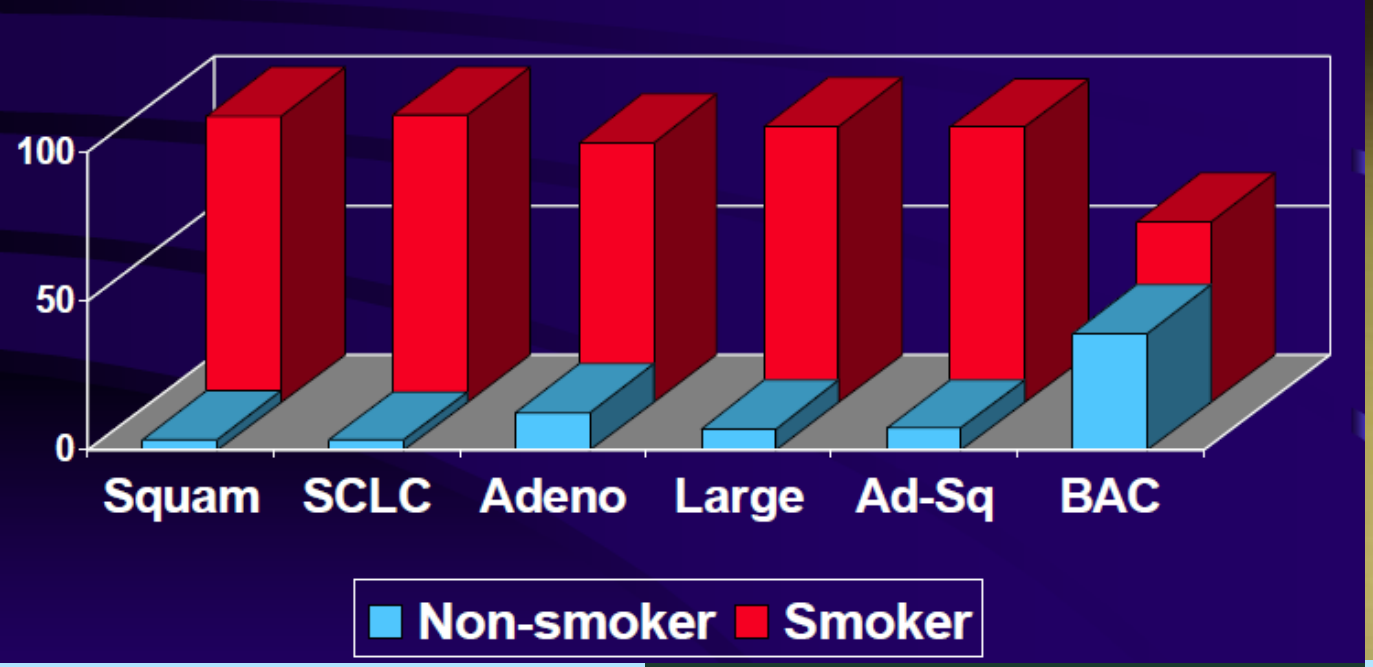
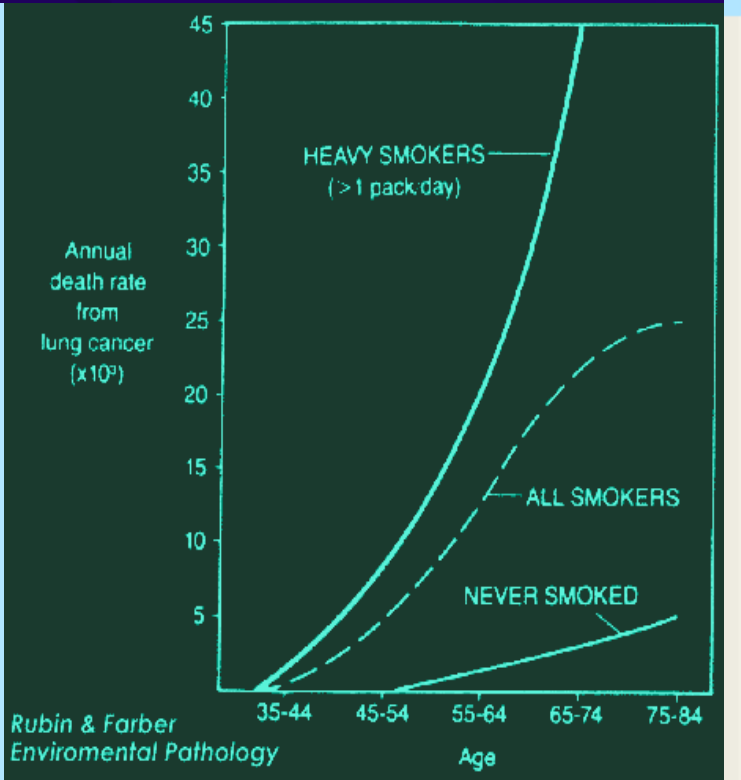
Lunge Cancer

Fra 1930 dramatisk økning i den vestlige verden!
Nå hyppigst diagnostiserte kreftsykdom i verden!

Årsaker: 85-95% røyking!

Stoff / prosess	Anvendelse / anmerkning
Kromater	Metallproduksjon og bearbeiding av rustfritt stål, forkromming, krompigment
Nikkel	Metallproduksjon og bearbeiding av rustfritt stål, fornikling, produksjon av smykker og lignende
Tjærestoffer	Arbeid som feier, asfalt, kreosot
Polysykliske aromatiske hydrokarboner (PAH)	Noen (lite raffinerte) oljeaerosoler og alle prosesser der det er røyk fra forbrenning av organisk materiale. I arbeidssammenheng kommer passiv røyking også inn her.
Arsen	Kobberproduksjon, plantevernmidler, glassproduksjon, gruver. Tidligere treimpregnering.
Asbest	Tidligere isolasjon, varmebeskyttelse, eternitt m.v. Aktuelt i Norge mest i forbindelse med asbestsanering eller tilfeldig eksponering.
Radon	Gruvearbeid. Kan også forekomme i vanlig innemiljø.
Sennepsgass	Produksjon av giftgass, annen kjemisk industri.
Skjæreoljer	Metallbearbeidende industri.
Bisklorometyleter	Kjemisk industri, baktericider, fungicider.
Arbeid i gummiindustri	Trolig diverse kjemiske påvirkninger som nitrosaminer, talkum (fiberholdig), PAH.
Krystallinsk silika (SiO_2)	Alle typer steinarbeid med kvartsholdig stein.


100
50
0
Squam
SCLC
Adeno
Large
Ad-Sq
BAC
Non-smoker
Smoker


45
40
35
30
25
20
15
10
5
HEAVY SMOKERS
(>1 pack/day)
Annual
death rate
from
lung cancer
(x10³)
ALL SMOKERS
NEVER SMOKED
35-44
45-54
55-64
65-74
75-84
Age
Rubin & Farber
Enviromental Pathology

Lungecancer

- 2500 oppdages/ år
- Tar flest liv av cancer (verden: 1,35 mill.)

Flere døde enn prostca.+brystca.+ colorectalca.

- 1 av 10 lever 5 år
- Ingen kjent familiær lungeca.

Teddy er 50 år - og vinner stadig nye venner

Moter har skiftet, en hel verden har vært i støpeskjeen siden J. L. Tiedemanns Tobaksfabrik lanserte sin "Teddy" for 50 år siden. Men gjennom alle disse år har Teddy holdt stillingen i kvalitet og popularitet, og vinner idag stadig nye venner.
Hvorfor?
Fordi dagliglivets tekniske revolusjon ikke kan gjøre en utsøkt sigarett bedre. Fordi Tiedemanns Teddy traff den riktige smak fra første stund og gir den kresne røker den reneste virginia.
Teddy gir utsøkt selskap - i dag som i 1912.

Jubileumskonkurranse - campingvogn til kr. 10.000,- i premie!

Teddy's jubileumsgave til sine venner er en campingvogn til en verdi av kr. 10.000,-. Den tid er fjern da mannen tillot seg å ha privilegier, og siden campinglivets trivsel i høy grad er avhengig av en ordnende kvinnelig hånd, bør begge kjønn få samme sjansen til å konkurrere om Teddy's jubileumsgave.

Oppgaven går ut på å finne én feil i bildene og én feil i teksten over bildene. - Blant de riktige besvarelser vil man så trekke ut den lykkelige vinner av jubileumsgaven. Dessuten blir det delt ut 50 badedrakter som ekstrapremier. Bruk spesielle deltagerkort som De får i forretningene. Svarfrist 20/6 1964.

1 av 5 blir operert. (Norge opr. 400/ år)

Bodø sykehus ”best” / flest operasjoner

Internasjonal interesse for lungekreftforskning i nord

- De funn vi har gjort kan legge grunnlag for en helt ny og målrettet lungekreftbehandling, sier overlege Khalid Al-Shibli ved Nordlandssykehuset. Foto. Wigdis Korsvik

”I analysen sto lungekreft bak 22 prosent av alle kreftrelaterte dødsfall, men bare tre prosent av de samlede kreftforskningsmidler går til forskning på dette området. Brystkreft stod til sammenlikning bak åtte prosent av kreftdødsfallene, men mottok 18 prosent av forskningsmidlene”.

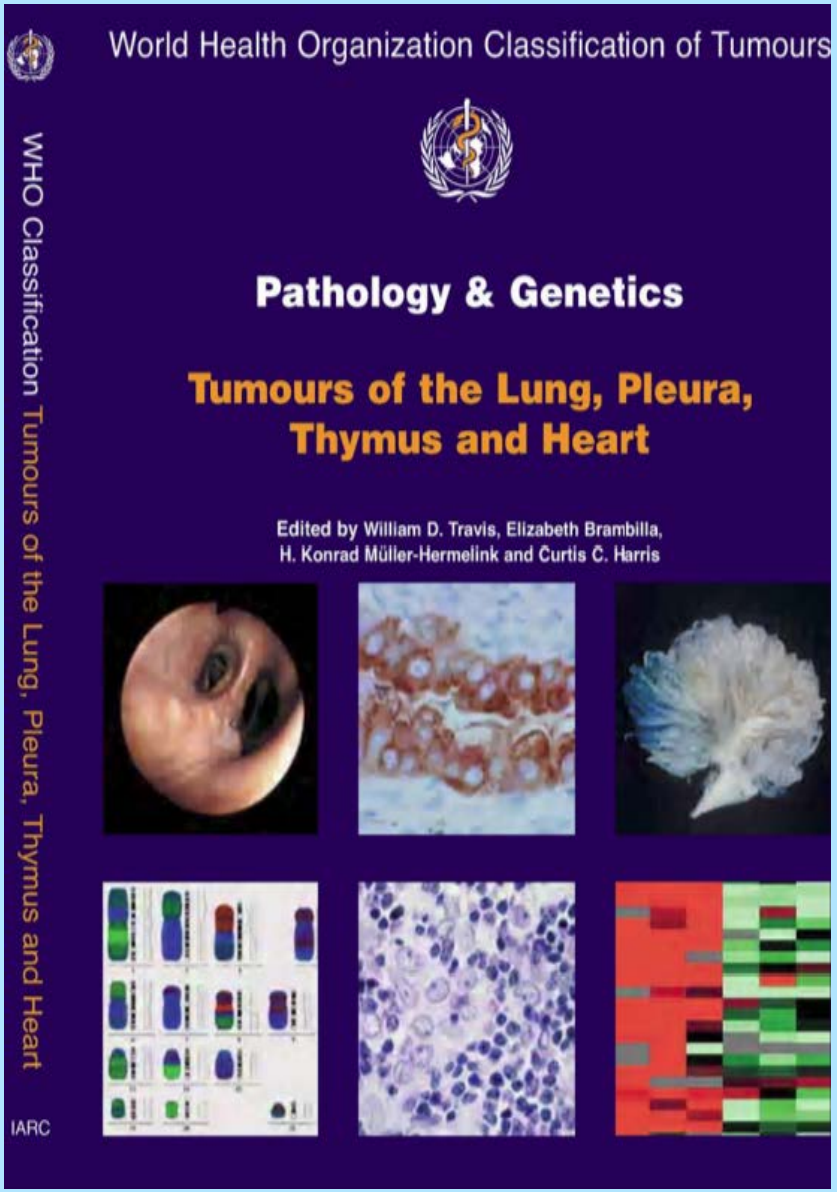
Patolog
Overlege dr. med.
Khalid Al- Shibli

Translasjonell Kreftforskning og består av ca. 20 forskere fra inn- og utland (Nord-Norge)

WHO Blue Books

Patolog
Prof. Leiv Kreyberg var leder for WHO- referansesenter for lungesvulster.
Hovedsted: Oslo (1958-74)

Skrev 1ste ”Blue Books”, WHO



- **Malignant epithelial tumours**
- Squamous cell carcinoma
  - Papillary
  - Clear cell
  - Small cell
  - Basaloid
- Small cell carcinoma
  - Combined small cell carcinoma
- Adenocarcinoma
  - Adenocarcinoma, mixed subtype
  - Acinar adenocarcinoma
  - Papillary adenocarcinoma
  - Bronchioloalveolar carcinoma
    - Nonmucinous
    - Mucinous
    - Mixed nonmucinous and mucinous or indeterminate
  - Solid adenocarcinoma with mucin production
    - Fetal adenocarcinoma
    - Mucinous ("colloid") carcinoma
    - Mucinous cystadenocarcinoma
    - Signet ring adenocarcinoma
    - Clear cell adenocarcinoma
- Large cell carcinoma
  - Large cell neuroendocrine carcinoma
  - Combined large cell neuroendocrine carcinoma
  - Basaloid carcinoma
  - Lymphoepithelioma-like carcinoma
  - Clear cell carcinoma
  - Large cell carcinoma with rhabdoid phenotype
- Adenosquamous carcinoma
- Sarcomatoid carcinoma
  - Pleomorphic carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma
  - Carcinosarcoma
  - Pulmonary blastoma
- Carcinoid tumour
  - Typical carcinoid
  - Atypical carcinoid
- Salivary gland tumours
  - Mucoepidermoid carcinoma
  - Adenoid cystic carcinoma
  - Epithelial-myoepithelial carcinoma

- **Mesenchymal tumours**

- Epithelioid haemangioendothelioma
- Angiosarcoma
- Pleuropulmonary blastoma
- Chondroma
- Congenial peribronchial myofibroblastic tumour
- Diffuse pulmonary lymphangiomatosis
- Inflammatory myofibroblastic tumour
- Lymphangioleiomyomatosis
- Synovial sarcoma
  - Monophasic
  - Biphasic
- Pulmonary artery sarcoma
- Pulmonary vein sarcoma

- **Lymphoproliferative tumours**
- Marginal zone B-cell lymphoma of the MALT
- Diffuse large B-cell lymphoma
- Lymphomatoid granulomatosis
- Langerhans cell histiocytosis

- **Miscellaneous tumours**
- Harmatoma
- Sclerosing hemangioma
- Clear cell tumour
- Germ cell tumours
- Teratoma, mature
- Immature
- Other germ cell tumours
- Intrapulmonary thymoma
- Melanoma

- **Metastatic tumours**

Lung Cancer Pathology

Non-small cell lung cancer

- Squamous cell
- Adenocarcinoma
  - Bronchioloalvelolar cell carcinoma
  - Adenosquamous
- Large cell undifferentiated

Small cell or "oat cell"

Preinvasive lesjoner

Plateepiteldysplasi,

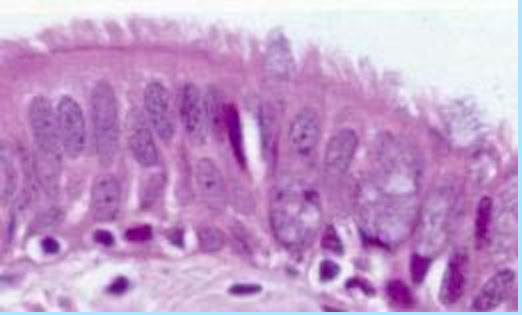
lett, middels og grov

ca. in situ

Atypisk adenomatøs hyperplasi (AAH)

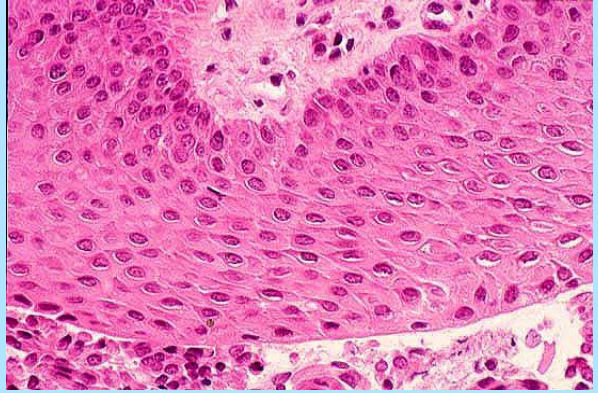
Diffus ideopatisk pulmonær

neuroendokrin celle hyperplasi

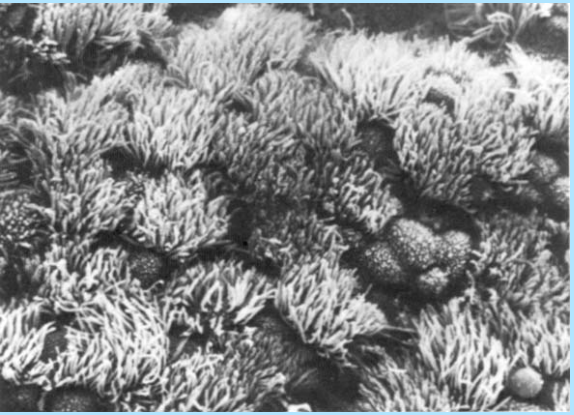


Normal

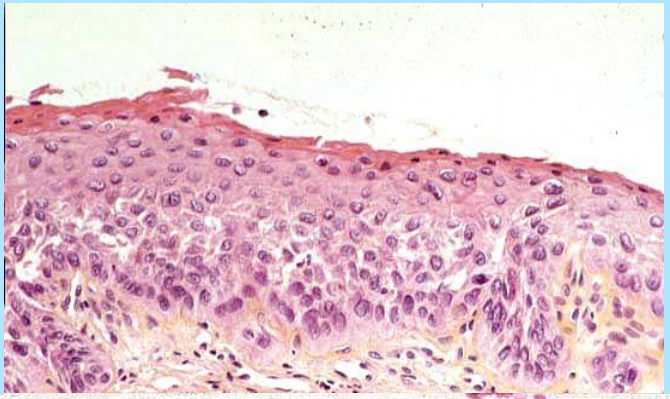
HYPERPLASI



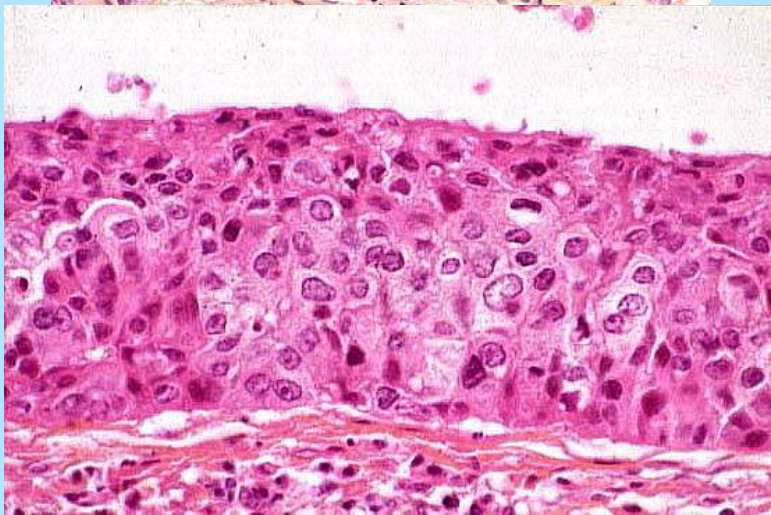
PATEEPITELMETAPLASI



Moderat dysplasi

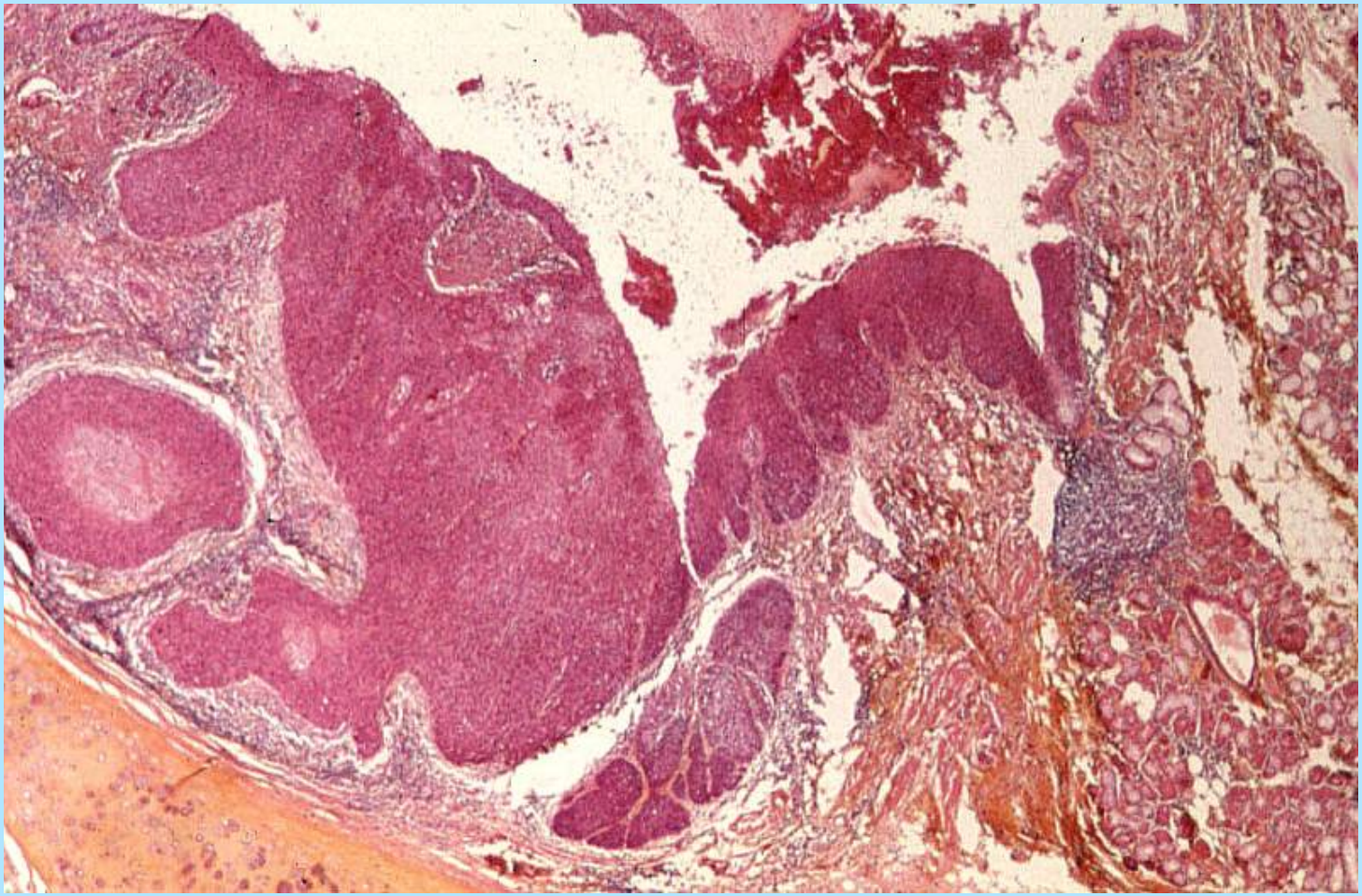


Lett dysplasi



Grov dysplasi

Invasiv ca.: T 1



Plateepitelcancer

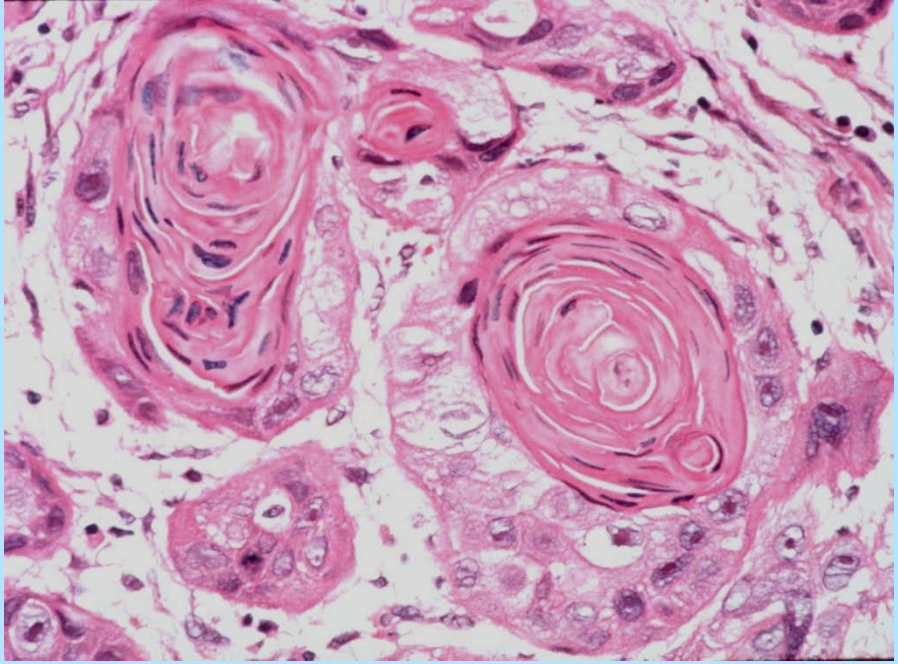
= Keratinisering og/ eller intercellularbroer

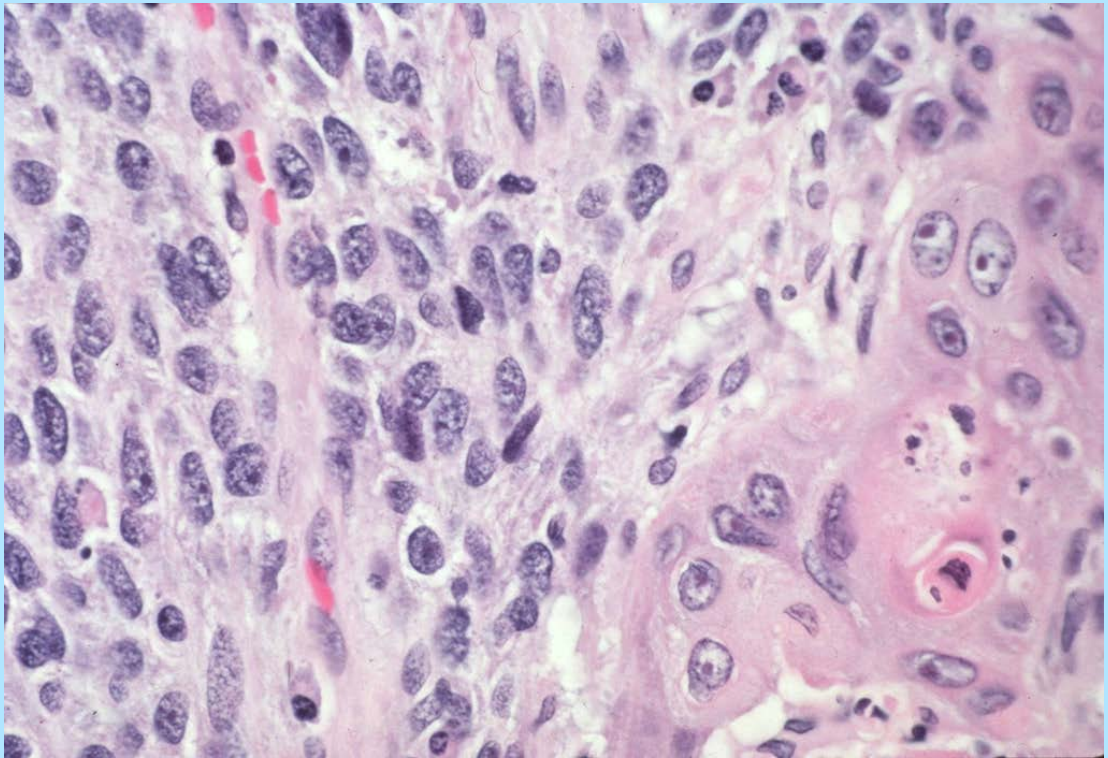
- M 45%, K 25%
- 35%.
- Røking X 25%
- 5 års overlevelse: 15%
- Lokalisert sentralt

  (i bronkial plateepitelmetaplasi)

Varianter:

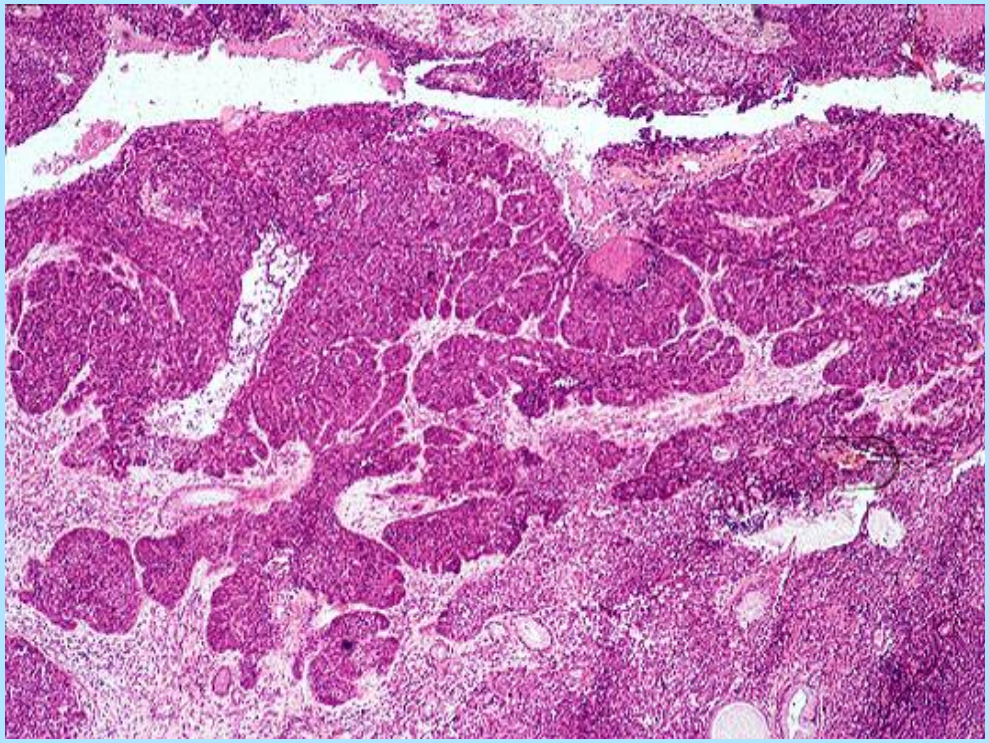
- Papillær
- Klarcellet
- Småcellet
- Basaloid

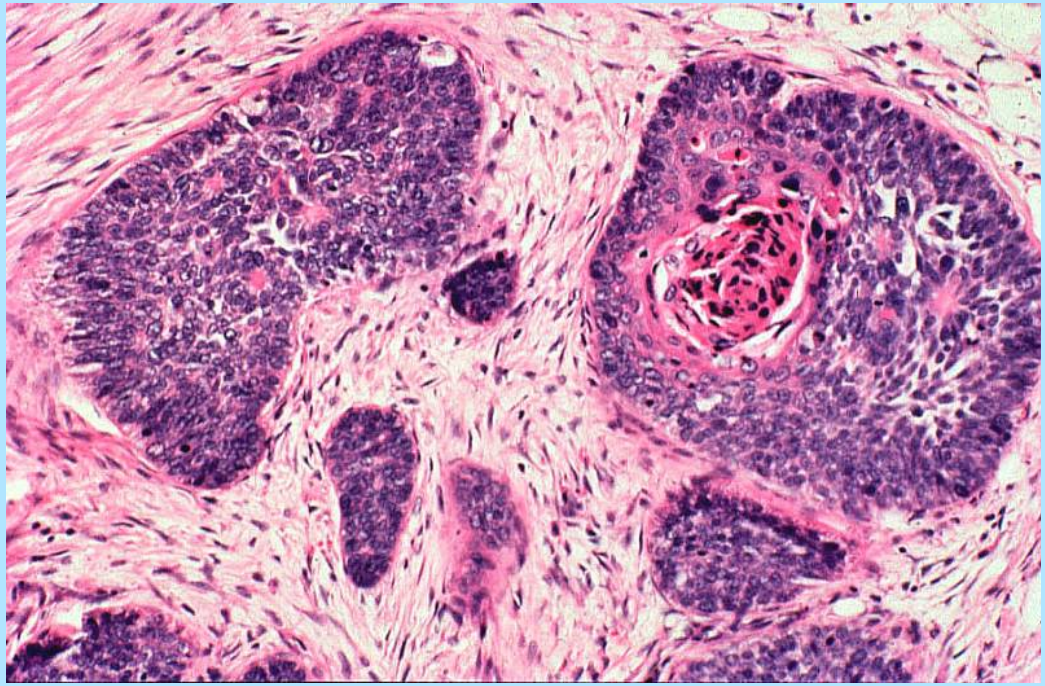




Basaloid carcinom

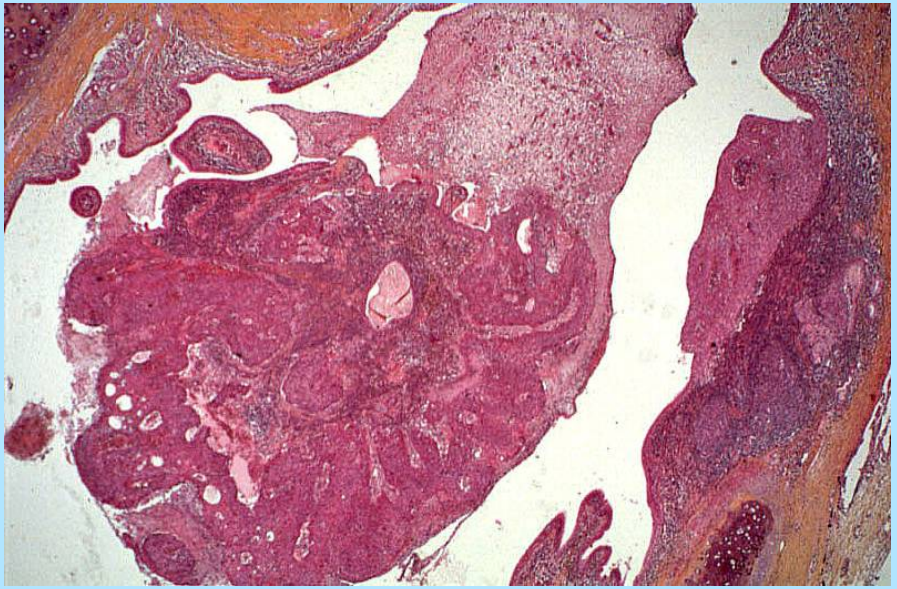
Ikke neuroendokrin markører
Dårlig prognose





Basaloid variant

Papillær variant



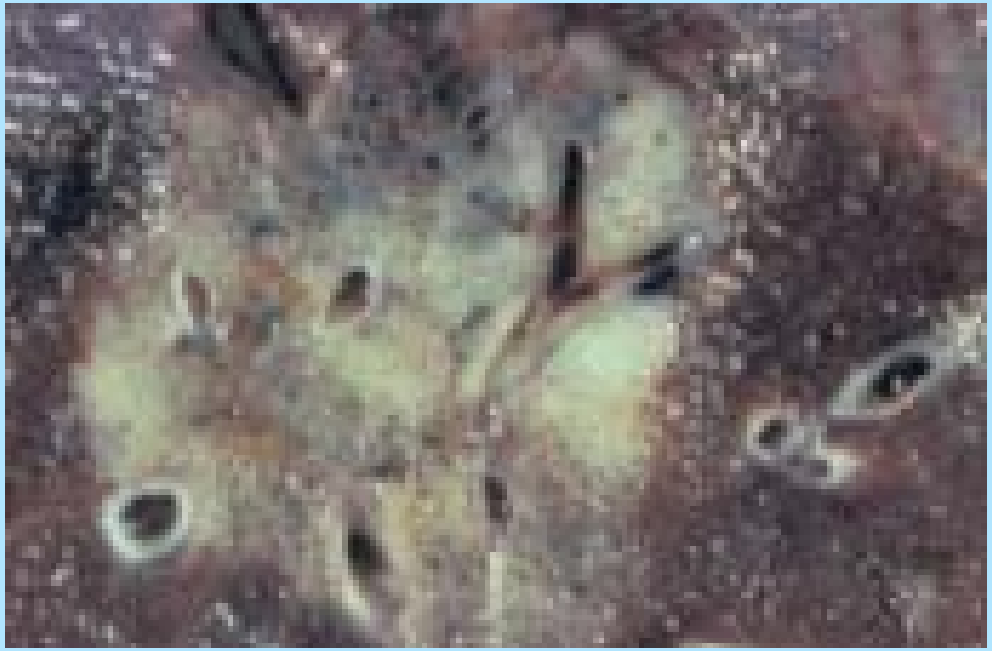
Adenocarsinom

- Hyppigst (30-70%)
- Meget heterogen(pat.,rad.,klinisk, molekular)
- Literatur forvirring:

  BAC forskjellig brukt

  Forskjellig klassifisering- økende
- Molekular forhold

Adenokarsinom

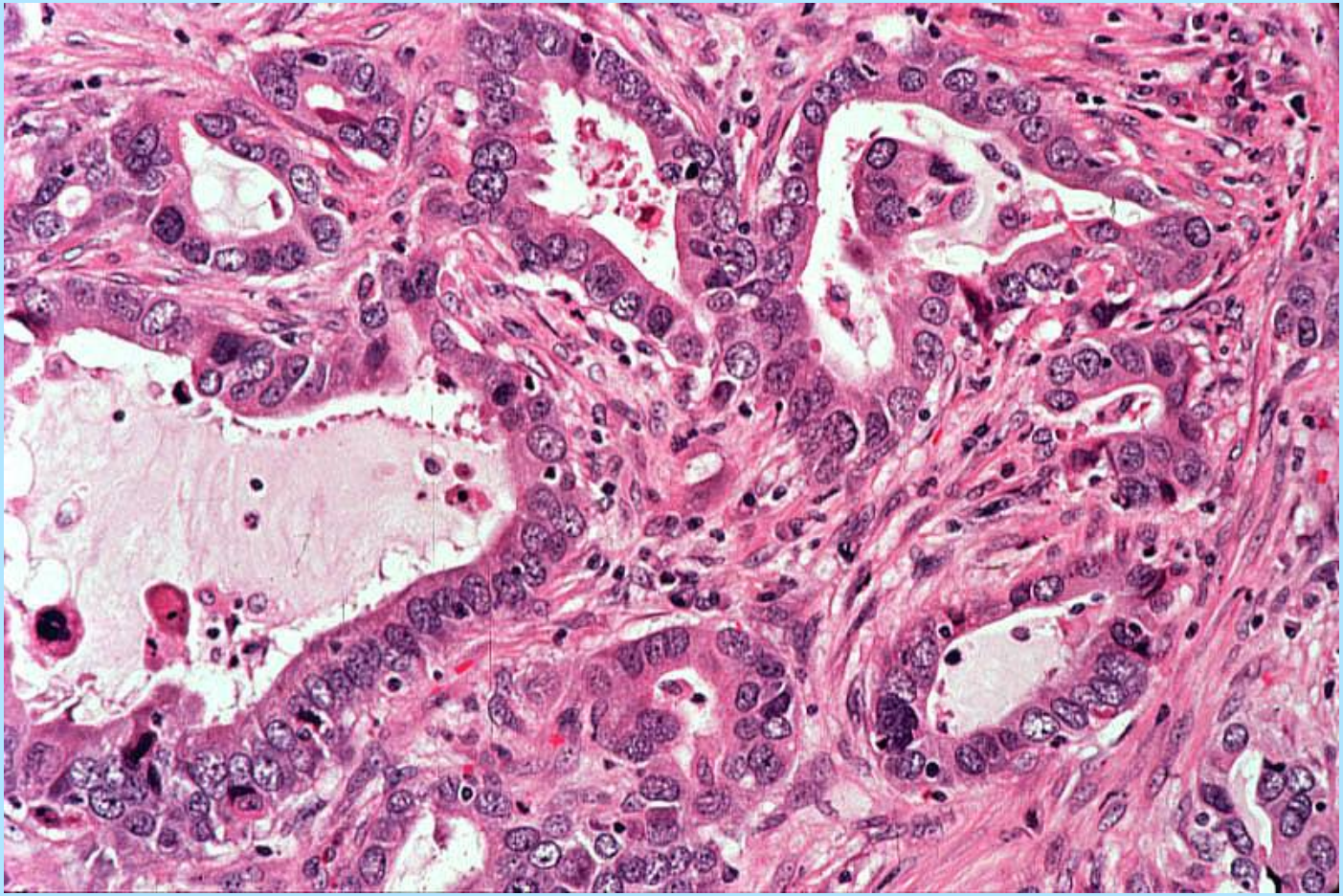


- M 30%, K 40%
- Perifer
- 80% blandet histologi (>1 subtype)
- Røking: X 3
- 5 år overlevelse: 15- 20%

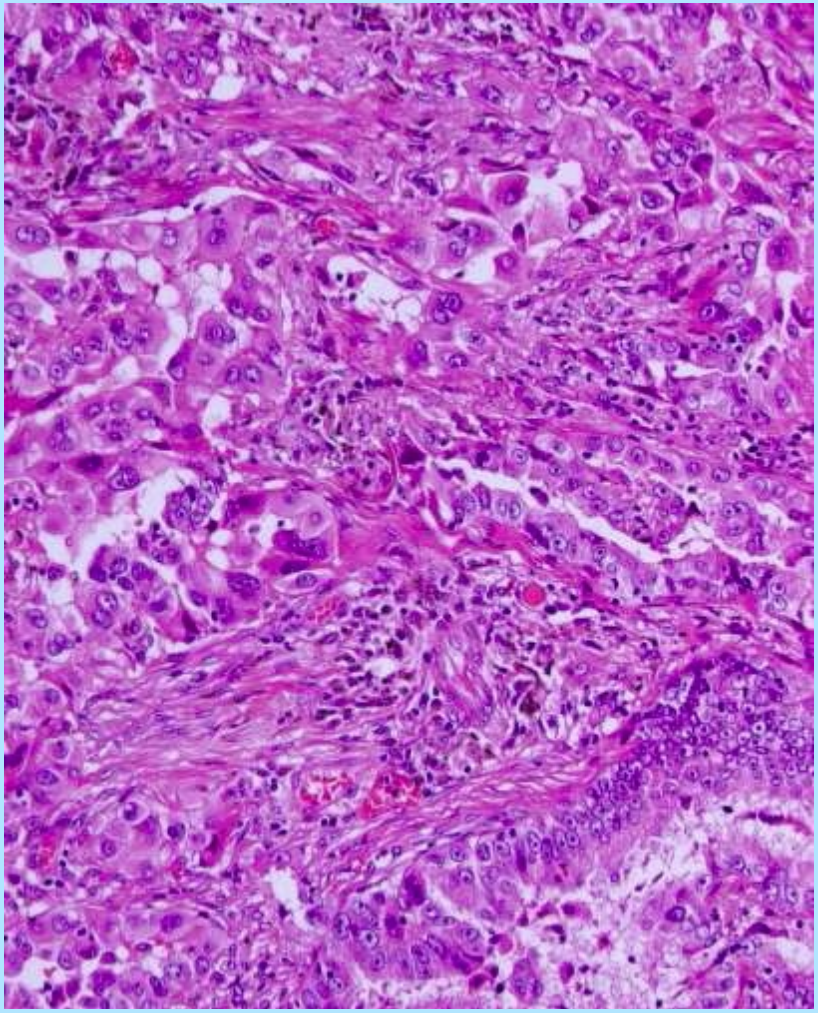
- Preinvasiv: Atypisk adenomatøs hyperplasi

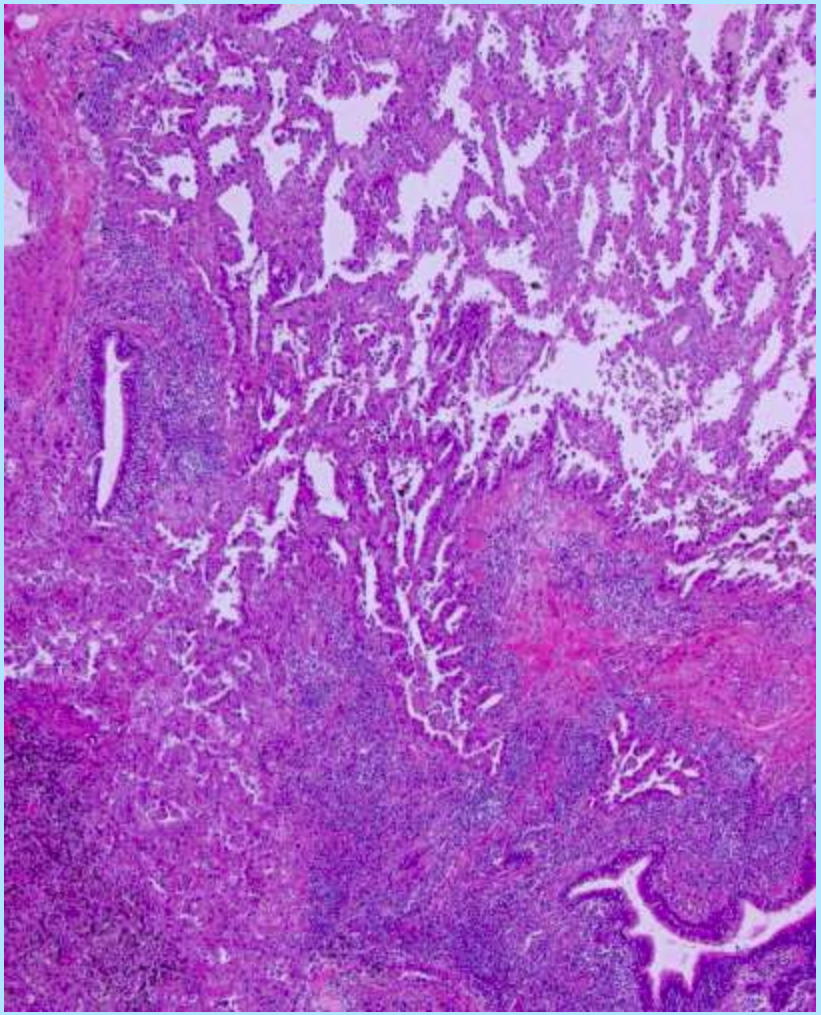
WHO 1999 - 2004	WHO 1981
Adenocarcinoma	**Adenocarcinoma**
. Adenocarcinoma mixed subtype	
. Acinar adenocarcinoma	a. Acinar
. Papillary adenocarcinoma	b. Papillary
. Bronchioloalveolar carcinoma Non-mucinous Mucinous Mixed mucinous - non mucinous	c. Bronchioloalveolar carcinoma
. Solid adenocarcinoma with mucin	d. Solid adenocarcinoma with mucus formation
. Variants:	

ADENOCARCINOMA ACINAR

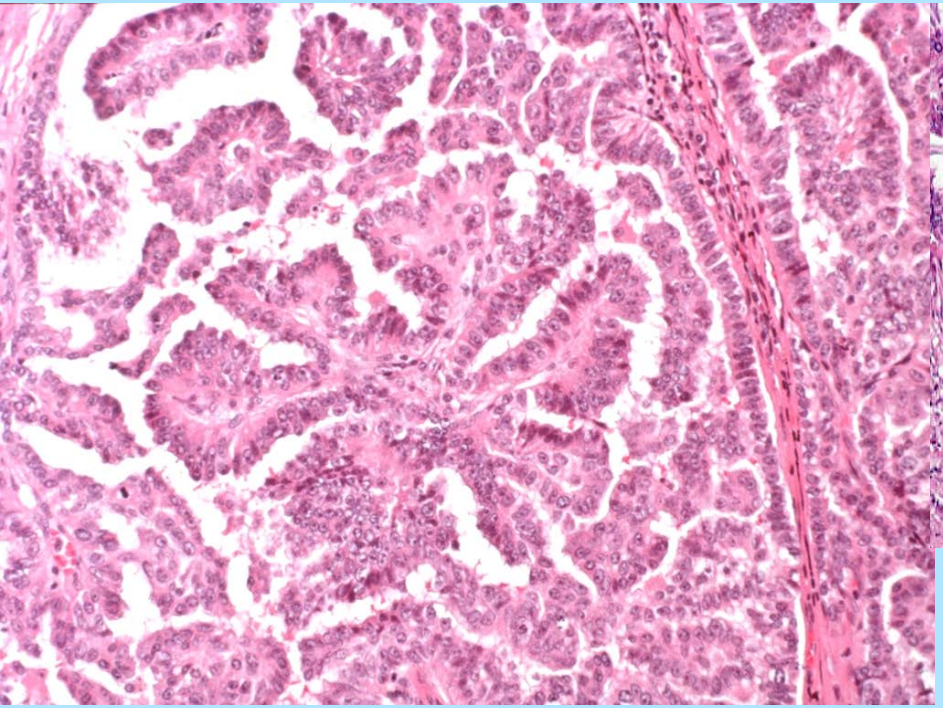


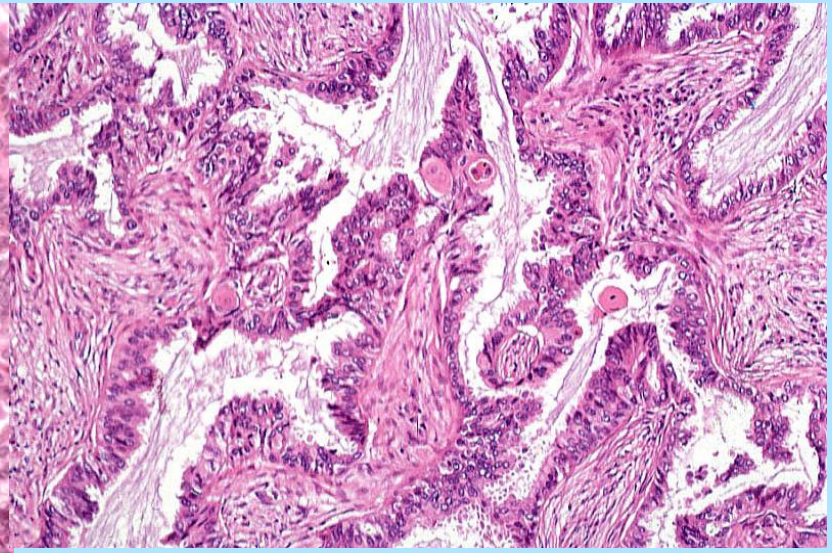
ADENOCARCINOM BLANDET SUBTYPE



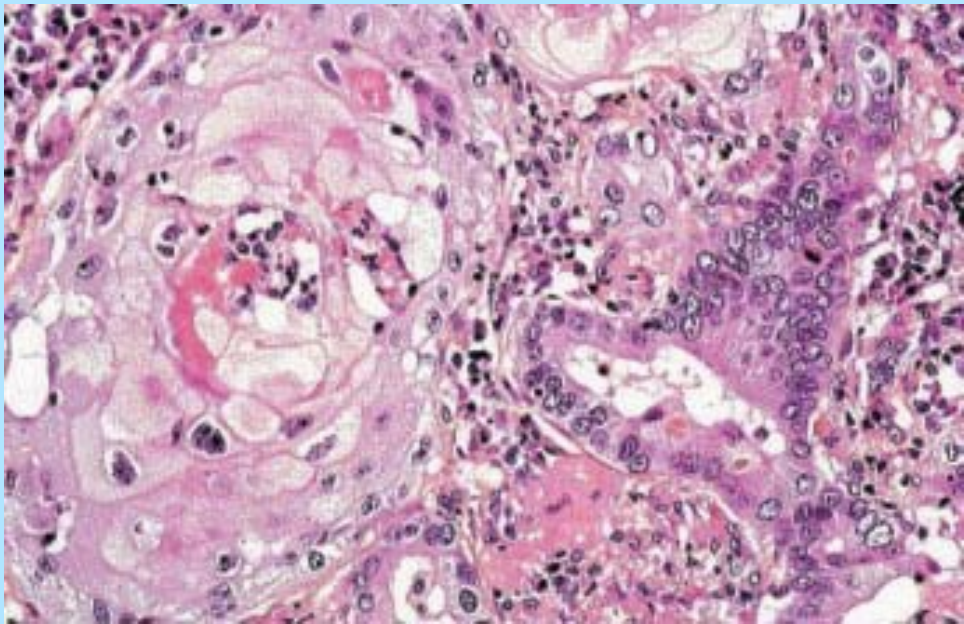


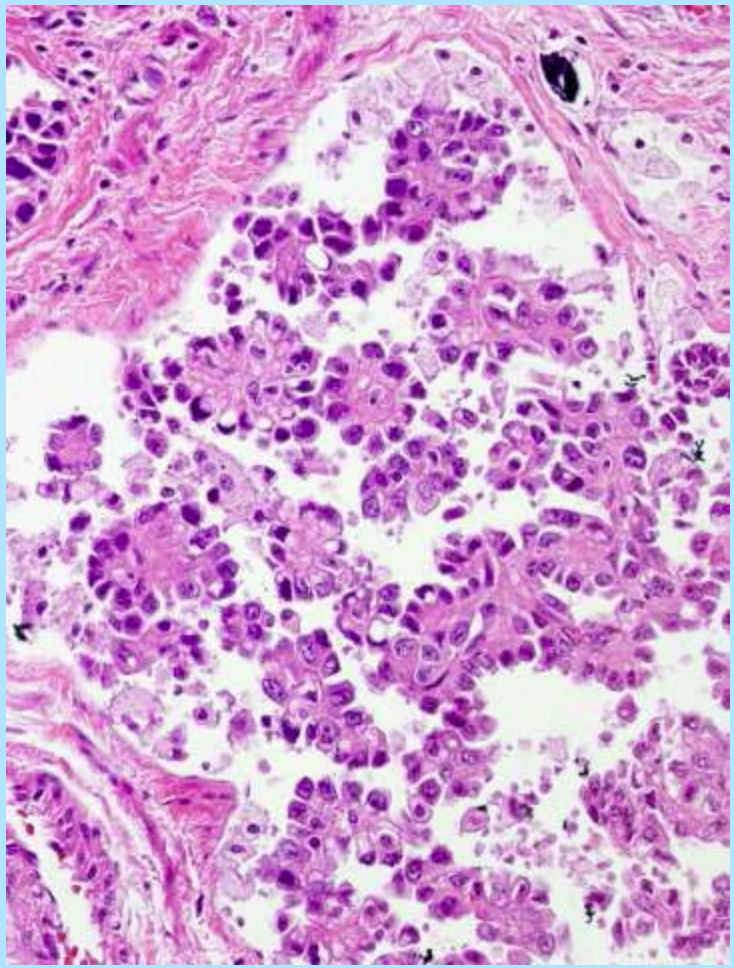
Papillært adenocarcinom

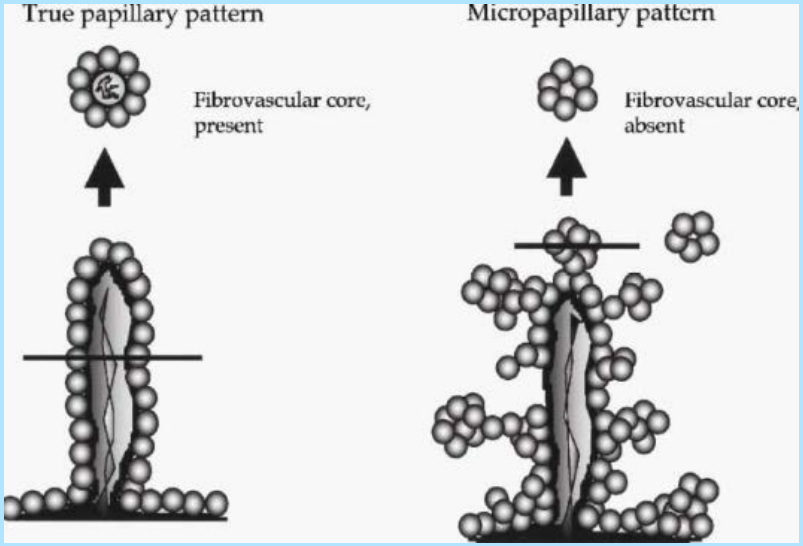




Adenosquamøst carcinom

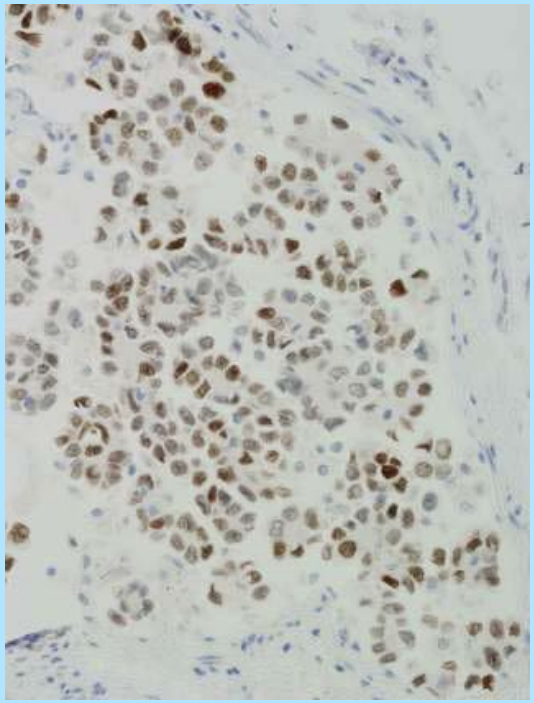




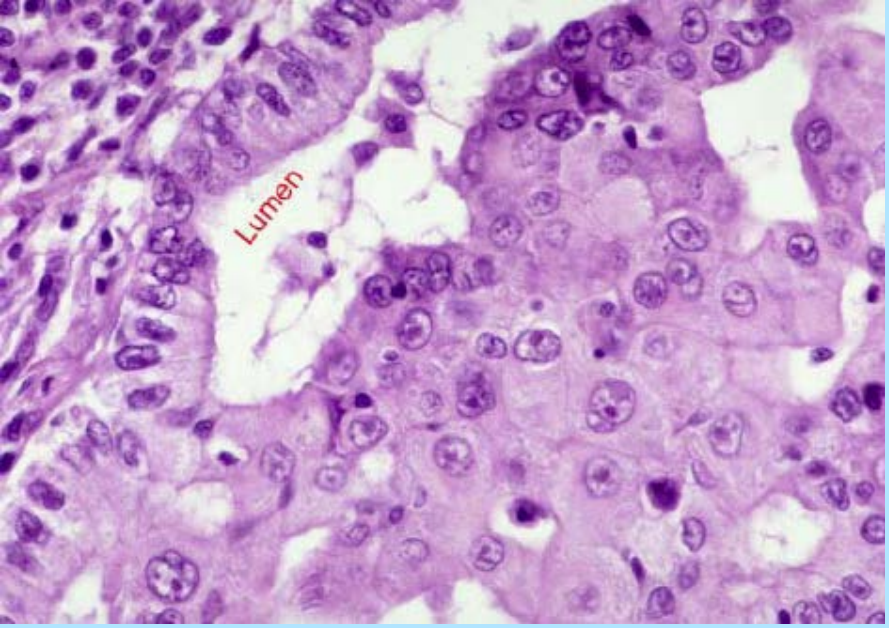


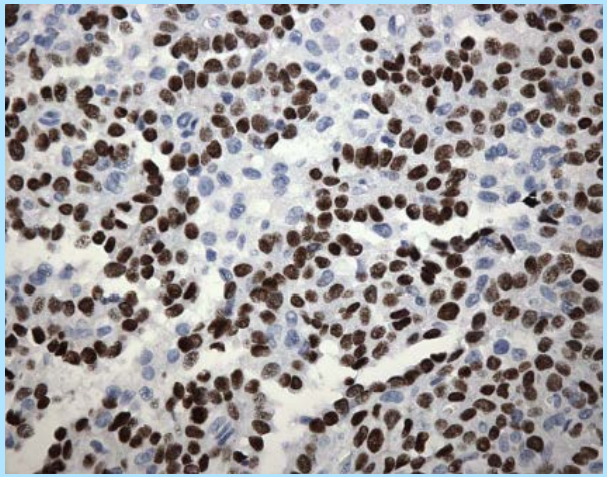
Miyoshi T, et al: AJSP 27:101, 2003

MICROPAPILLÆRT ADENOCARCINOMA

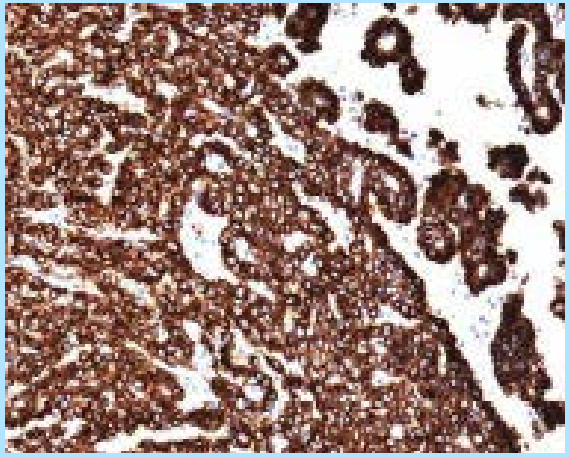


TTF-1



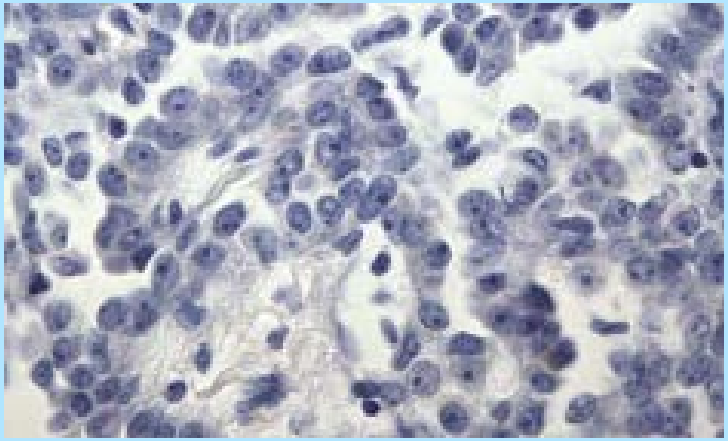


TTF-1



Cytokeratin 7 (CK7) +
Adenocarcinom lunge

Colon cancer -

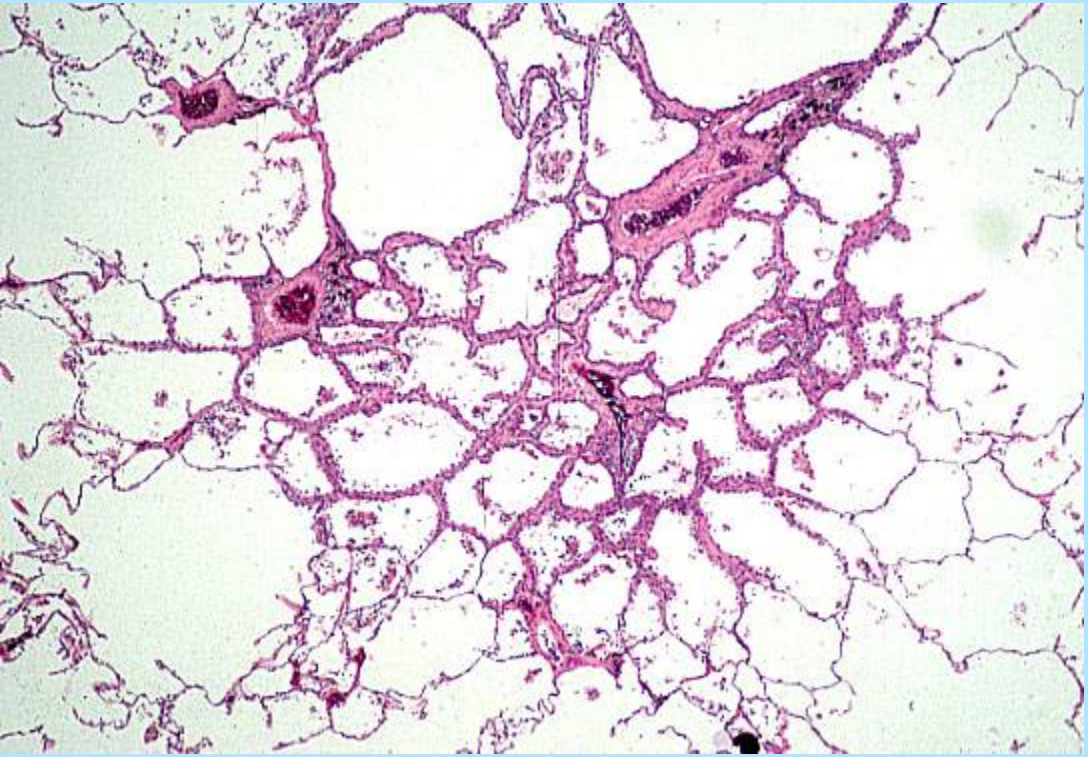


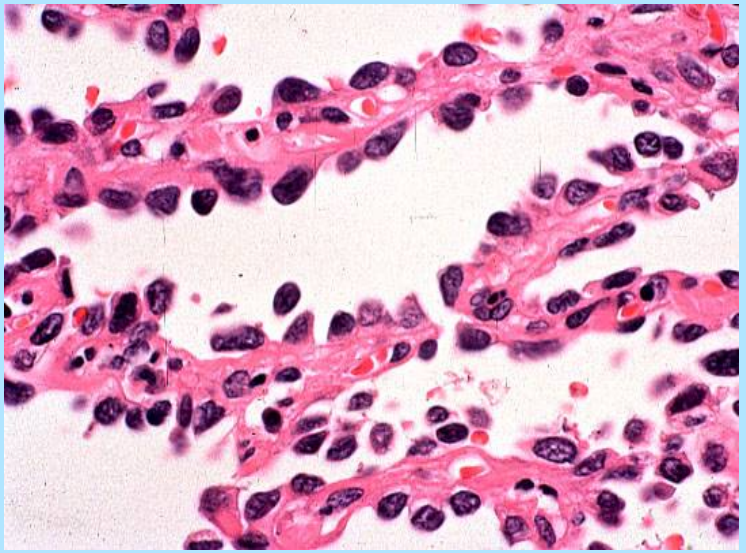
Cytokeratin 20 (CK20) –
Adenocarcinom, lunge

Colon cancers ofte +

Bronchioloalveolært carcinom (BAC)

- 2%
- Røking: ja
- M= K
- 5 år overlevelse: 25-40 %
- Presentasjon:
- Single- multiple knuter
- Miliary tumor
- ”pneumonisk form”
- (”restriktiv”: en ikke- invasiv tumor)





Atypisk adenomatøs hyperplasi
Adenocarcinom

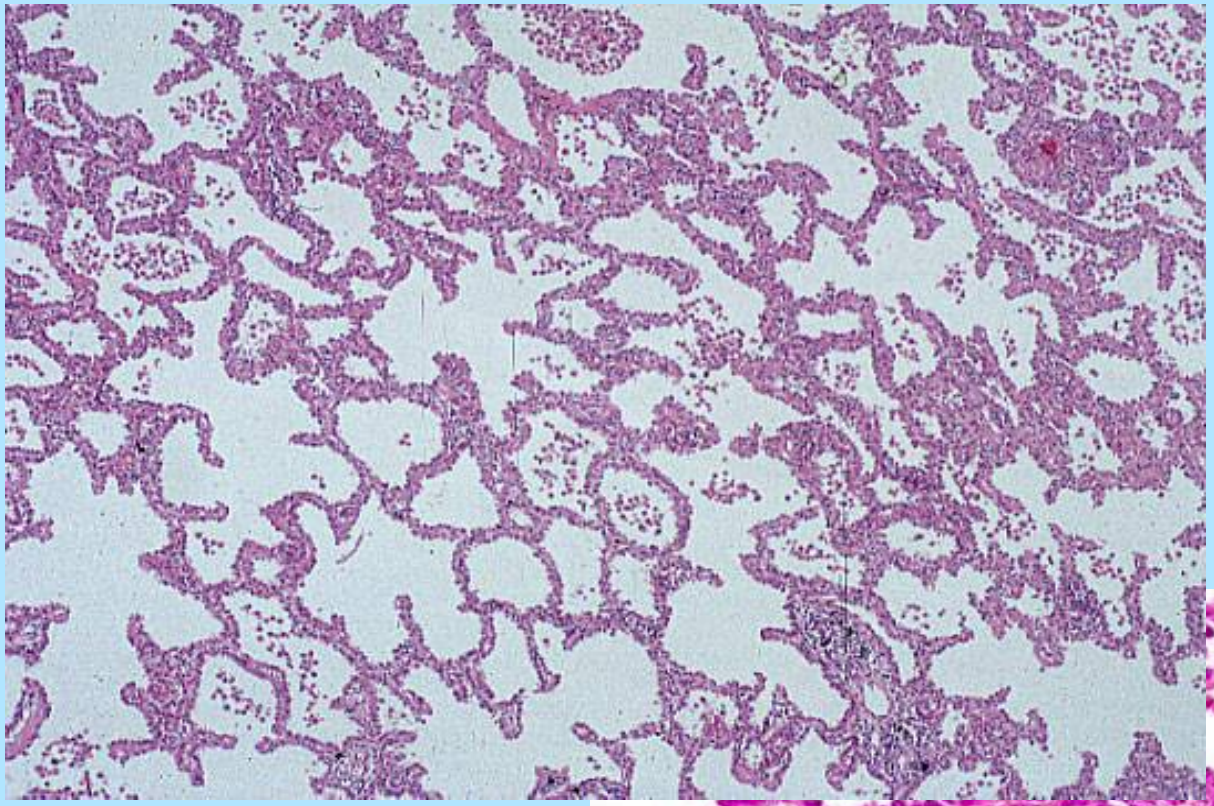
BAC

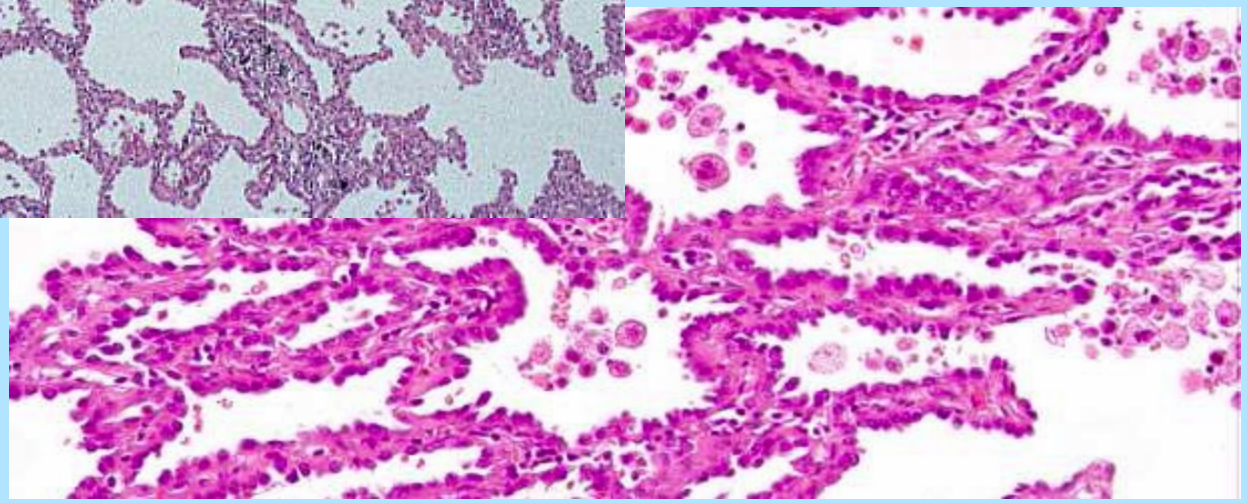
Ren vekst langs alveolar vegg

- Ikke invasjon (stromal, vaskulær, plaural)
- Ikke sentralt arr, ikke desmoplastisk stroma reaksjon
- Ikke papillære strukturer i lumen
- Tidl. rapporterte BAC: nå ad. ca., blandet subtype

- **Diagnosen (BAC) kan ikke stilles i små biopsier!**

BRONCHIOLOALVEOLÆRT CARCINOM (BAC), NONMUCINØS

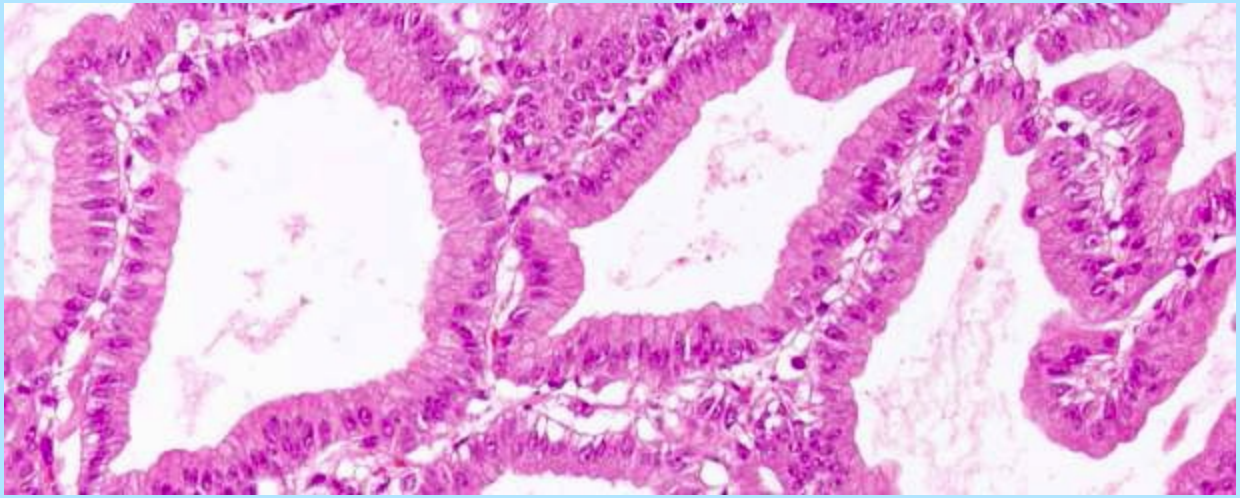




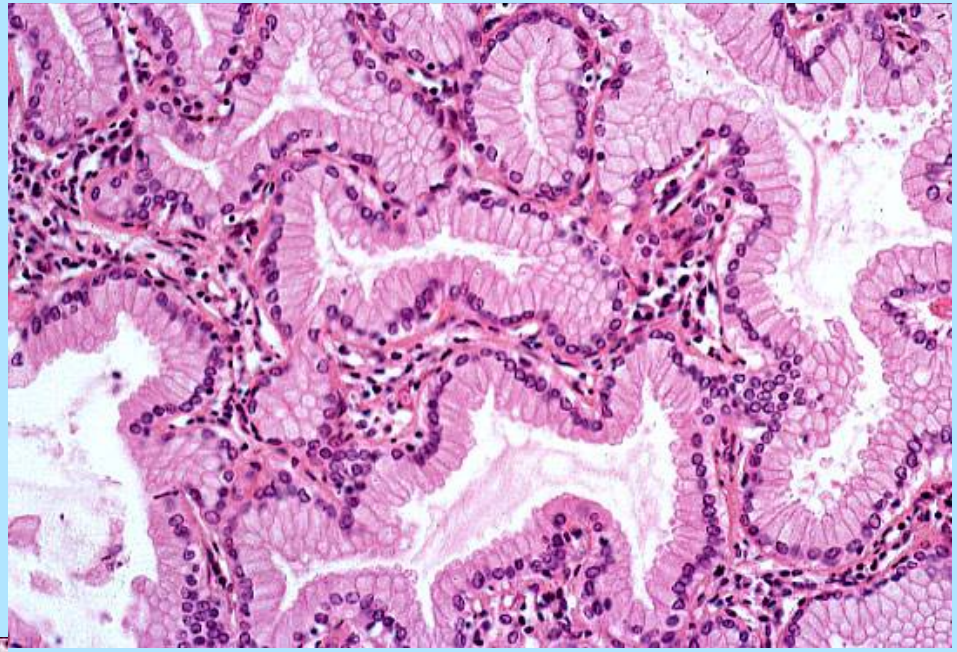
BRONCHIOLOALVEOLÆRT CARCINOM, MUCINØST

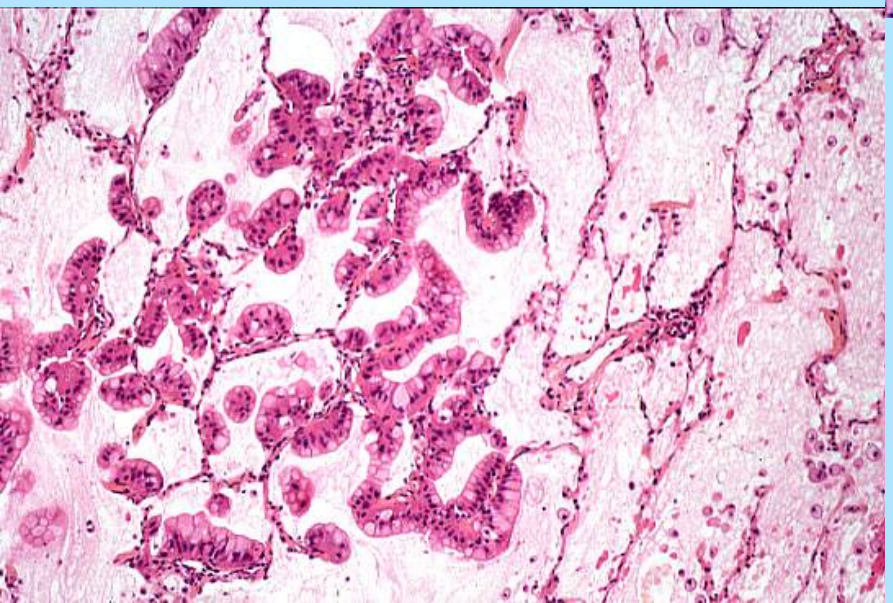
Sammenlignet med nonmucinøs BAC:

Oftere Kras mutationer
Oftere multicentrisk
Dårligere prognose

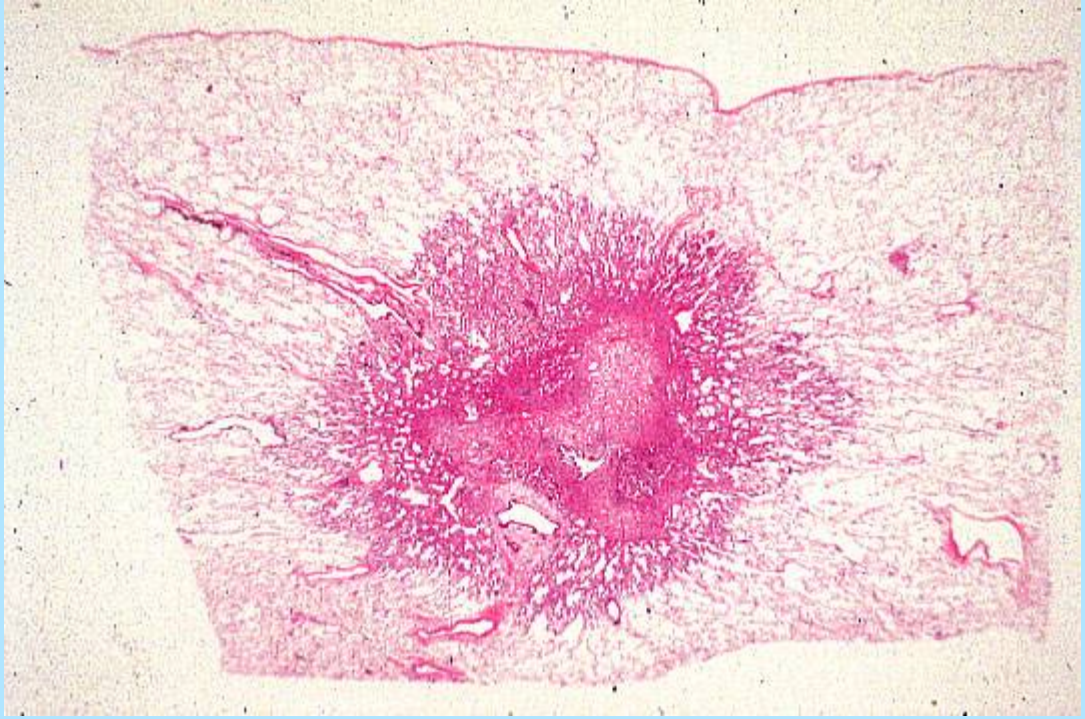


BRONCHIOLOALVEOLÆRT CARCINOM, MUCINØST

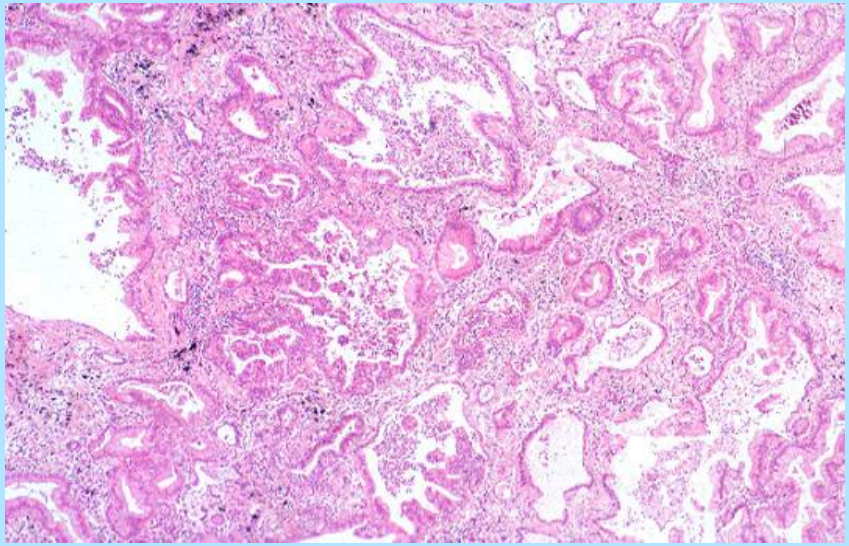




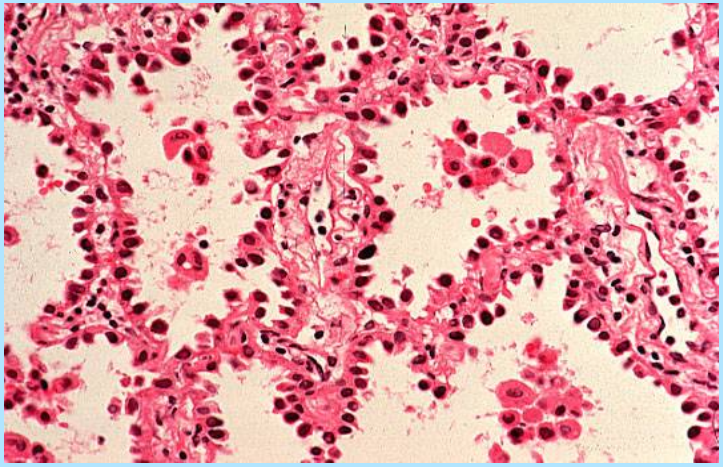
Mucinøs BAC : satellite lesion



Adenocarcinom

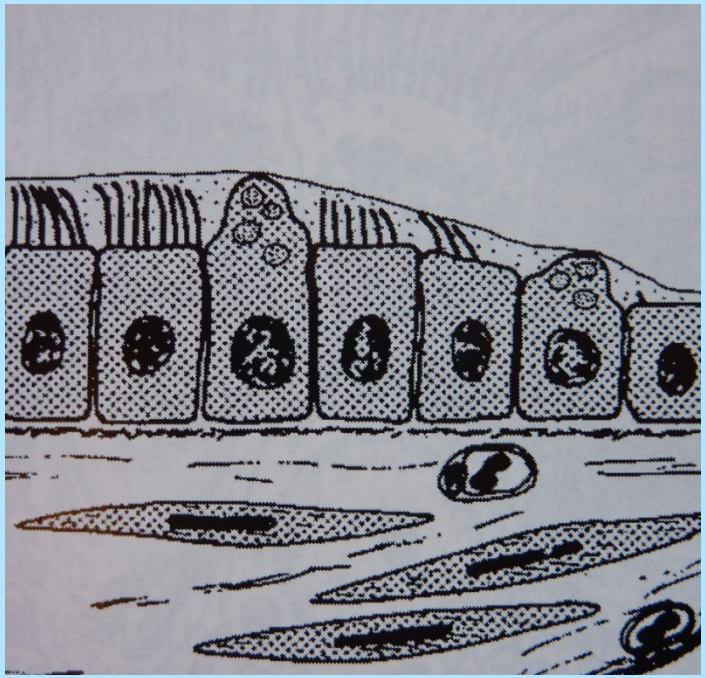


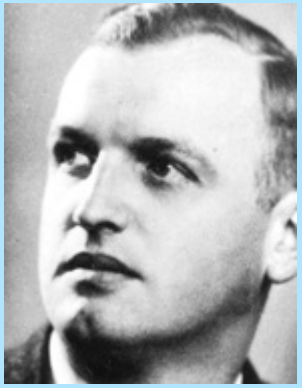
Centralt



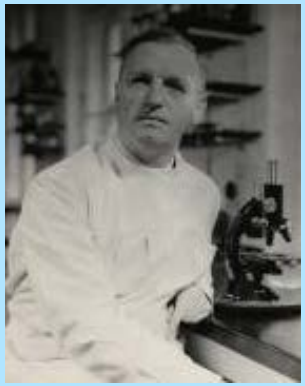
Perifert

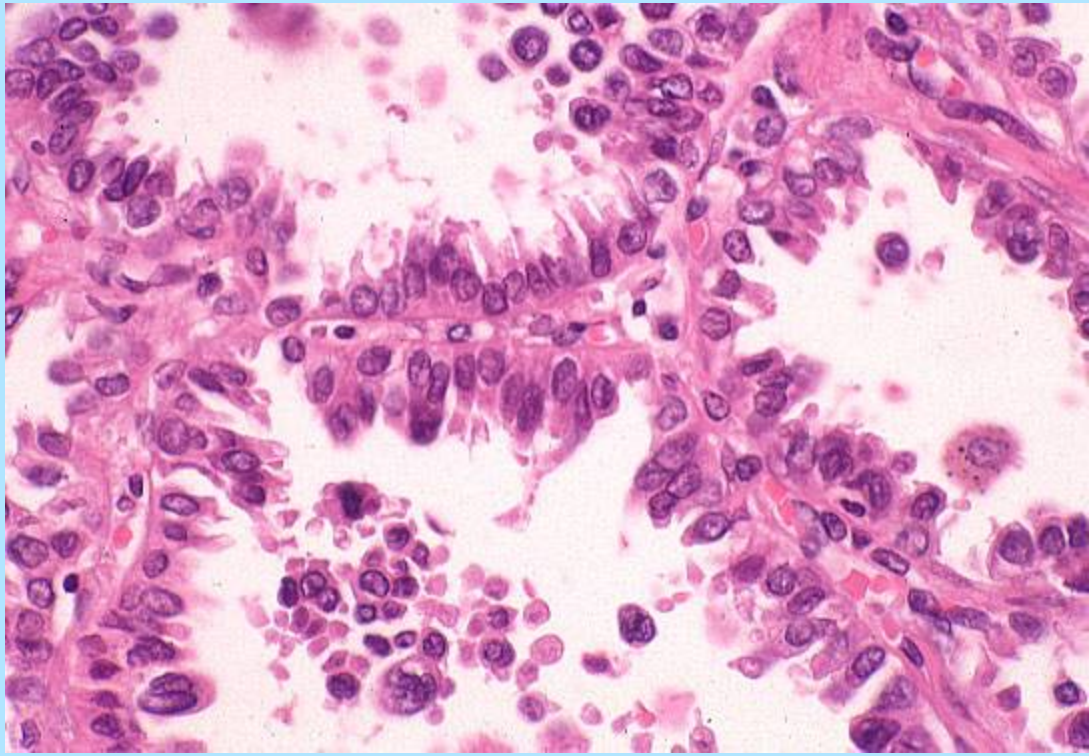
BAC : Clara Cell Type





Max Clara , 1937





Bronchioloalveolar carcinoma: clinical significance

- Less than 2 cm BAC can be curable by economic surgical resection:

  100% - 5 year survival

  Noguchi et al Cancer 1995

- Size of central scar in ADC with peripheral BAC less than 3cm
  - < 5mm 100% 5 year survival
  - 5-15mm 71% 5 year survival
  - ≥ 15mm 40% 5 year survival

  independent prognostic factor p = 0.01

  Suzuki et al. Ann Thorac Surg 2000

  Terasaki et al Am. J. Surg. Pathol. 2003

Småcellet carcinom

- 25%
- Mann>>Kvinner
- Røking: 95%
- 5 år overlevelse: 1-5 %

- Ingen kjent preinvasiv type til småcellet ca. !

SCLC history

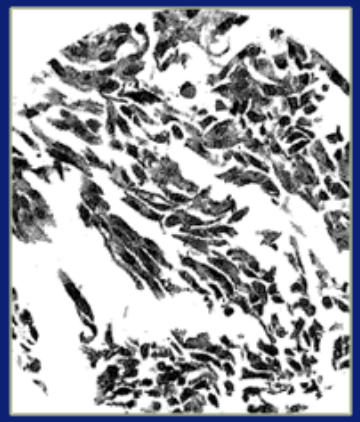
1st description by Barnard 1926

THE NATURE OF THE "OAT-CELLED SARCOMA" OF THE MEDIASTINUM.

W. G. BARNARD.

University College Hospital Medical School, London.

FIG. 5.—Oat-celled neoplasm. Near the centre a group of larger cells enclosing a minute space.



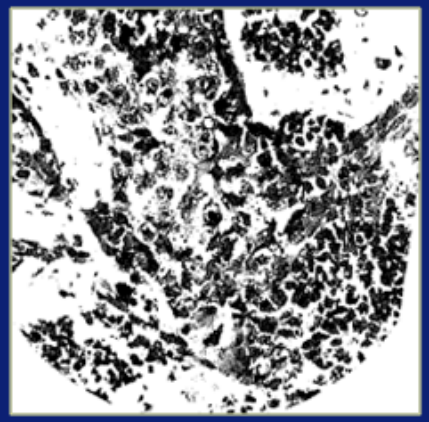


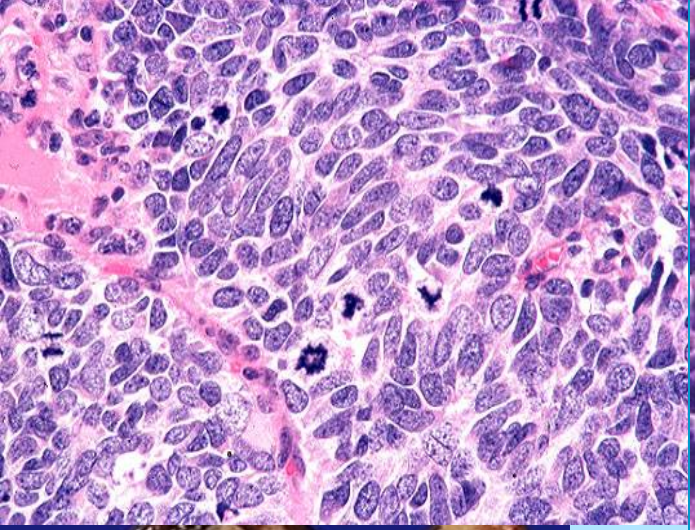
TABLE 1. *Classification of small cell lung carcinoma*

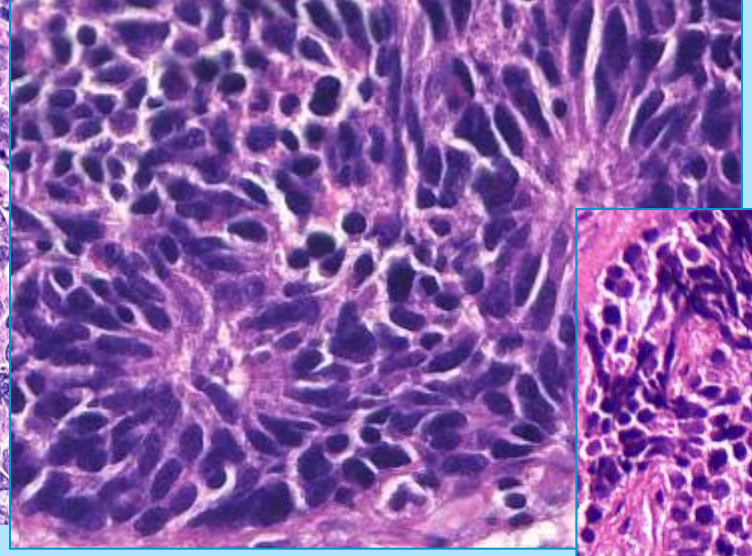
Kreyberg[31] 1962	WHO[59] 1967	1973 WP-L WHO[60] 1981	IASLC[21] 1998	WHO/IASLC[50] 1999
Oat cell	Lymphocyte-like	Oat cell	Pure SCLC	SCLC
Polygonal	Polygonal	Intermediate		
	Fusiform		Mixed (with large cells)	
	Other (containing squamous and glandular foci)	Combined	Combined	Combined SCLC (containing any other NSCLC component)

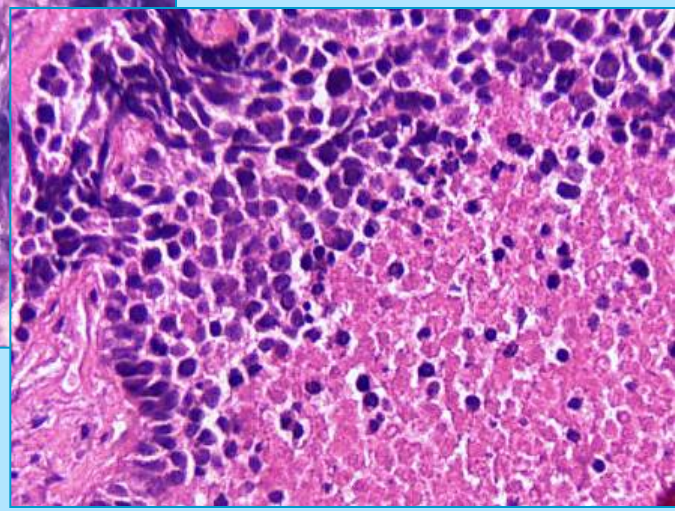
Am J Surg Pathol 26(9): 1184–1197, 2002.

Small Cell Carcinoma

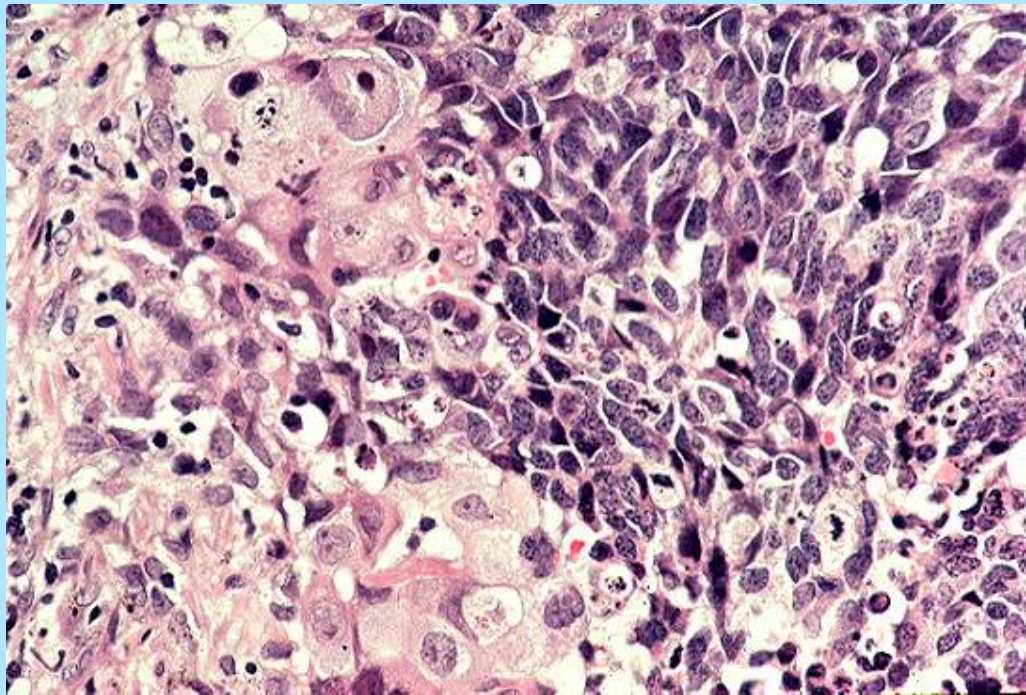
WHO 1999-2004	WHO 1981
Small Cell Carcinoma	Small Cell Carcinoma
Variant • Combined Small Cell Carcinoma	Oat cell Intermediate Combined



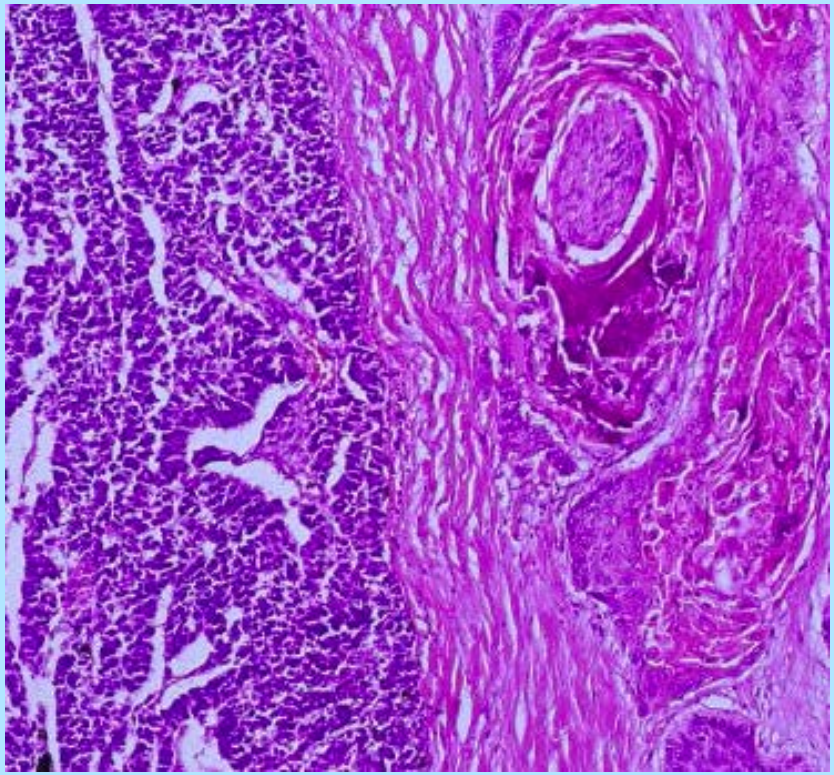




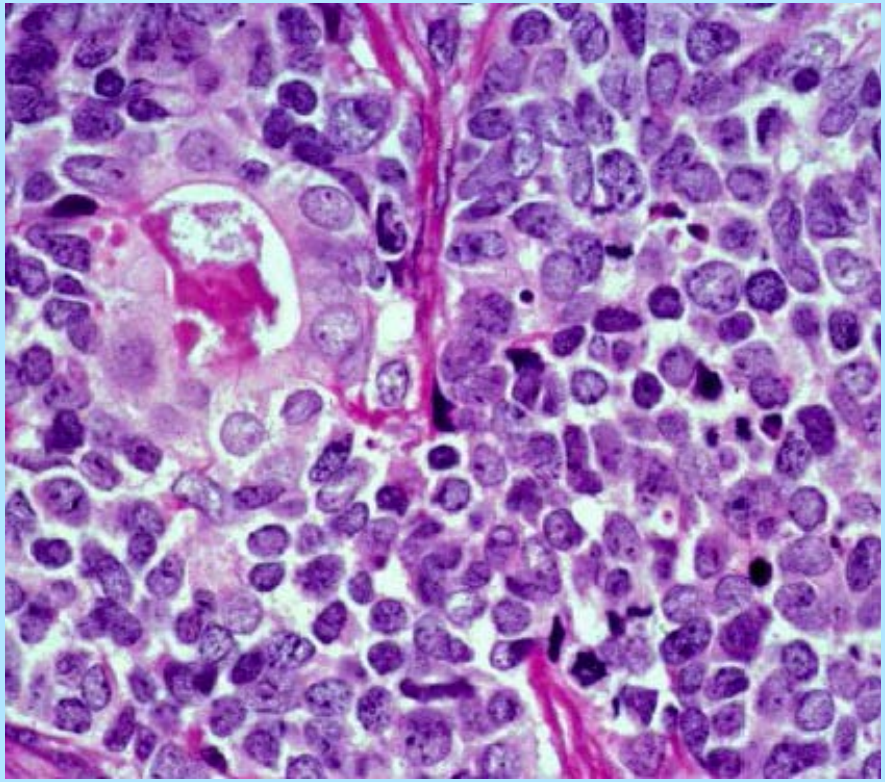
Kombinert



Kombinert SCLC &---

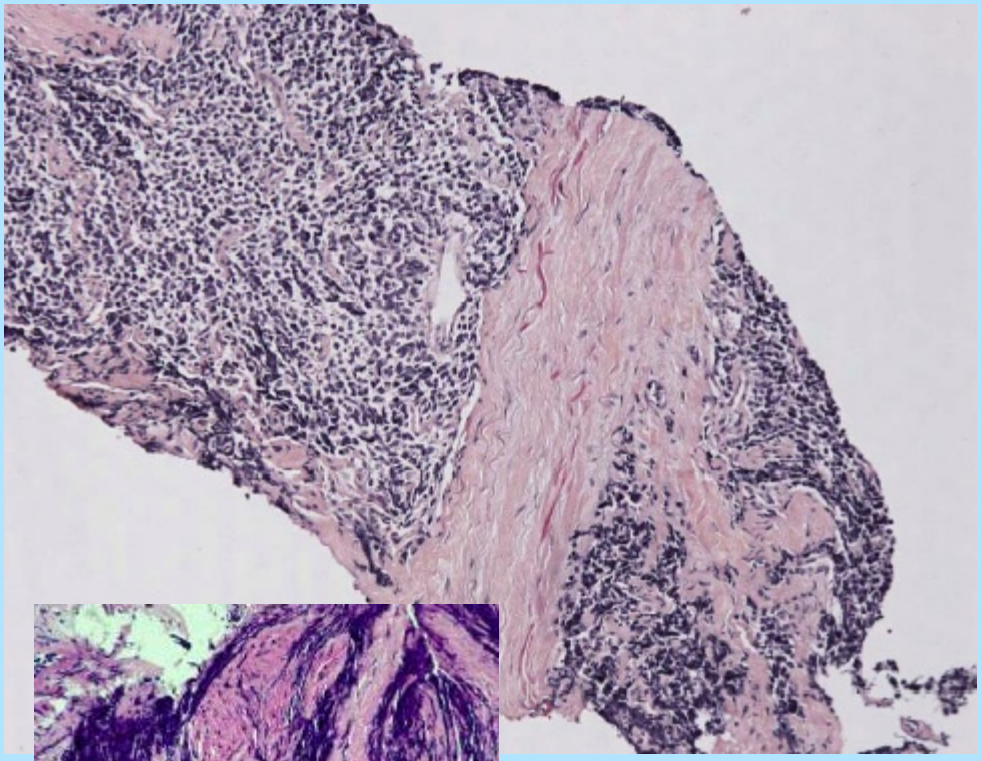


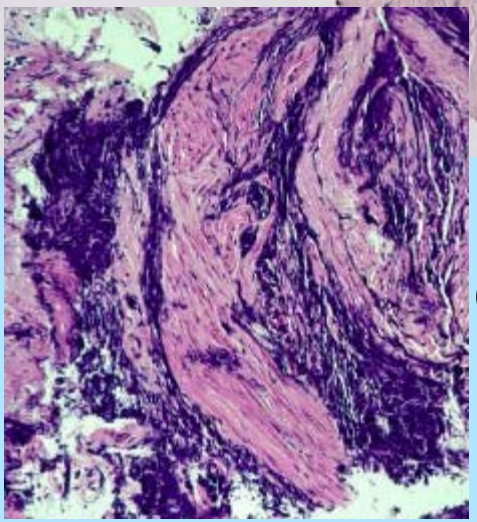
Kombinert SCLC &
PLATEEPITEL CA



Kombinert SCLC & ADENOCA

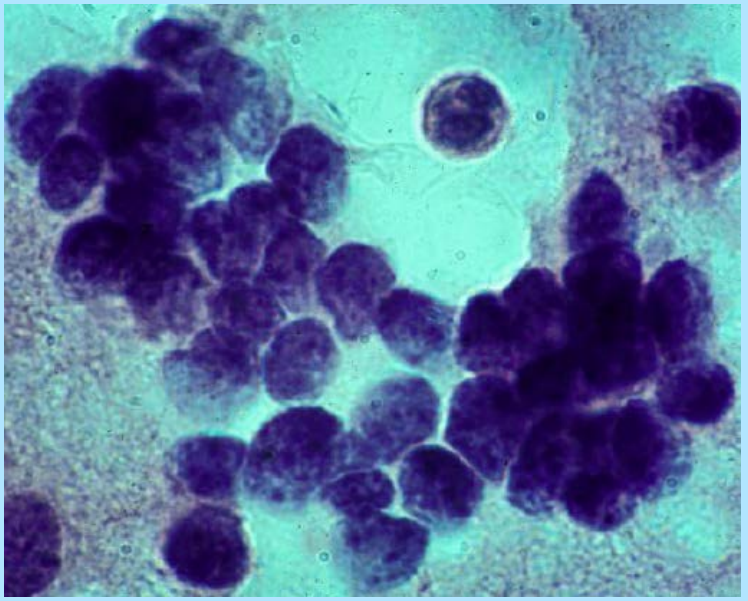
Småcellet lungecancer, biopsi





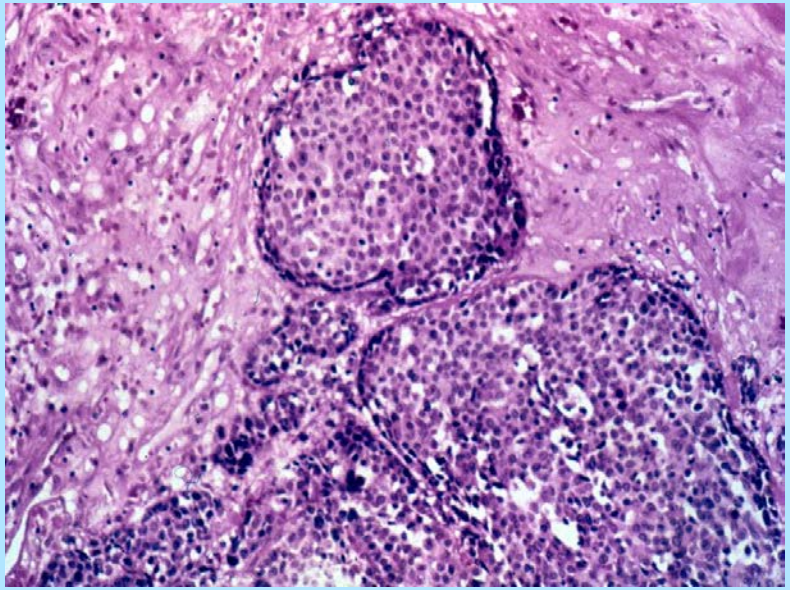
CRUSH ARTIFACT

Cytologi

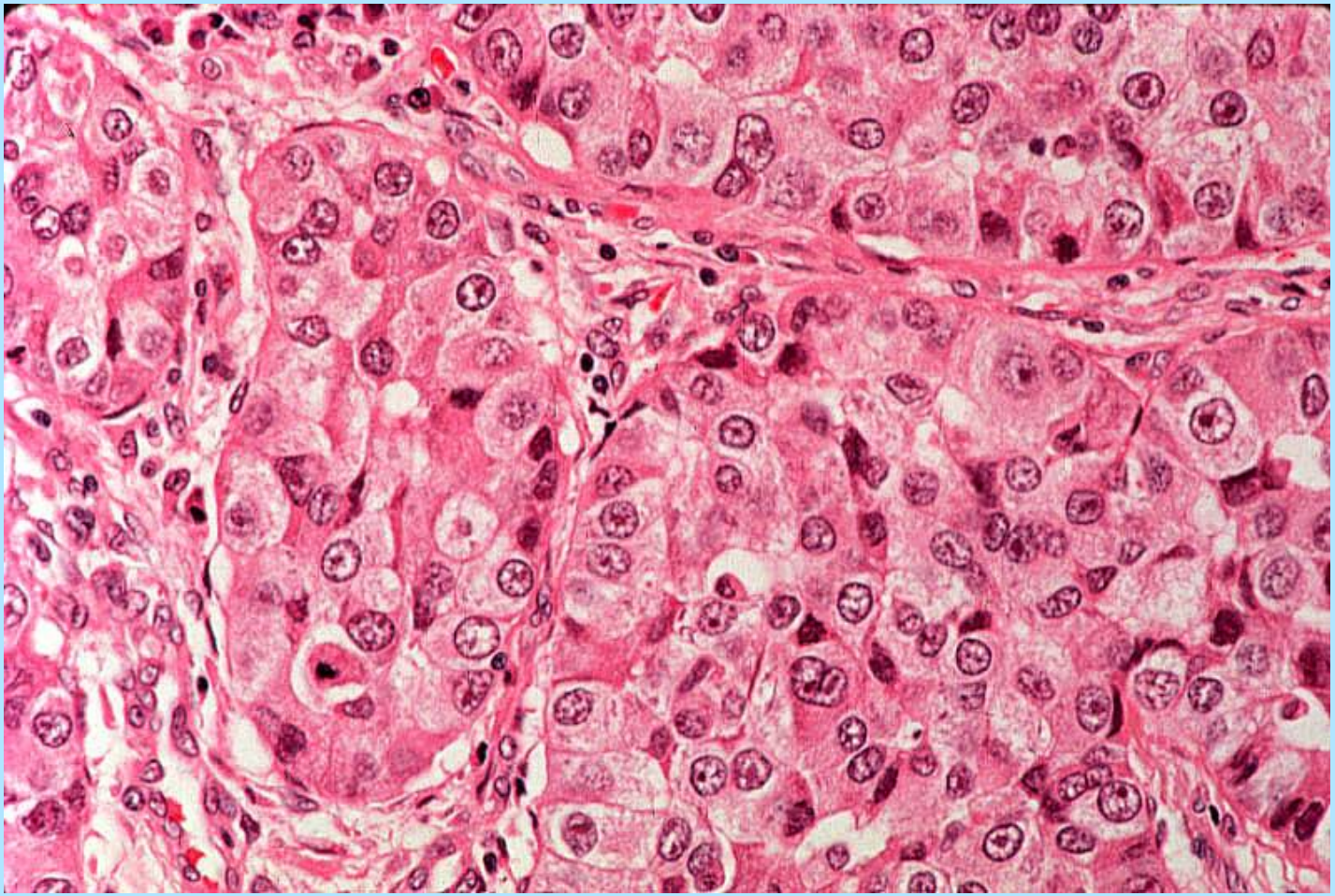


Storcellet carcinom

- ”Wastebasket group”:
- - plate-, - adeno-, - småcellet
- 10%
- Perifer
- Prognose som adeno. ca.



Storcellet lungecarcinom: NOS



The spectrum of neuroendocrine (NE) proliferation and neoplasms

I - NE cell hyperplasia and tumorlets

- A. NE cell hyperplasia
- B. Tumorlets

II - Tumors with NE morphology

- A. Typical carcinoid
- B. Atypical carcinoid
- C. Large cell neuroendocrine carcinoma
- D. Small cell carcinoma

III - Non small cell carcinomas with NE differentiation

PULMONARY NE TUMORS
CLASSIFICATION

- LOW GRADE
  - TYPICAL CARCINOID
- INTERMEDIATE GRADE
  - ATYPICAL CARCINOID

- HIGH GRADE
  - LARGE CELL NEUROENDOCRINE CARCINOMA
  - SMALL CELL CARCINOMA

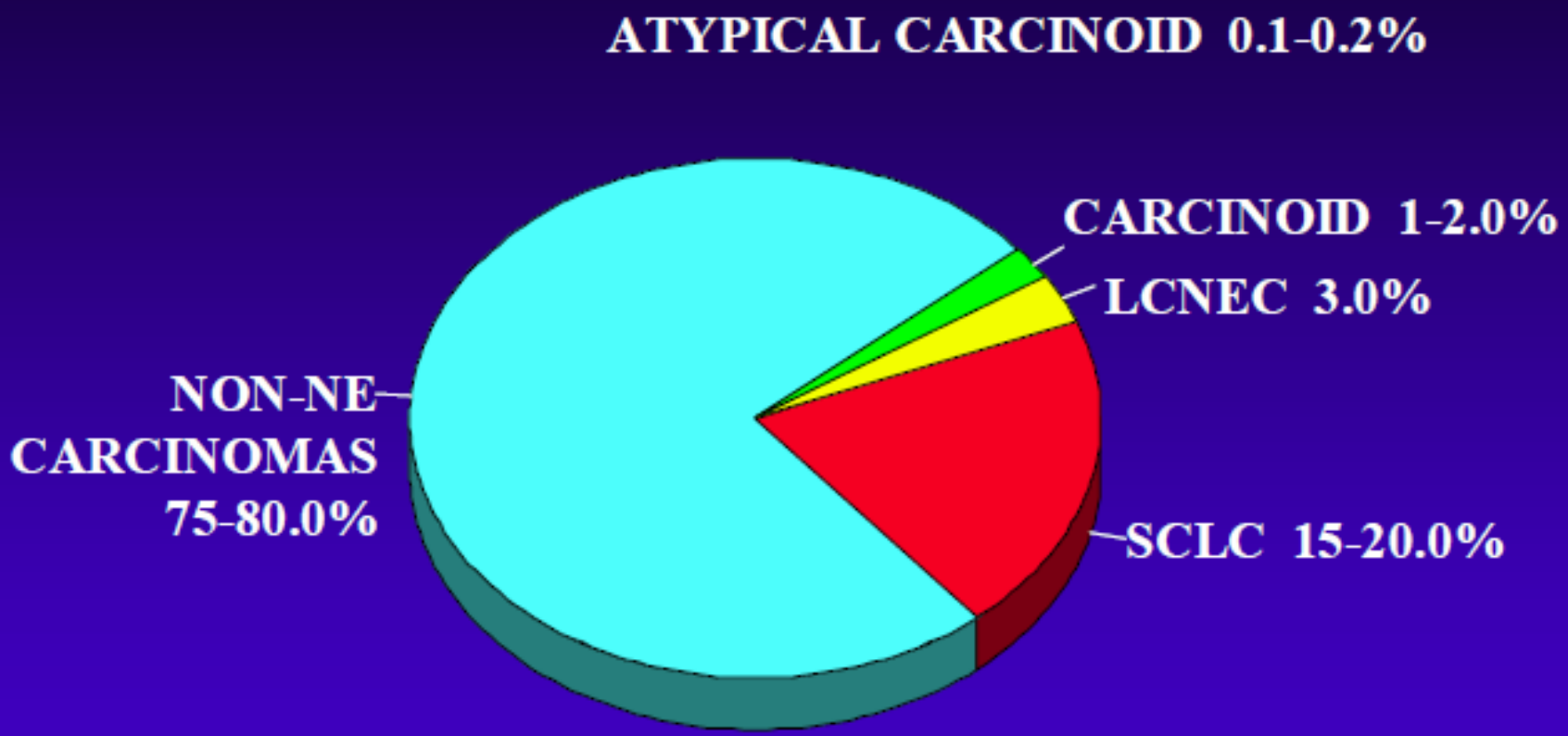
Storcellet carcinom

Storcellet neuroendokrint carcinom

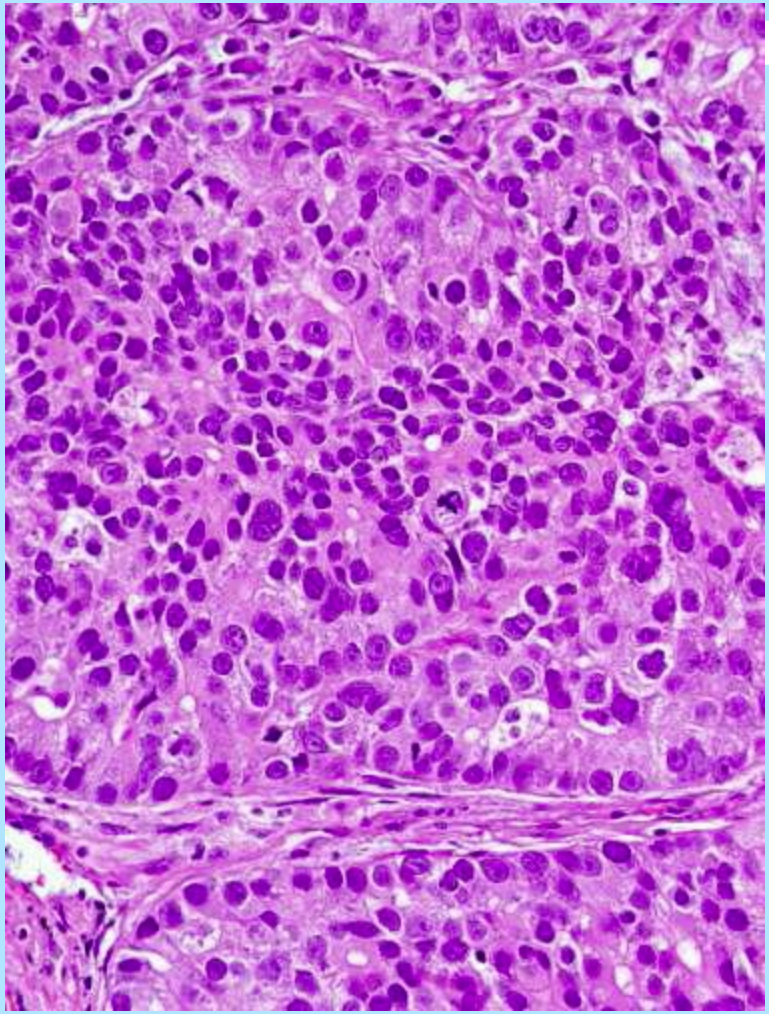
Immunhistokjemi: + Chromogranin A
Synaptophysin, CD56
TTF-1 (40%)

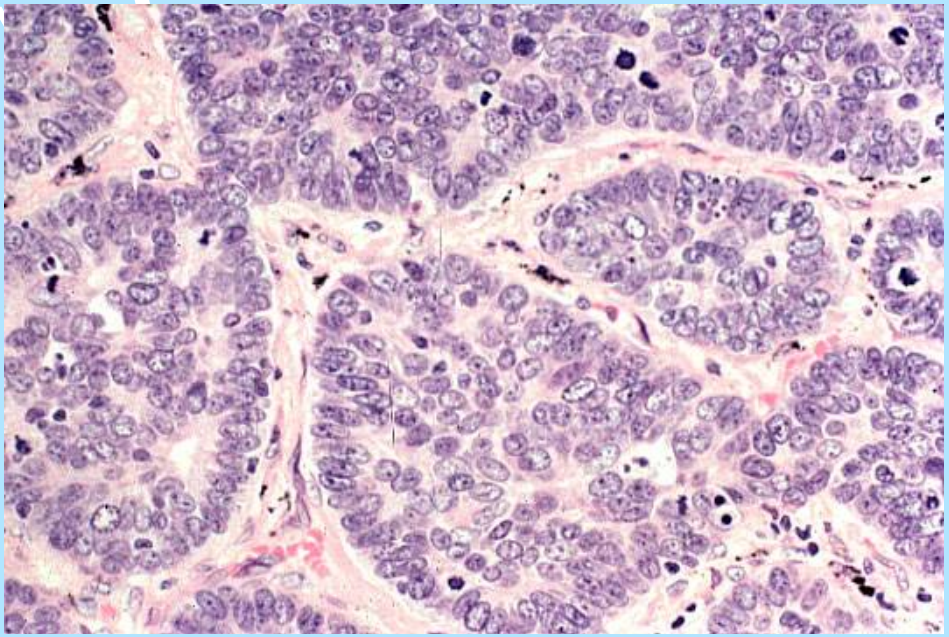
Kombinert storcellet neur.ca.
Basaloid ca. CK5/6, 34bE12,NE(-),
comedonekrose, ikke pl.ep.diff.
Lymfoepitelioma liknende ca. (lymfoid
infiltrat, EBV
Klarcellet ca.
Storcellet ca. med rhabdoid phenotype

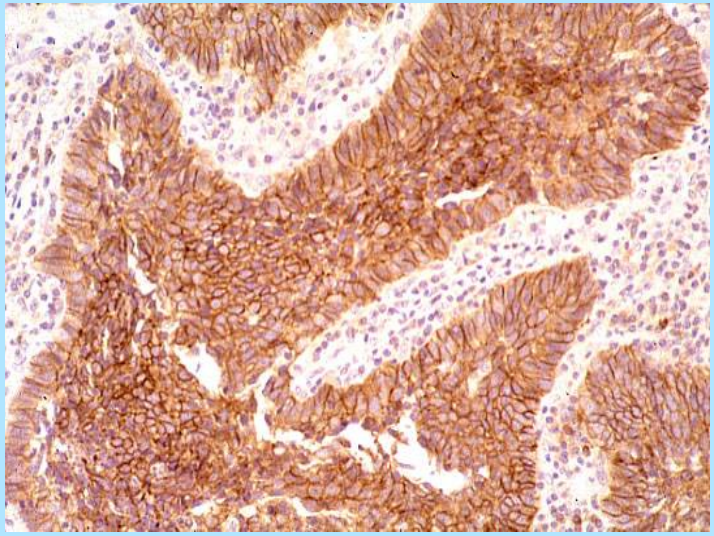
LUNG NE TUMOR FREQUENCY



Stor Cellet Neuroendocrint Carcinom

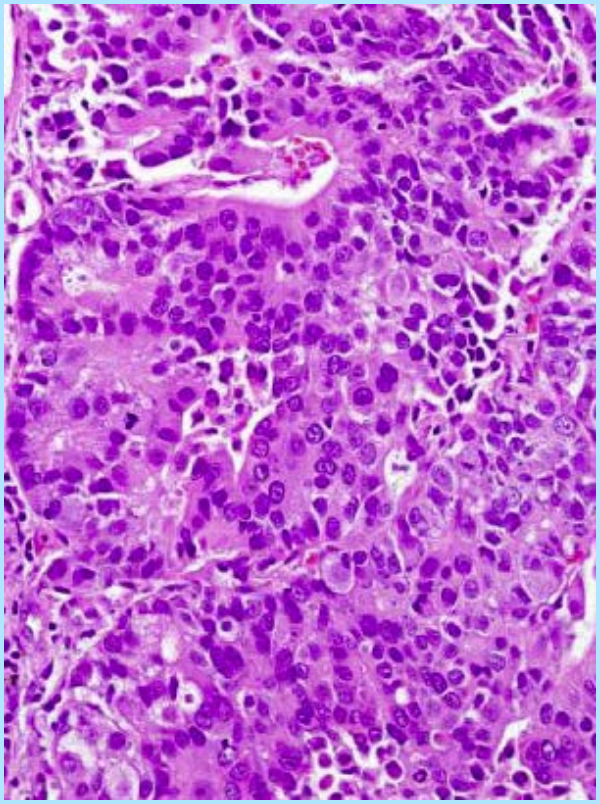




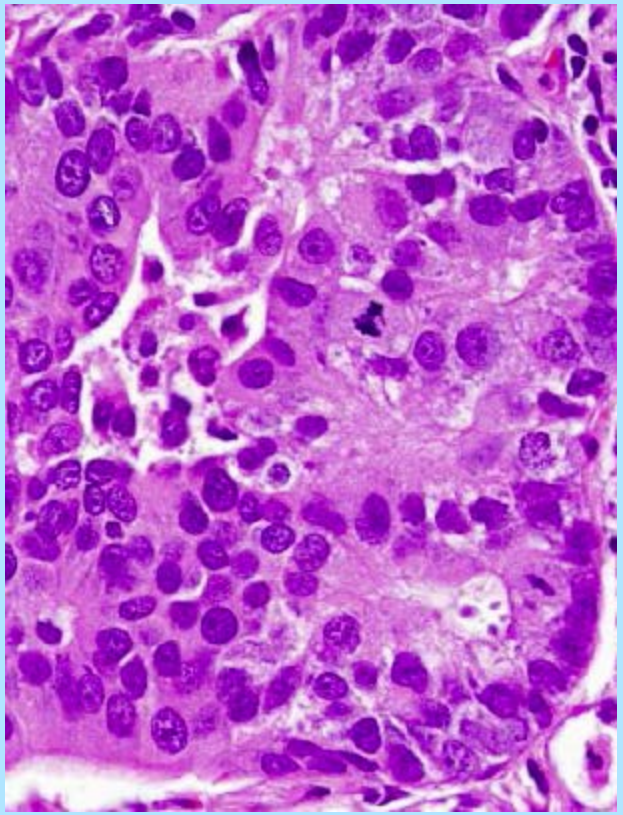


NCAM (CD 56)

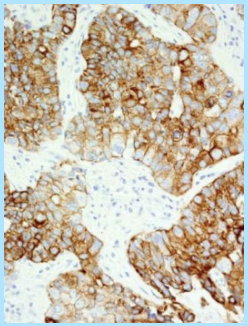
LCNEC



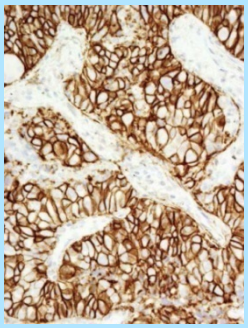
(Storcellet neuroendokrint carcinom)



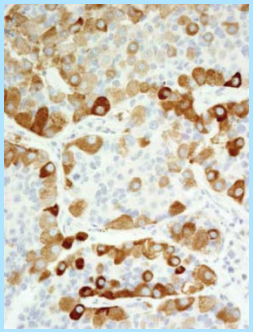
AE1/AE3



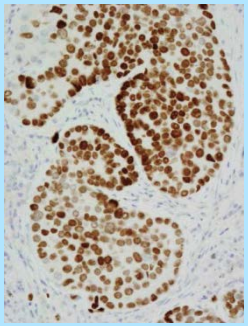
CD56



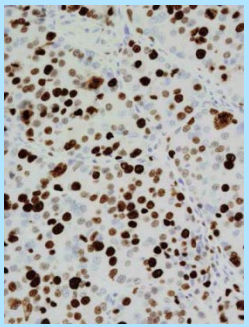
SYN



TTF-1



Ki-67



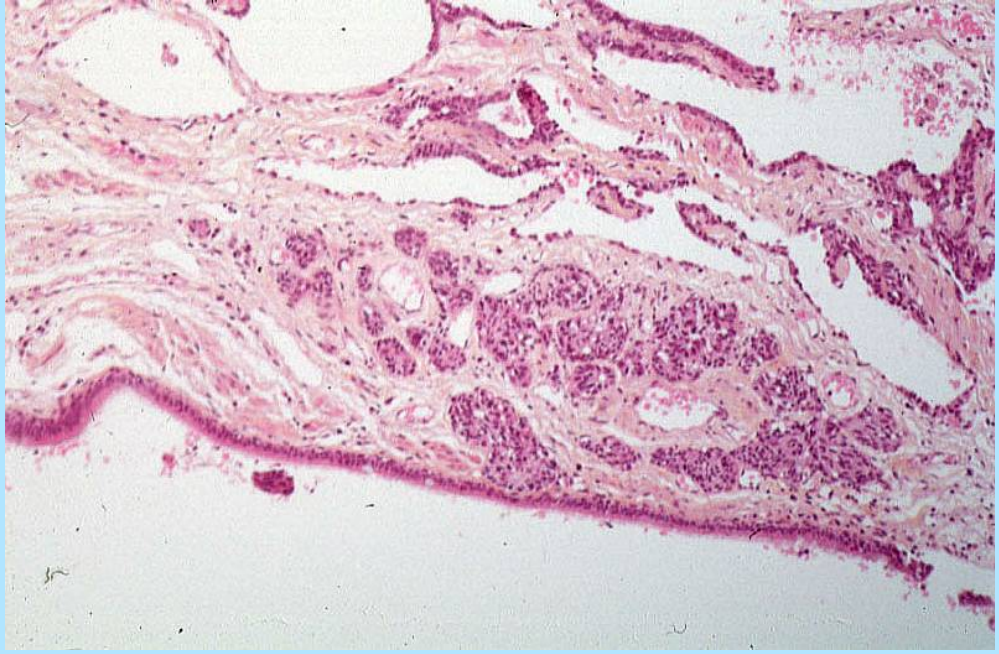
SCLC VS LCNEC: DDX

FEATURE	SCLC	LCNEC/LCC
Cell Size	Smaller (< 3 small resting lymphocytes)	Larger
N/C Ratio	Higher	Lower
Nuclear Chromatin	Finely granular, uniform	Coarsely granular, vesicular, Less uniform
Nucleoli	Absent or faint	Often (not always) present, may be prominent or faint
Nuclear molding	Characteristic	Uncharacteristic
Fusiform shape	Common	Uncommon
Polygonal shape with ample pink cytoplasm	Uncharacteristic	Characteristic
Nuclear smear	Common	Uncommon
Basophilic staining of stroma and vesssels	Occasional	Rare

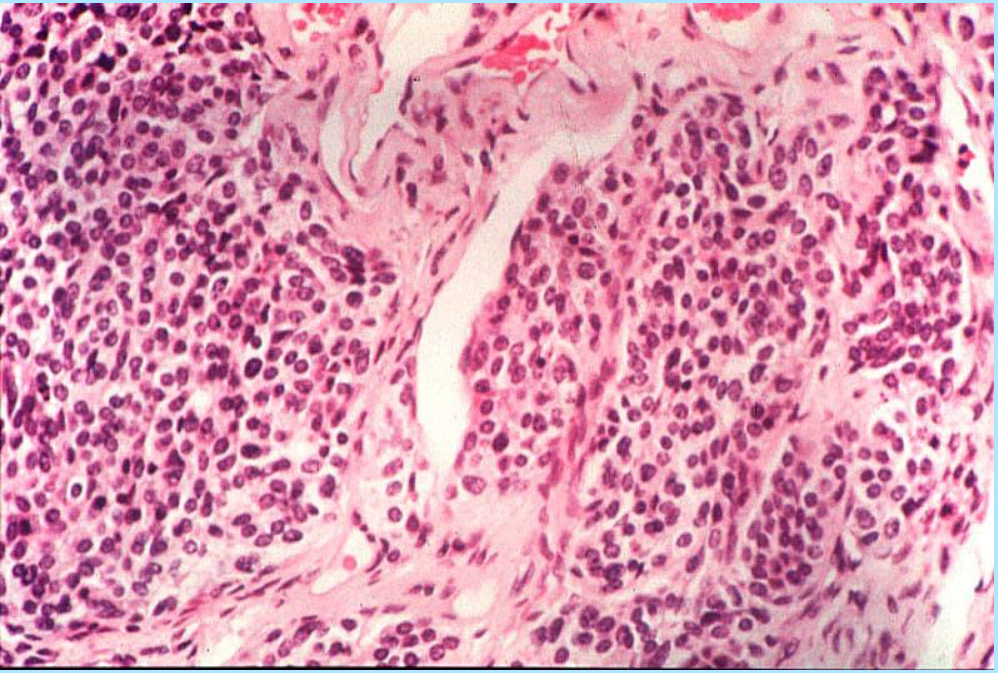
Storcellet neuroendokrint carsinom

Småcellet carsinom

Neuro-endocrine tumor: Carcinoid tumor, central og perifer



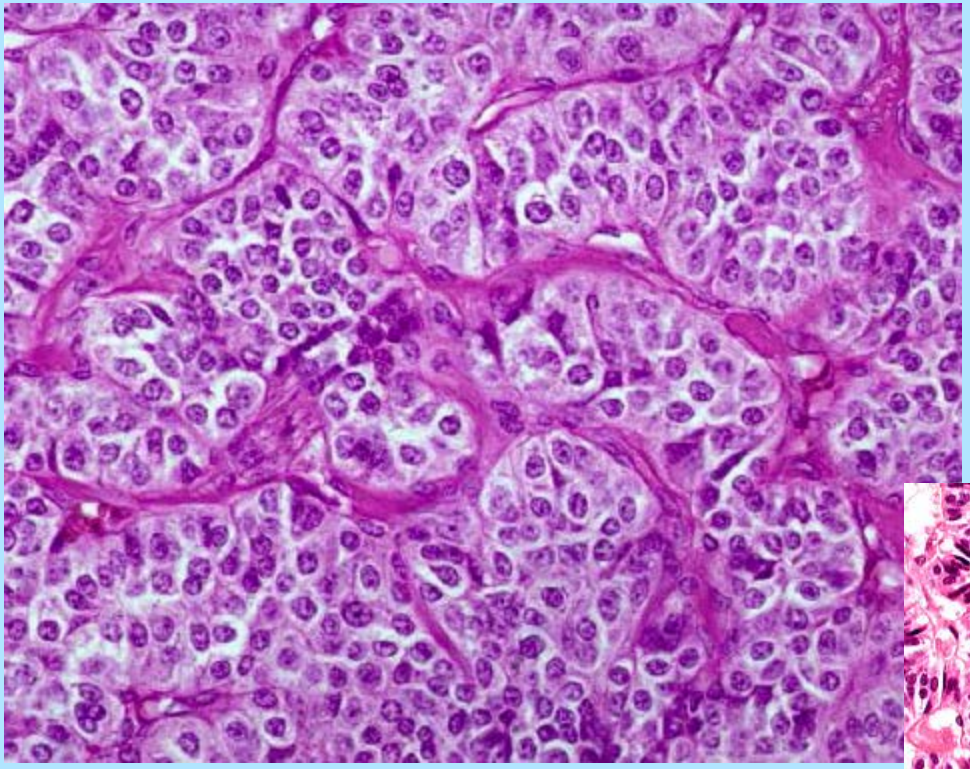
Tumorlet

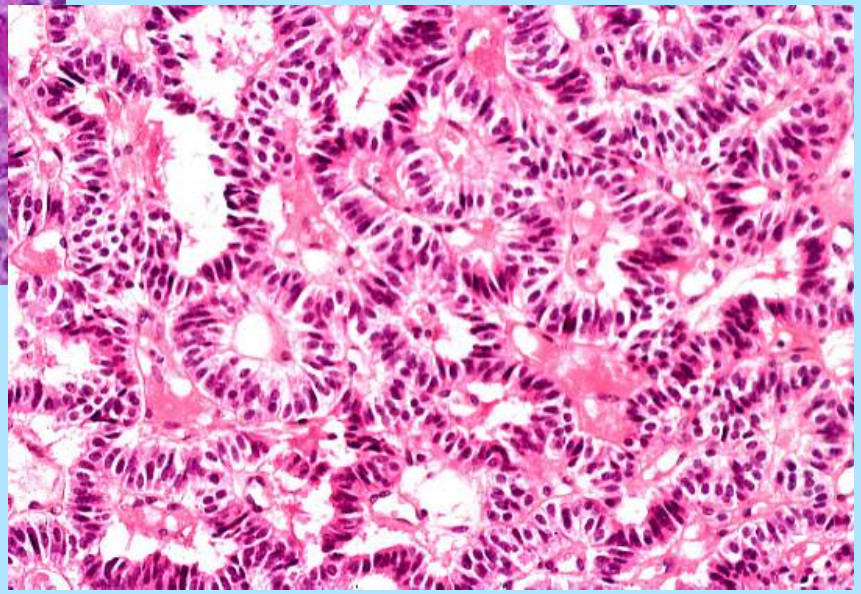


<5 mm. : Tumorlet

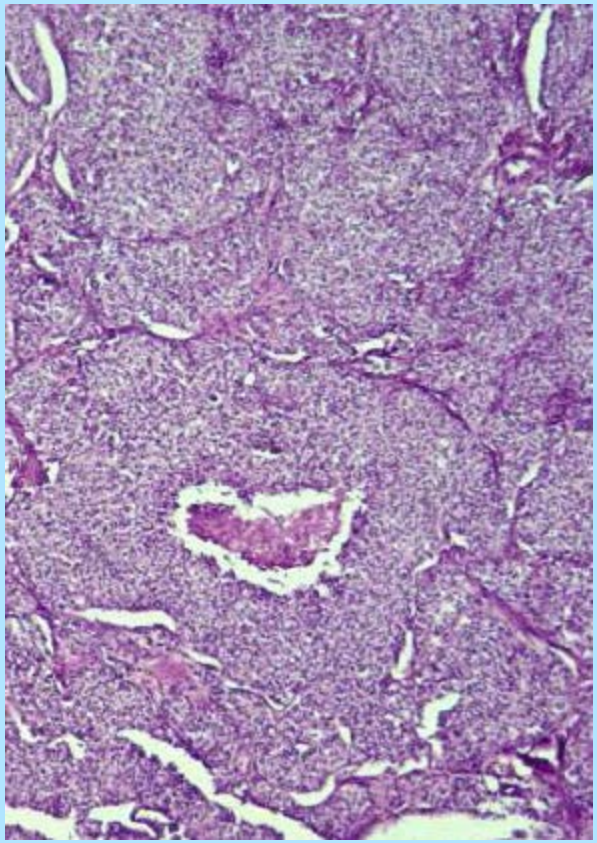
>5 mm. : Carcinoid

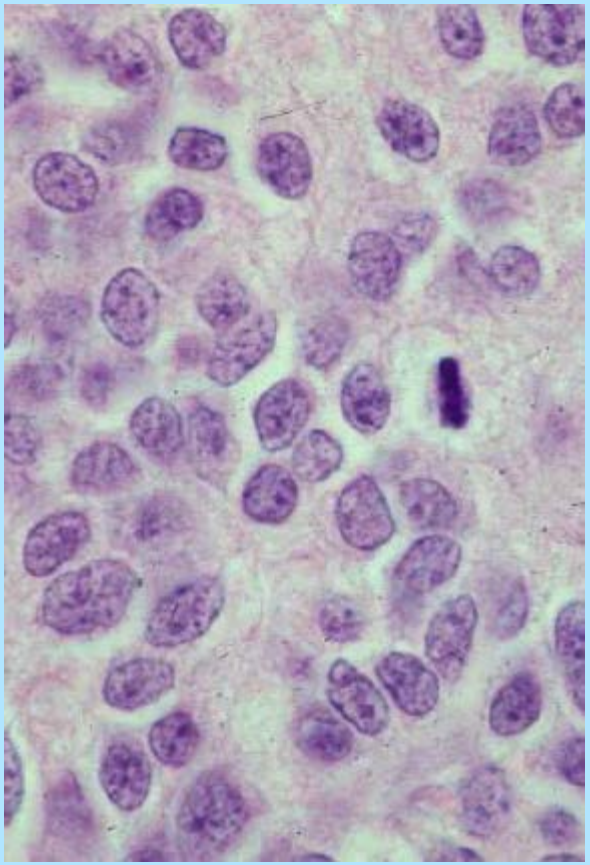
Carcinoid: organoid nesting

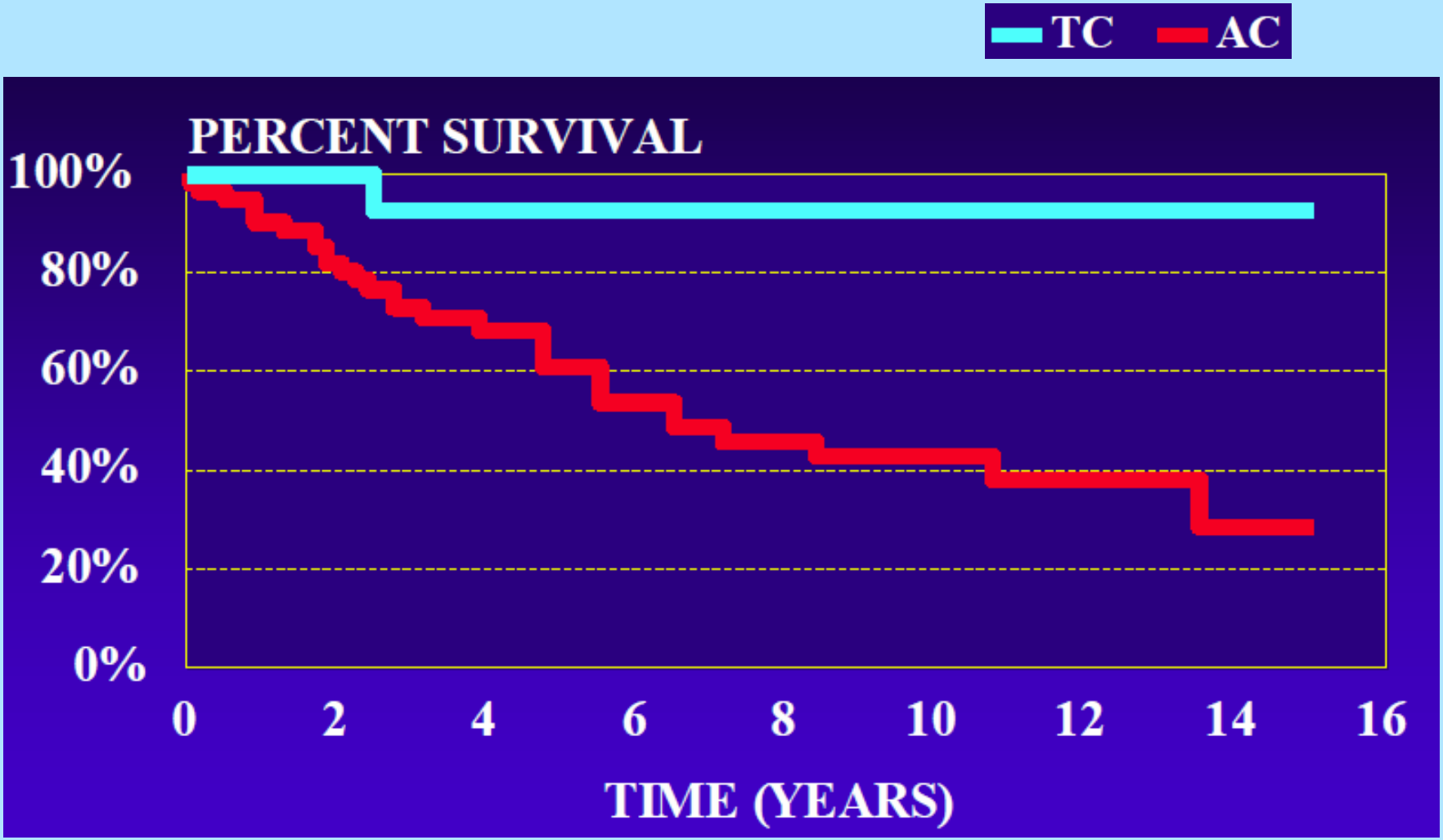




Atypisk carcinoid







Typisk / atypisk carcinoid

Morfologi viktigst!

Table 3. – Immunohistochemical differential diagnosis of lung cancer

Squamous cell lung cancer	Adenocarcinoma	Adenosquamous lung cancer	Large cell lung cancer-NEC	Small cell lung cancer	Typical carcinoid	Atypical carcinoid
HMW CK (CK5/6)+	CK7+>CK20+	CK7+/CK20-	CK5-/CK20-	CK7+	CK+ (80%)	CK+ (80%)
CEA+	CEA+	CAM5.2+			CD57+	Focal
TTF-1-	TTF-1+ (75%)	TTF-1+ (AD)	TTF-1+ (50%)	TTF-1+	TTF-1+ (30%)	TTF-1+
	SP-A/B/C+ (60%)	EMA+	CD56+	CD56+	CD56+	Focal
			CHR-A+	CHR-A+	CHR-A+	Focal
				SYN+	SYN+	Focal
					CD99+ (30%)	Ki-67+
Differential diagnosis	Metastatic adenocarcinoma			PNET	Paraganglioma	
	CDX2 (CRC)			CD99+	CHR-A+	
	PSA (PrCA)			CK-	CK-	
	ER/PR (BRC)					
	Mesothelioma			Merkel CA	Glomus tumour	
	Calretinin +			CK20+/CK7-	NSE-	
				TTF-1-	SMA+	

NEC: neuroendocrine cancer; HMW: high molecular weight; CK: cytokeratin; CEA: carcinoembryonal antigen; CAM: cell adhesion molecule; TTF: thyroid transcription factor; AD: adenocarcinoma; SP-A/B/C: surfactant protein A/B/C; EMA: epithelial membrane antigen; CHR: chromogranin; SYN: synaptophysin; PNET: peripheral nerve sheet tumour; CRC: colorectal cancer; PSA: prostate specific antigen; PrCA: prostatic cancer; BRC: breast cancer; CA: carcinoma; NSE: neuron specific enolase; SMA: smooth muscle actin. Data obtained from [11].

Immunohistochemistry : the markers

- Epithelial markers:
  - Cytokeratins
  - Low Molecular weight
    - CK7 CK20
  - High Molecular weight
    - CK 5/6, 34bE12
  - Cocktails
  - Epithelial membrane antigen
- Neuroendocrine markers:
  - Chromogranin A
  - Synaptophysin
  - CD 56
- Specific :
  - Thyroid Transcription Factor 1 (TTF1)
- Other markers:
  - Lymphoid
  - CD99
  - Ki67 (MIB-1)
  - Connective tissue
    - Vascular
    - Adipose
    - Nervous

Diff. / Metastase

Table 1. Common CK7 and CK20 immunoreactivity patterns in different carcinomas	
Immunoreactivity pattern	Carcinomas
CK7+ / CK20-	Non-small cell adenocarcinoma of lung Breast carcinoma Ovarian carcinoma (non-mucinous) Endometrial carcinoma
CK7- / CK20+	Colorectal adenocarcinoma
CK7+ / CK20+	Transitional cell carcinoma Ovarian mucinous carcinoma Prostatic adenocarcinoma*
CK7- / CK20-	Hepatocellular carcinoma Renal cell carcinoma

* Chu et al (2000, cited above) reported 18/18 prostatic adenocarcinomas to have the CK7-/CK20- pattern.

Table 6. – Gene defects in lung cancer

	Squamous cell lung cancer	Adenocarcinoma	Adenosquamous lung cancer	Large cell lung cancer-NEC	Small cell lung cancer	Typical carcinoid	Atypical carcinoid
Amplification	C-MYC 20%	20%			High		
	CCDN1 10%					5%	20%
	HER-2 5%	10%					
	EGFR (10–20%)	15%?					
	PI3K 30%	MET 3%					
Deletion	FHIT 80%	80%		80%	80%		
	INK4/p16 70%	50%		50%	ARF	6 %	40%
	Rb rare	20%		90%	90%	0%	20%
		LKB1 30%			RASSF1 70%	70%	70%
Mutation	P53 50%	50%	50%	50%	70%	0%	20% (unique)
	K-RAS 5%	30%		20%			
	β-catenin 5%						
	APC 5%		High				
	EGFR rare	15–40%					
		EML-4-ALK-fusion 5%			MET 10%	MEN1 65%	MEN1 65%

NEC: neuroendocrine cancer; EGFR: epidermal growth factor receptor. Modified from [10] and [23].

EGFR: Epidermal growth factor receptor

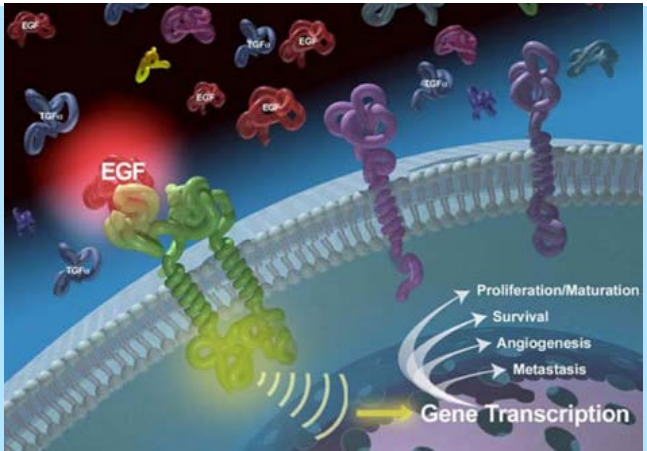


Table 7. – Prognostic markers of lung cancer

	NSCLC	SQCLC	AC	LCLC	SCLC
Prognostic gene signature					
Poor	P16	EGFR-1	P53 mutation	P53 mutation	BCL-2 amplification
	P21/WAF1	CSF1	K-RAS mutation	Rb-loss	gGH
	BCL-2	HER-2	HER-2 amplification	FHIT-loss	INSM1
	VEGF	VEGF	P16-loss	FOX-C	NRCAM1
	HIF1α	HIF1α	Rb-loss	TSGA1	ASCL1
		NTRK2			
Favourable			EGFR mutation		Carboxypeptidase E
			TTF-1		
			SP-A/B/C		
Prognostic protein markers					
Poor	P16	FHIT	MUC1		
	P21/WAF1		c-kit		
	BCL-2		COX-2		
	VEGF				
	HIF1α				
Favourable		BAX	ER/PgR		

NSCLC: nonsmall cell lung cancer; SQCLC: squamous cell lung cancer; AC: adenocarcinoma; LCLC: large cell lung cancer; SCLC: small cell lung cancer. EGFR: epidermal growth factor receptor; VEGF: vascular endothelial growth factor; TTF: thyroid transcription factor; SP-A/B/C: surfactant protein A/B/C; ER/PgR: oestrogen receptor/progesterone receptor.

Preliminary analysis

kappa coefficient value	
< 0.00	poor agreement
0.00 to 0.20	slight agreement
0.21 to 0.40	fair
0.41 to 0.60	moderate
0.61 to 0.80	substantial
0.81 to 1.00	almost perfect agreement

- Interobserver variability

SCLC

LCNEC

Combined

Carcinoid

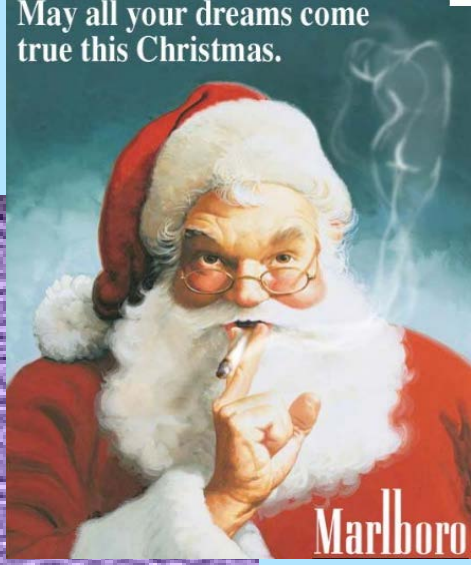
Large cell carcinoma

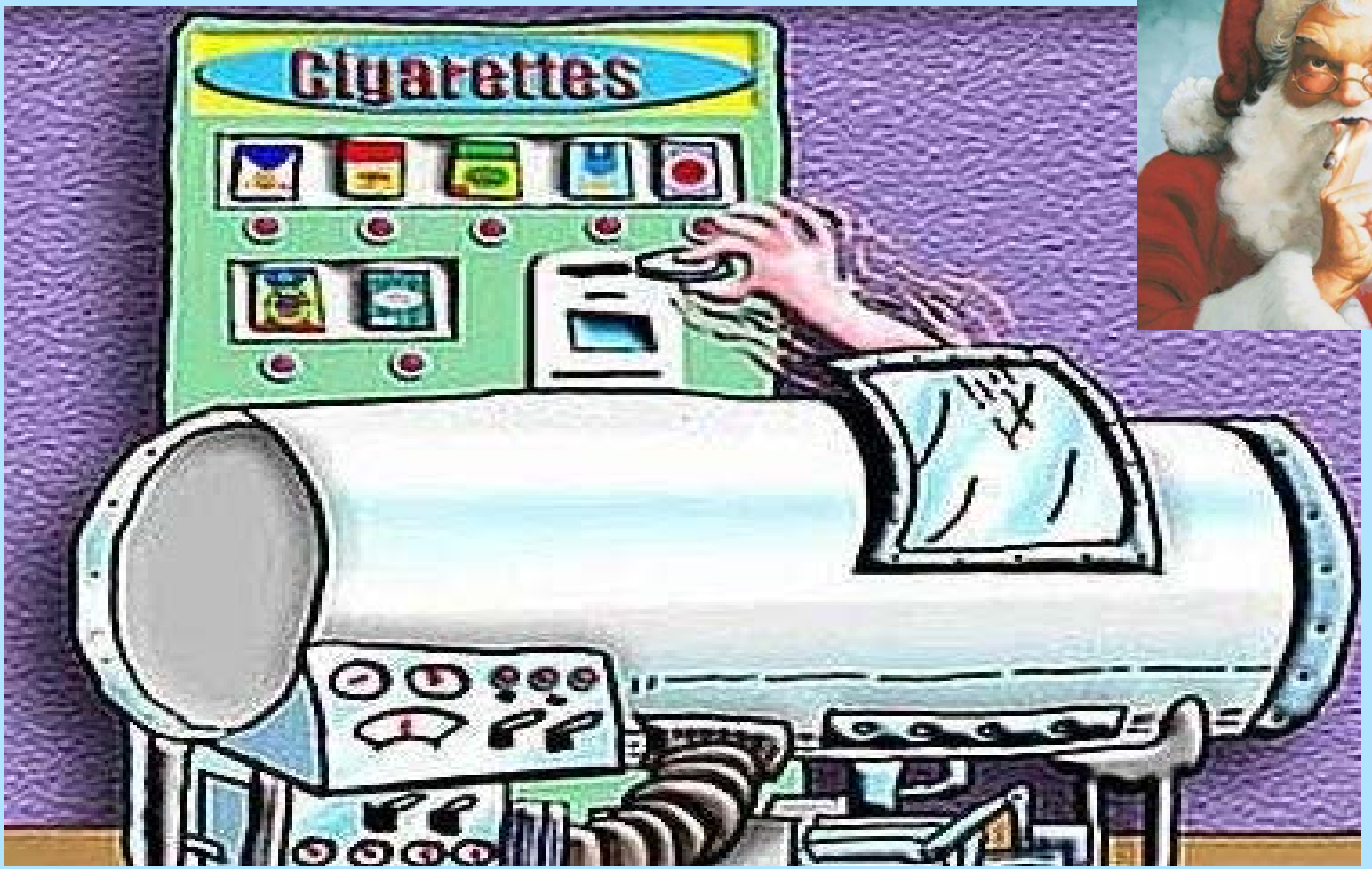
Not suitable

Kappa value = 0,4

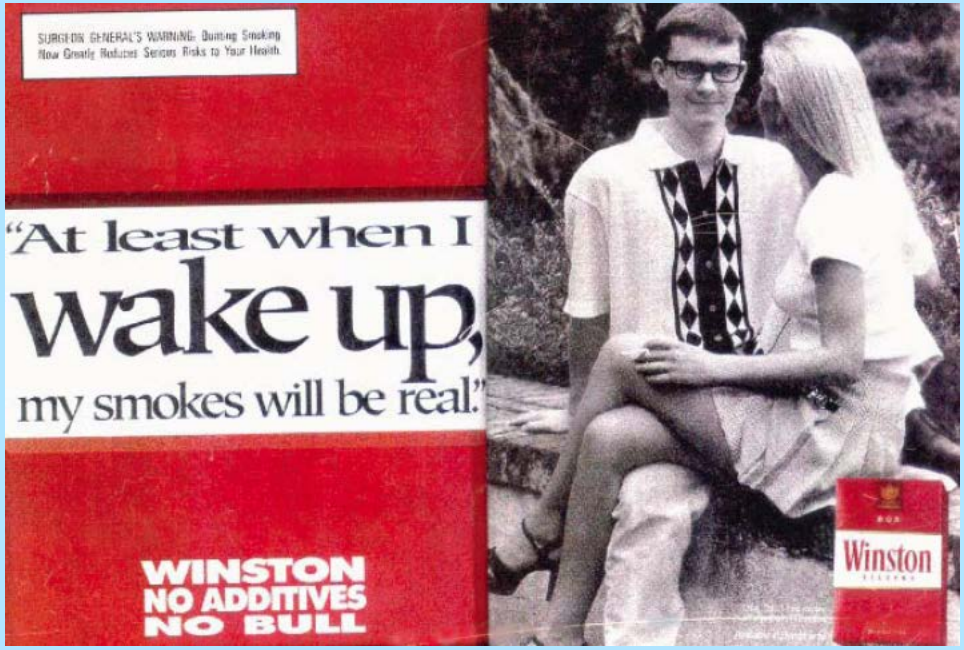
Viktig ved vurdering av små biopsier!

- Heterogenitet:
  Histologisk variasjon i utseende og differensiering i tumor
- 50% har mer enn en histologisk hovedtype


May all your dreams come
true this Christmas.
Marlboro


Cigarettes

FIN


SURGEON GENERAL'S WARNING: Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
"At least when I
wake up,
my smokes will be real."
WINSTON
NO ADDITIVES
NO BULL
Winston


REWARD
LOST
PUPPY