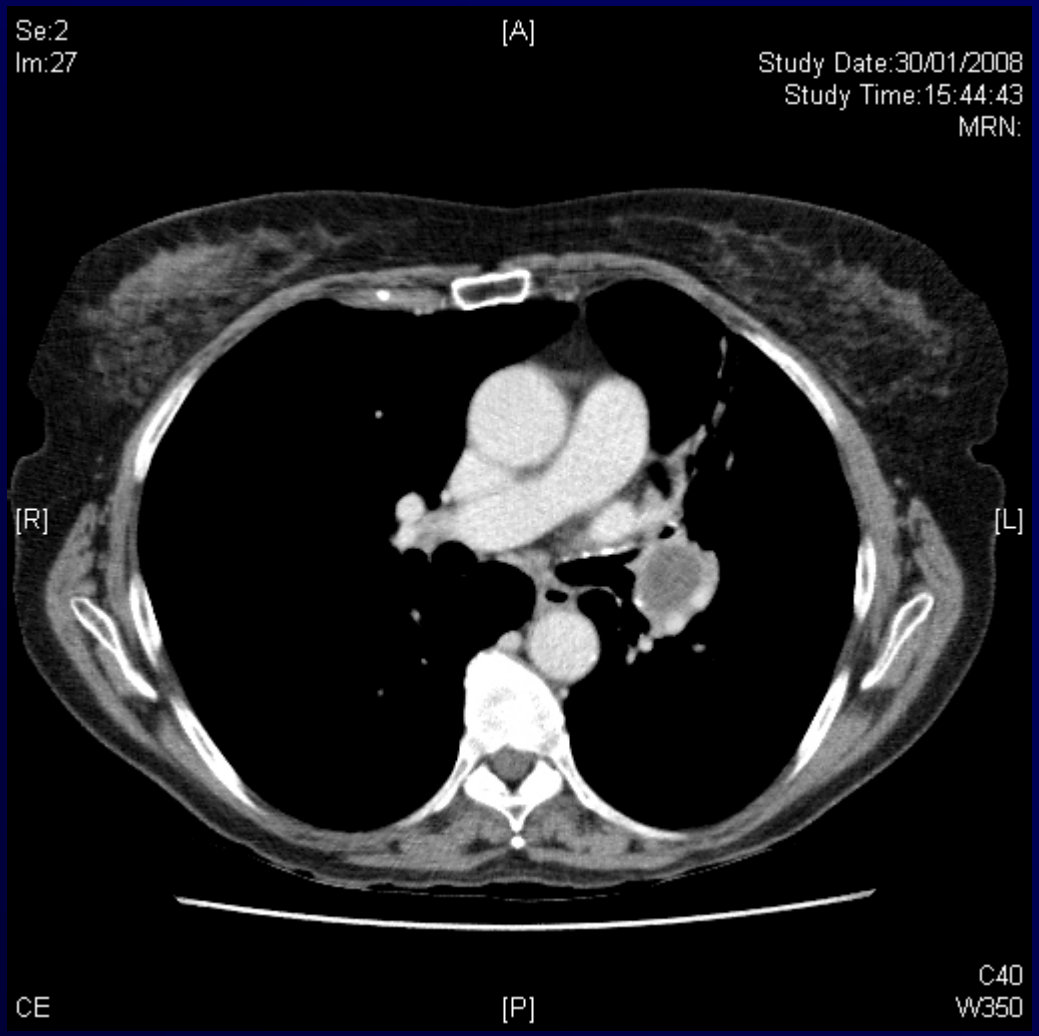
AM







- Mixed population of lymphocytes including tingible body macrophages
- Numerous granulomas
- No malignant cells seen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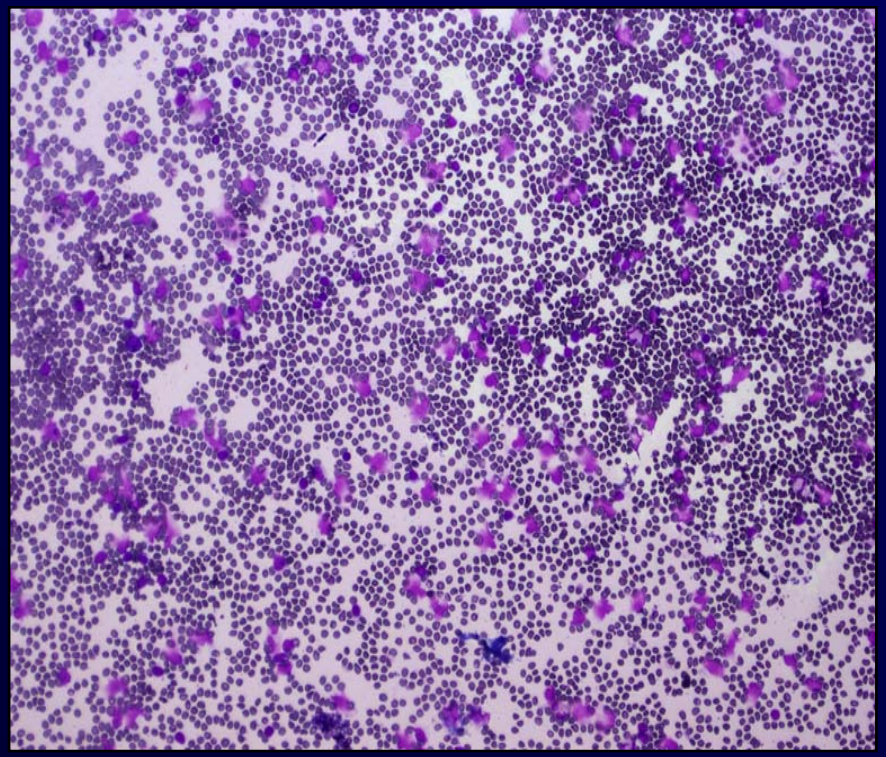


- Scanty and degenerate population of mixed lymphocytes including tingible body macrophages
- Bronchial epithelial cells
- No malignant cells seen but ?representative

Can EBUS-FNA samples provide more than diagnostic information?

EGFR & *K-RAS* mutation analysis in GSTT EBUS-derived aspirates

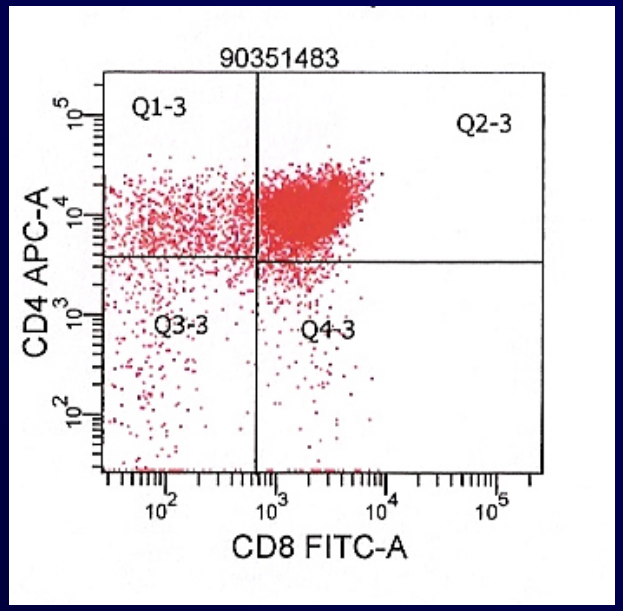
Frequency of EGFR and KRAS mutations in metastatic lymph nodes in NSCLC*		
Tumour type	**EGFR mutations (%)**	**KRAS mutations (%)**
Adenocarcinoma	11/89 (12.3%)	18/93 (19%)
NSCLC-NOS+	2/18 (11.1%)	5/18 (27.7%)
Large cell neuroendocrine	0/2	0/2
Large cell carcinoma	0/1	0/1
Squamous cell	0/16	0/16
Non-squamous	13/110 (12%)	23/114 (20%)

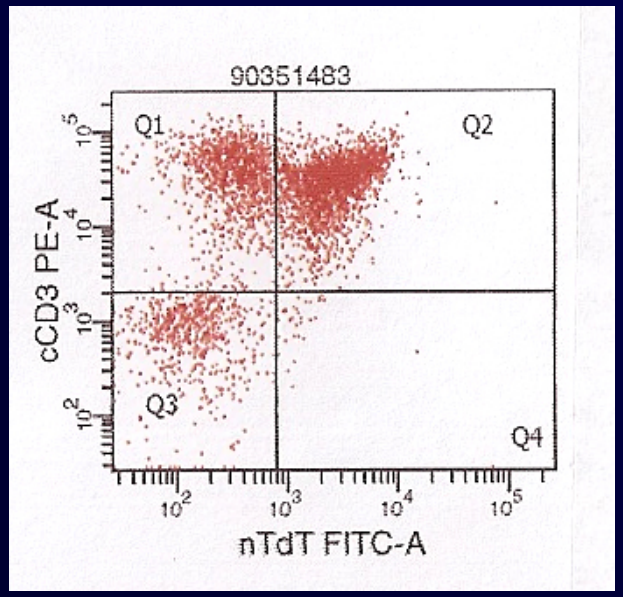
- *Refers to data for fully analysed patient samples

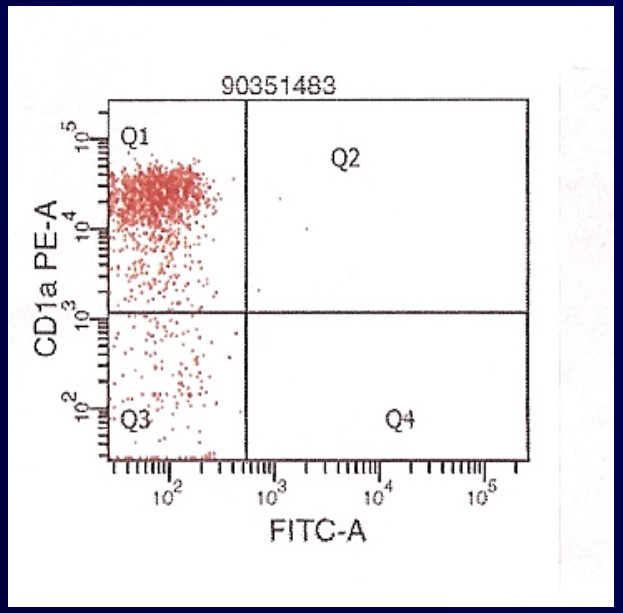
DNA obtained from EBUS-FNA samples in 99% cases.

EGFR and *KRAS* mutations detected by cold-PCR			
	EGFR		**Number of cases**
Adenocarcinoma	G719A+	Exon 18	2
Adenocarcinoma	L747P+	Exon 19	1
NSCLC-NOS^	2481-2495del15	Exon 19	1
Adenocarcinoma	P733S+	Exon 19	1
Adenocarcinoma	V760M*	Exon 19	1
Adenocarcinoma	H805L*	Exon 20	1
Adenocarcinoma	2319 insertion CAG2320+	Exon 20	1
Adenocarcinoma	L858R+	Exon 21	2
Adenocarcinoma	L833V+L858R+	Exon 21	1
Adenocarcinoma	L861E+	Exon 21	1
NSCLC-NOS^	L858R+	Exon 21	1
	KRAS		
Adenocarcinoma	G12C	Exon 2	13
Adenocarcinoma	G12V	Exon 2	4
Adenocarcinoma	G61H	Exon 3	1
NSCLC-NOS^	G12C	Exon 2	3
NSCLC-NOS^	G12V	Exon 2	1
NSCLC-NOS^	G61H	Exon 3	1

*Refers to known *EGFR* mutations, +Refers to novel *EGFR* mutations, ^Refers to not-otherwise specified


90351483
Q1-3
Q2-3
Q3-3
Q4-3
CD4 APC-A
CD8 FITC-A

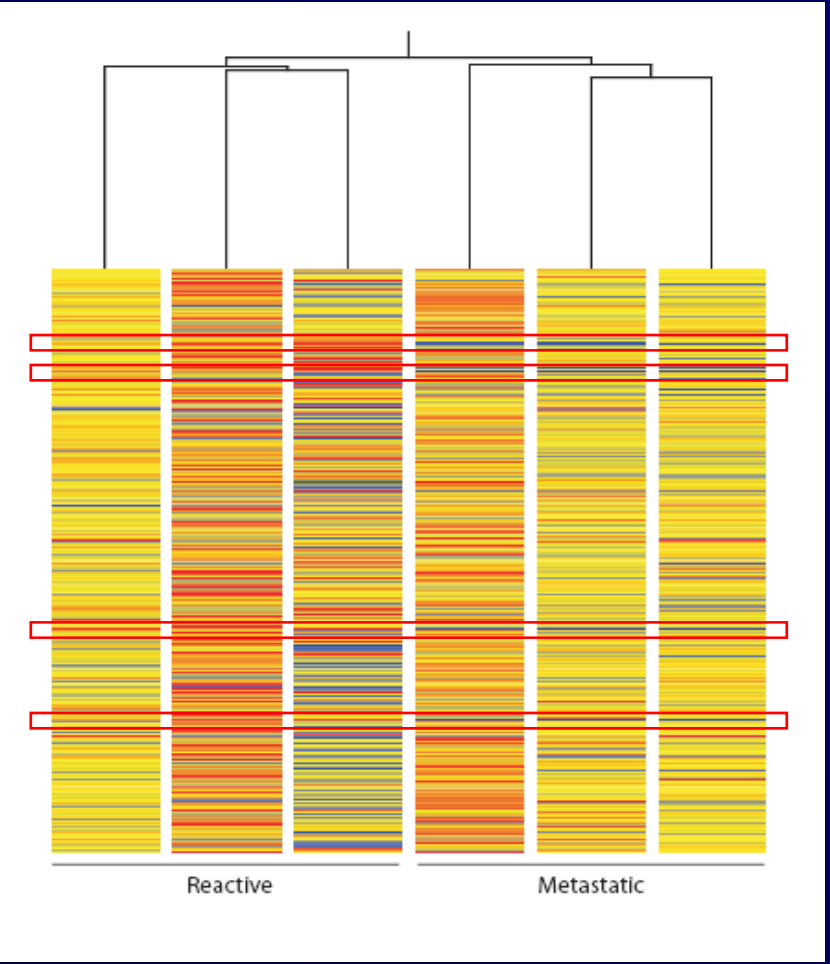

90351483
Q1
Q2
Q3
Q4
cCD3 PE-A
nTdT FITC-A


90351483
Q1
Q2
Q3
Q4
CD1a PE-A
FITC-A

Analysis of global gene expression in EBUS-derived cytological aspirates

Hierarchical clustering

- ”Unsupervised” approach
- Groups genes segregating benign and malignant nodes by genes defining similarity.
- Use to define tumour “signature” of predictor genes: e.g. metastasis, lymph node involvement



ASSESSING THE LUNG AND MEDIASTINUM IN CANCER-TISSUE IS THE ISSUE!!

Classical Hodgkin lymphoma

Final EBUS diagnosis	N (%)	Reasons / Pitfalls	Histological diagnosis
Classical Hodgkin lymphoma	16 (73%)		
Suspect Hodgkin lymphoma	6 (27%)	2 cases no cell blocks for IHC – early days of service (08-09).	CHD - NS CHD - MC
		1 case no material on cell block. No / few eosinophils. Could not morphologically exclude T-cell rich large B-cell lymphoma.	CHD - NS1
		1 case insufficient material on cell block for IHC.	CHD - NS1
		1 case partial immunophenotype only.	CHD - NS1
		1 case partial immunophenotype; suspected as CHL with aberrant CD20 expression – turned out to be DLBCL on neck node biopsy	DLBCL

Confidence of CHD diagnosis with development of service