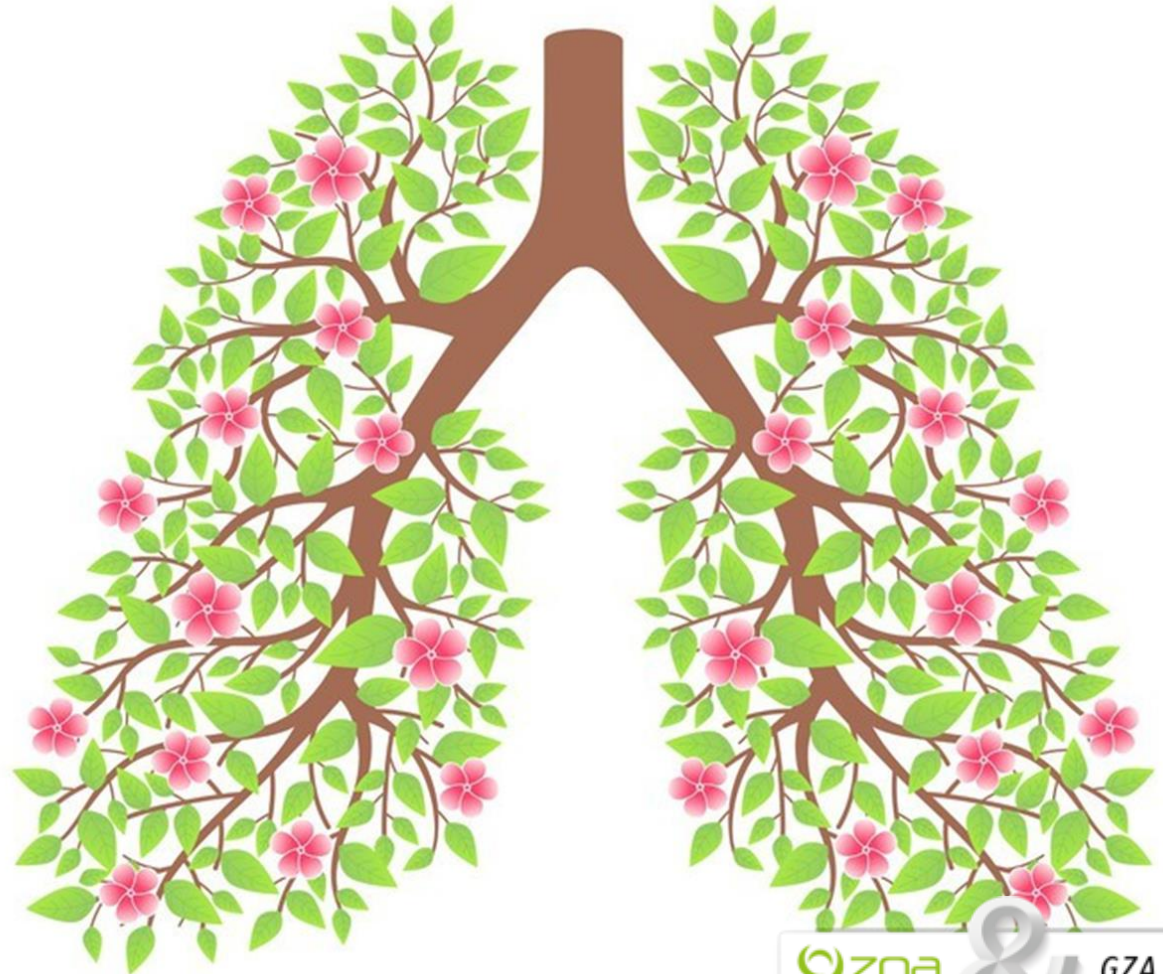


Pathologie van neuro-endocriene neoplasmata van de long



TOGA lentesymposium 2023
Marjan Hertoghs



Pathologie NEN long

1. Inleiding
2. Huidige classificatie
3. Carcinoiden
4. LCNEC
5. SCLC
6. Toekomstige classificatie?

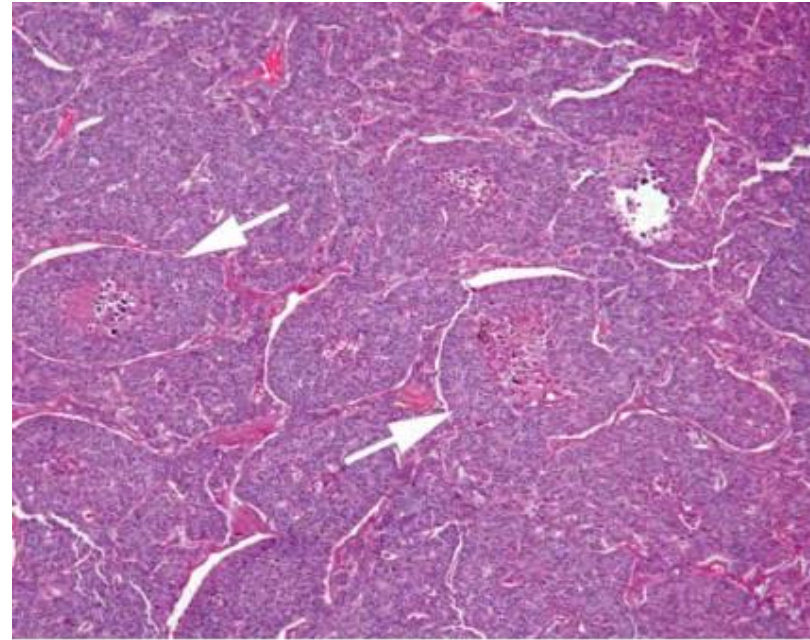
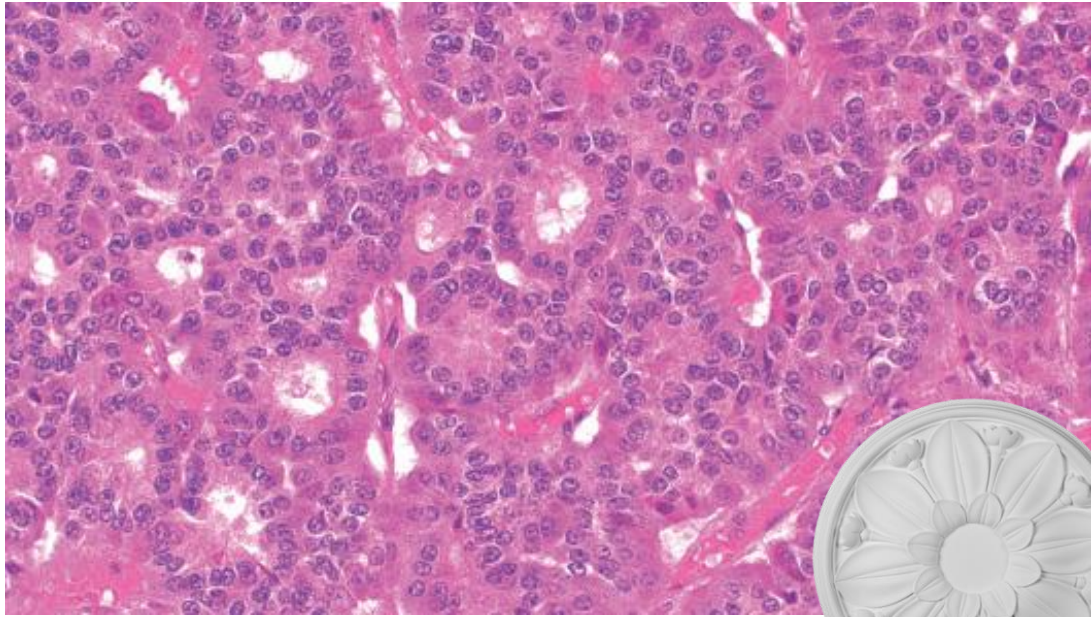
Pathologie NEN long

1. Inleiding

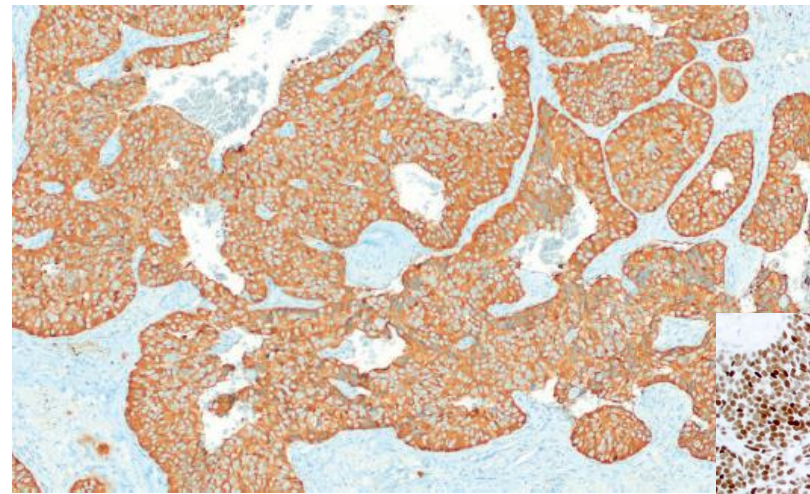
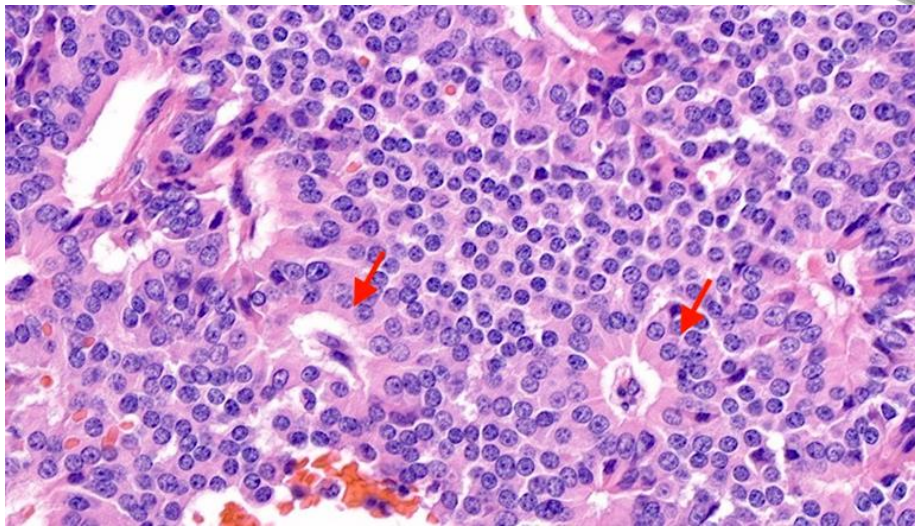
2. Huidige classificatie
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6. Toekomstige classificatie?

NEN Algemene kenmerken

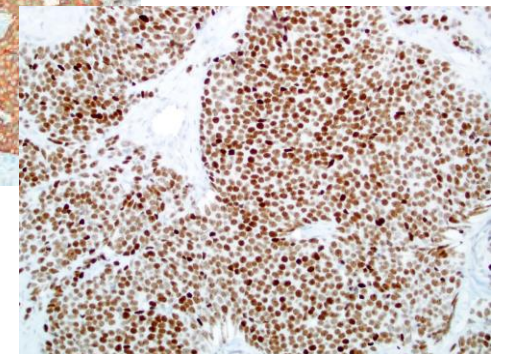
- Karakteristieke en gelijkaardige morfologie:
 - (Pseudo-)Rozetten, trabekels, organoid
 - Solied, pseudoglandulair, papillair, folliculair, ...
- Neurosecretoire granules bij ultrastructureel onderzoek
- Neuro-endocriene IHC-merkers:
 - Chromogranine A: meest specifiek
 - Synaptophysine: meer sensitief
 - CD56: minst specifiek
- INSM1 (insulinoma-associated protein 1): nieuwer, nucleair, geen 'standalone'



Organoid - 'Nested'



Synaptophysine



INSM1

Pathologie NEN long

1. Inleiding

2. Huidige classificatie

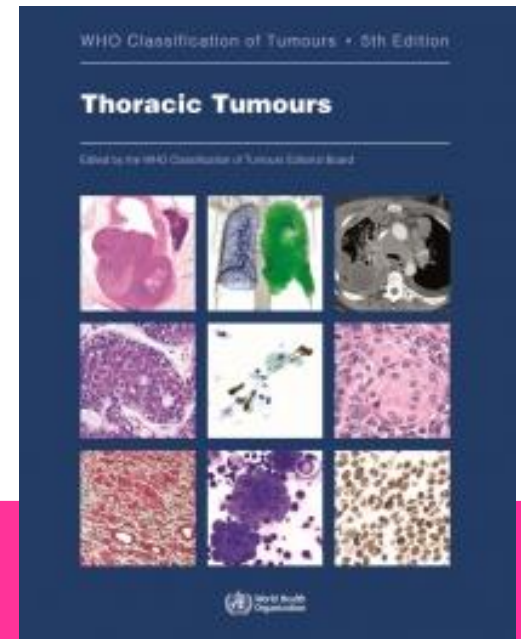
3. Carcinoiden

4. LCNEC

5. SCLC

6. Toekomstige classificatie?

Huidige indeling WHO 5TH ed.



Laaggradig

NET

1. TYPISCH CARCINOID (TC)

Intermediair

2. ATYPISCH CARCINOID (AC)

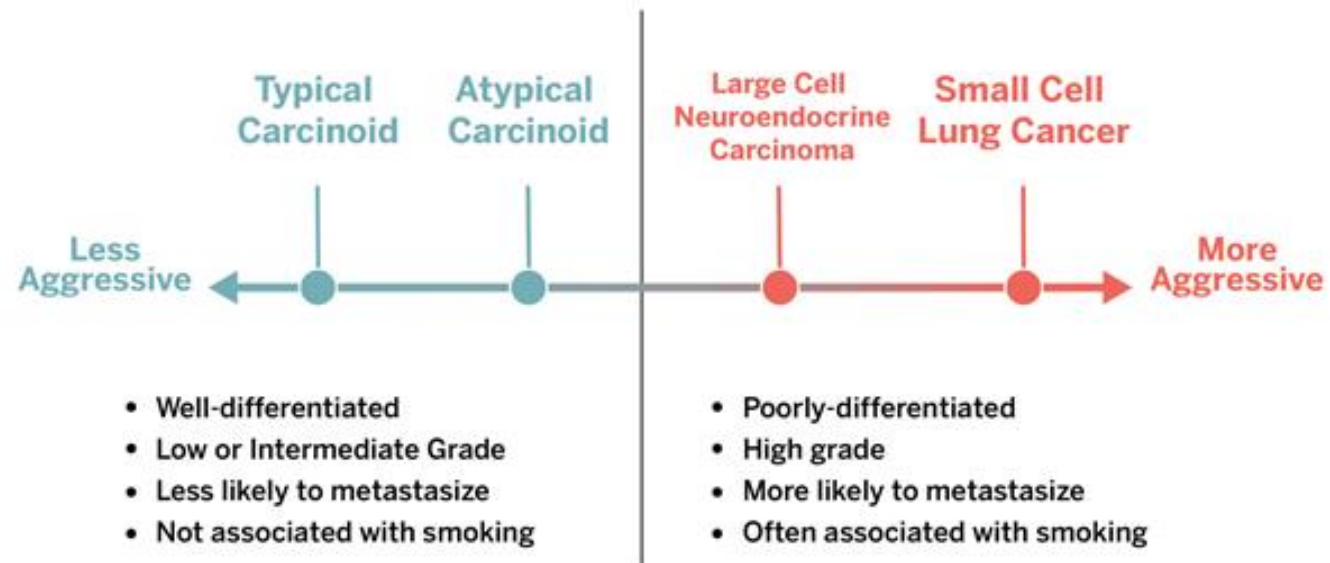
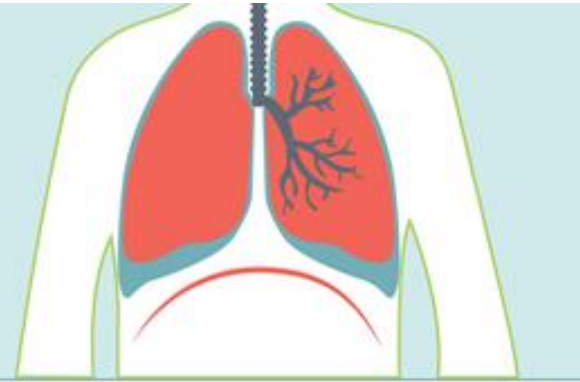
Hooggradig

NEC

3. LARGE CELL NEUROENDOCRINE CARCINOMA (LCNEC)
4. SMALL CELL NEUROENDOCRINE CARCINOMA (SCLC)

Spectrum?

Four Types of Lung NETs



Huidige indeling: Criteria

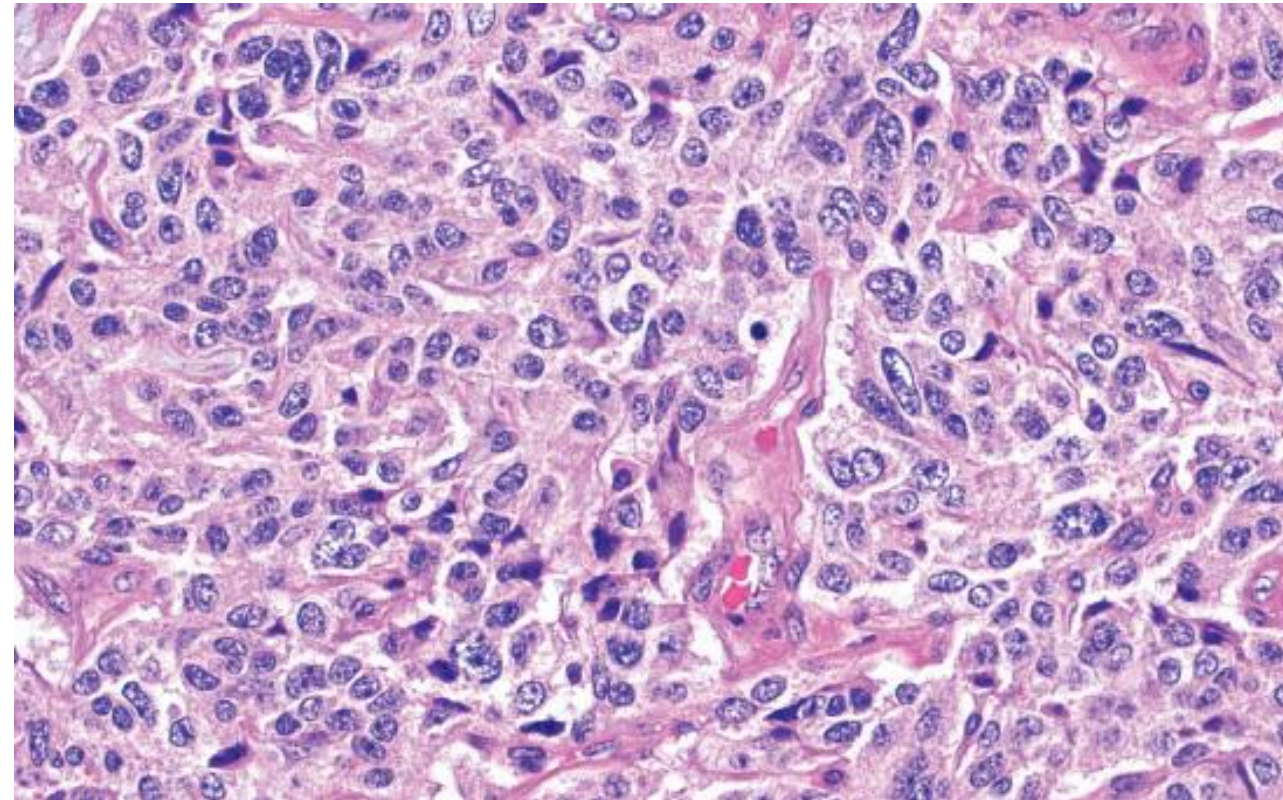
TC	AC	LCNEC	SCLC
<2 mitosen/2mm ²	2-10 mitosen/2mm ²	>10 mitosen/2mm ²	>10 mitosen/2mm ²
Geen necrose	en/of Necrose	Necrose	Necrose

+ celkenmerken en architecturale kenmerken

Pathologie NEN long

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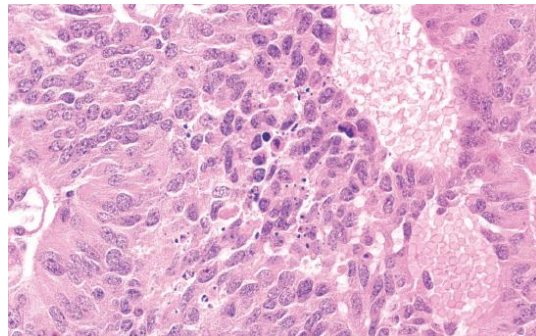
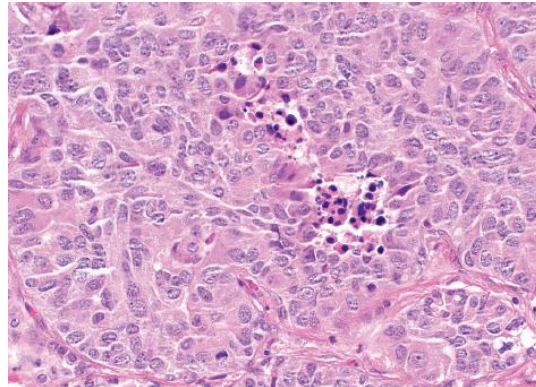
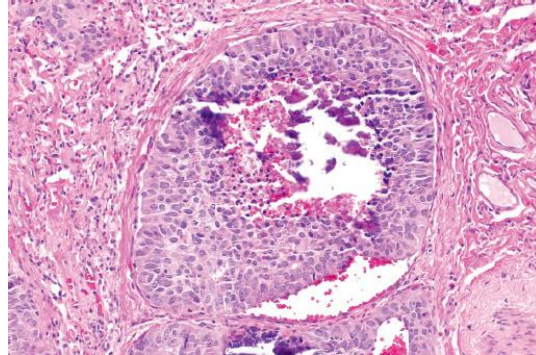
- Karakteristieke groeipatronen
- Monomorfe ronde/ plasmacytoïde cellen, matig ruim eosinofiel cytoplasma en fijn granulaire chromatine ("zout en peper")
- Merkers:
 - Synapto+ ChromoA+
 - TTF1 variabel
 - 20% keratine -
- Lymfovasculaire invasie, metastase
- 5-12% ptn mutatie MEN1 gen
- Geen combi met NSCLC



Typisch

0-1 mitose/ 2 mm²
geen necrose

- Centraal
- Soms spoelcellig
- ≥ 5 mm



Atypisch

> 2-10 mitosen/ 2 mm²
en/of necrose

- Frequenter perifeer
- Frequenter spoelcellig

Carcinoid NOS (not otherwise specified)

= term gebruikt wanneer onderscheid TC vs AC niet mogelijk is:

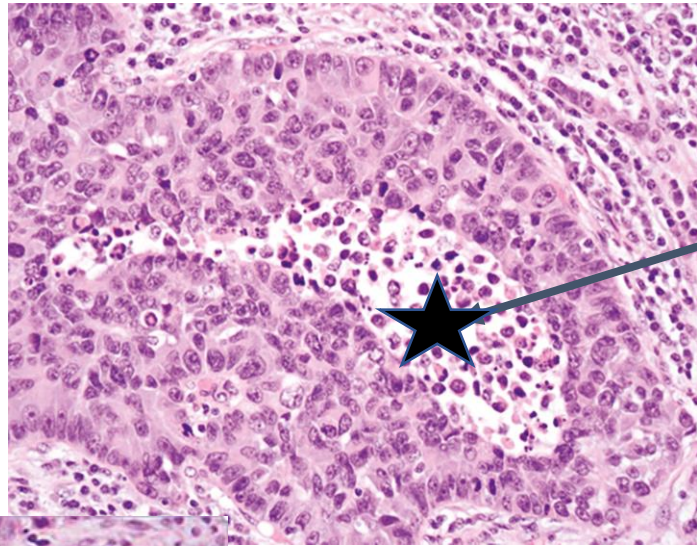
- Diagnose op cytologie of biopsie
- Metastase

Met vermelding #mitosen/2mm², necrose en evt KI67%

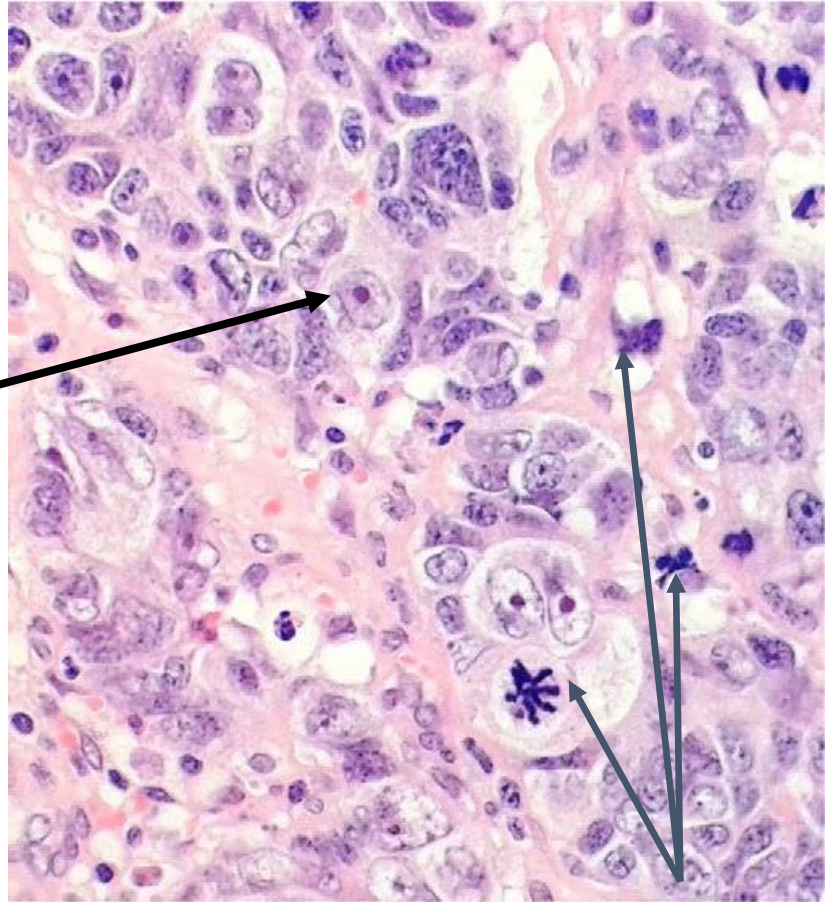
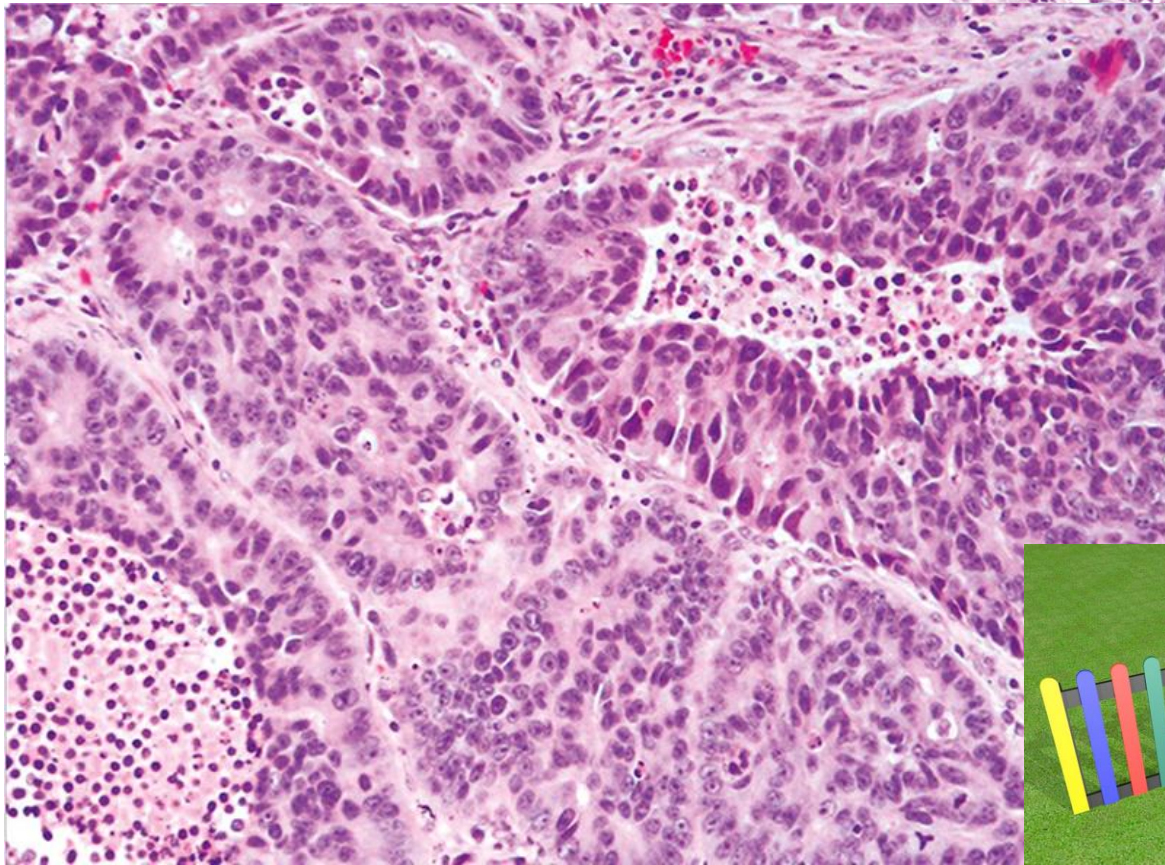
Pathologie NEN long

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6. Toekomstige classificatie?

- NE morfologie, nesten met palissadering
- Cellen met ruim cytoplasma en grote kernen met vaak grote nucleoli
- Necrose
- >10 mitosen/ 2 mm²
- NE IHC +, 50% TTF1+, panKeratin+ en CK7+
- Combi met NSCLC en met SCLC



NECROSE



NUCLEOLUS

MITOSEN



LCNEC ≠

- “Grootcellig carcinoom”
 - Niet-kleincellige carcinomen zonder typische morfologische, immunofenotypische of moleculaire kenmerken
- “Grootcellig carcinoom met neuro-endocriene morfologie”
 - CA met morfologie LCNEC, maar NE IHC-
 - Weinig klinische data
 - Aggresief gedrag zoals LCNEC
- “Niet-kleincellig carcinoom met neuro-endocriene differentiatie”
 - NSCLC zonder NE morfologie maar NE IHC+
 - 10-20% SCC, adenoca
 - Geen klinische implicatie
 - Geen NE IHC uitvoeren in afwezigheid van NE morfologie!

Diagnostiek op kleine biopten

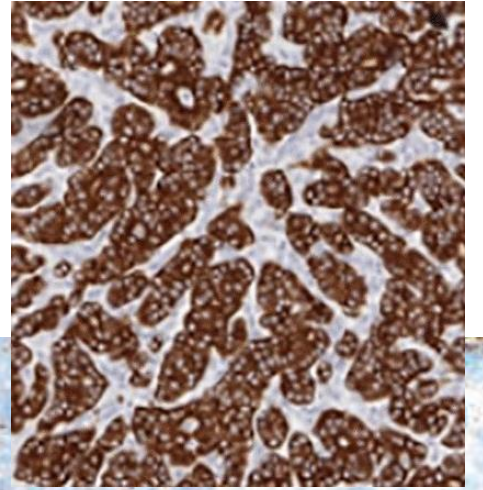
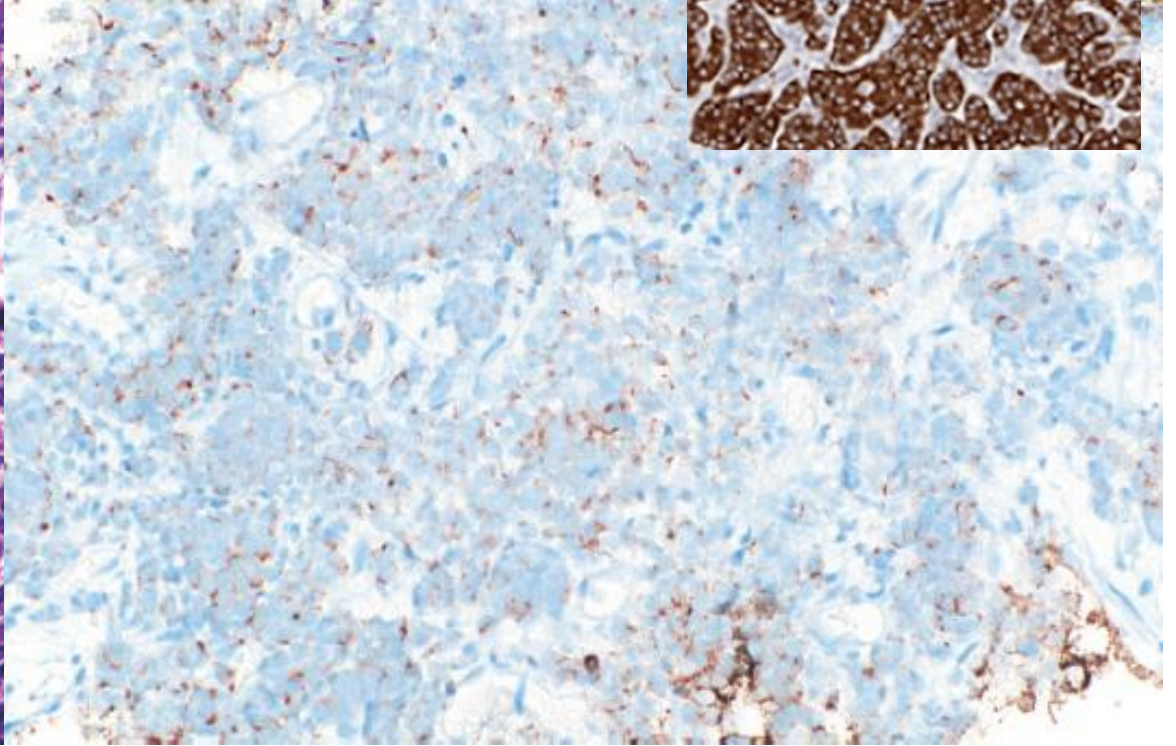
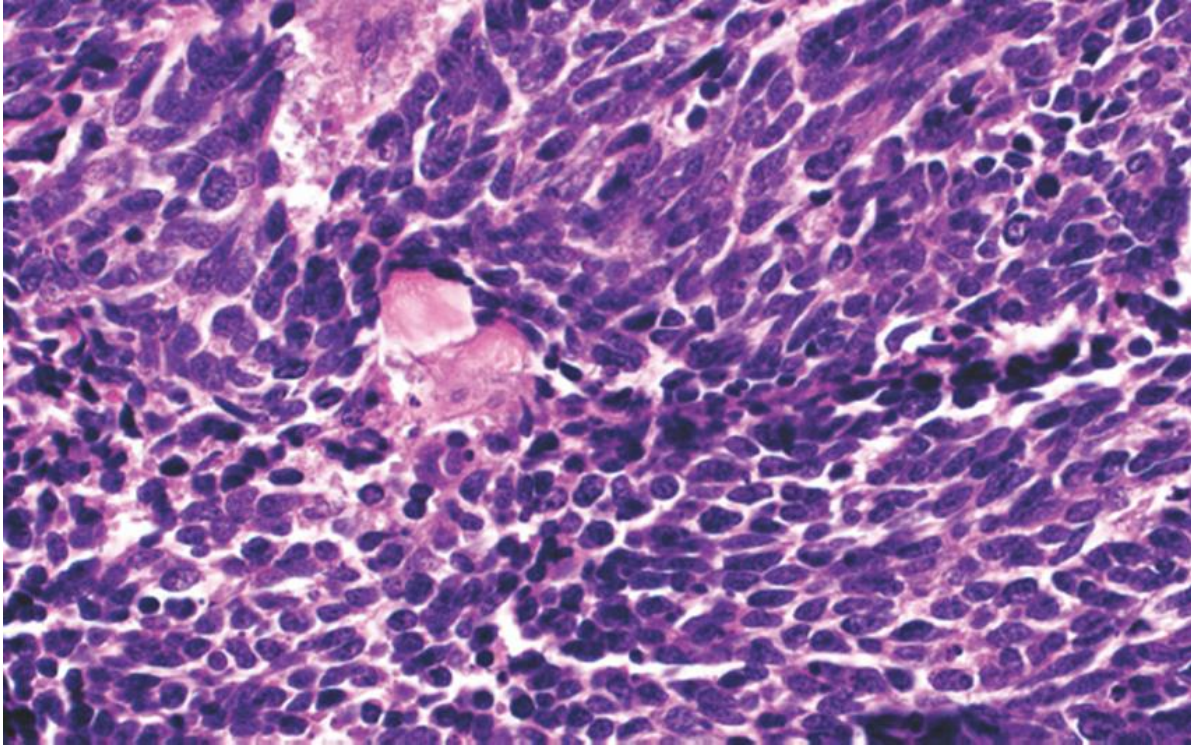
- Terminologie
 - Carcinoid, NOS
 - NSCLC, mogelijks LCNEC
 - Hooggradig neuro-endocrien carcinoma, NOS

Pathologie NEN long

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6. Toekomstige classificatie?

- Dense velden, molding, crush-artefact
- Cellen kleiner dan de diameter van 3 lymfocyten in rust
- Geen zeer kleine cellen, maar cellen met weinig cytoplasma en onzichtbare celgrenzen!!
- Hyperchromatische kernen met fijn granulair chromatine, geen zichtbare nucleoli
- > 10 mitosen/ 2mm², apoptose en necrose
- NE IHC+ (5-10% -), TTF1++, Pankeratin+ (dot of rim-like); Rb1 - en P53 aberrant
- Combi met NSCLC 5%

NSCLC

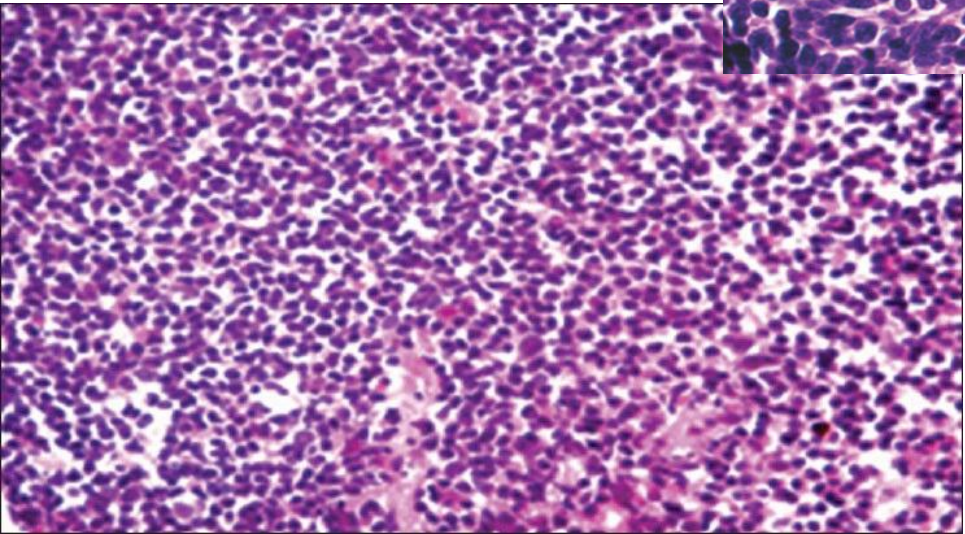
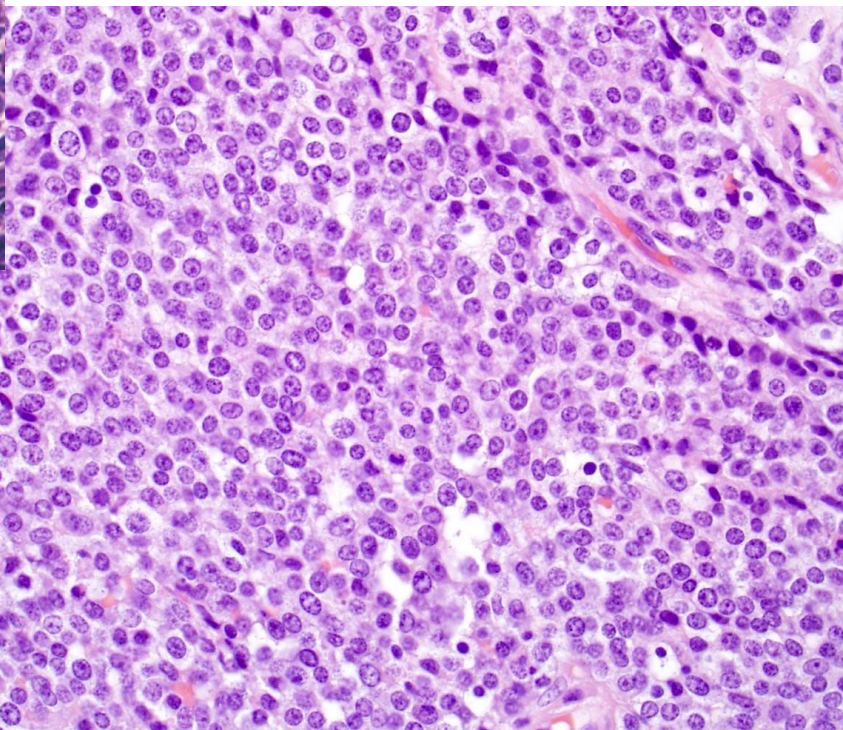
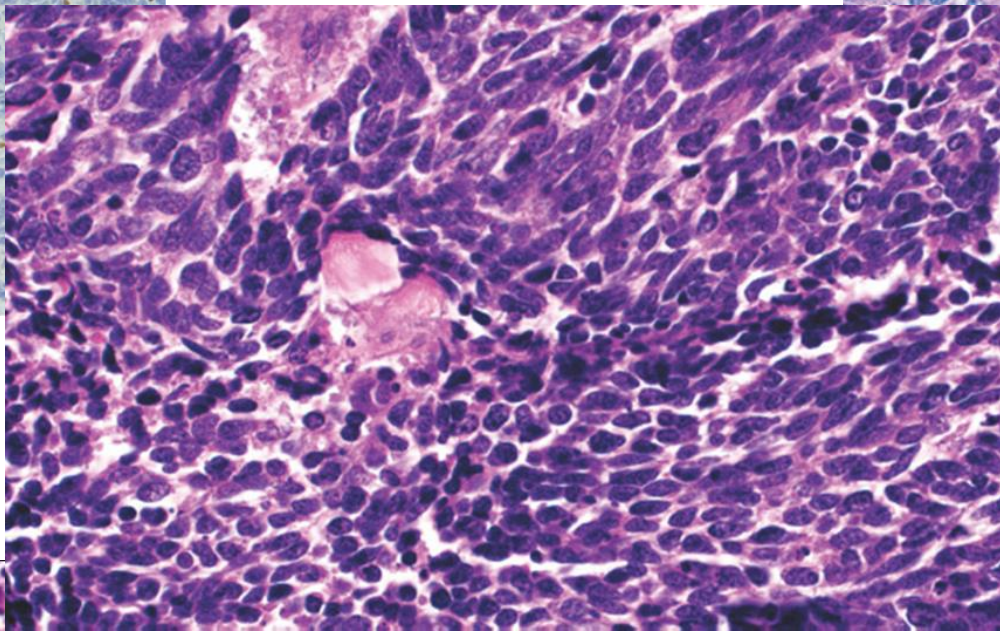
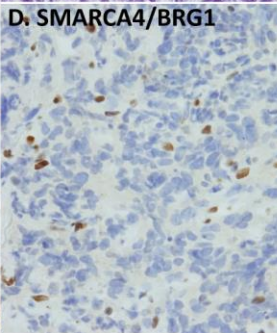
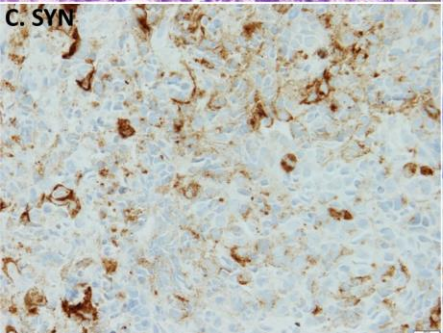
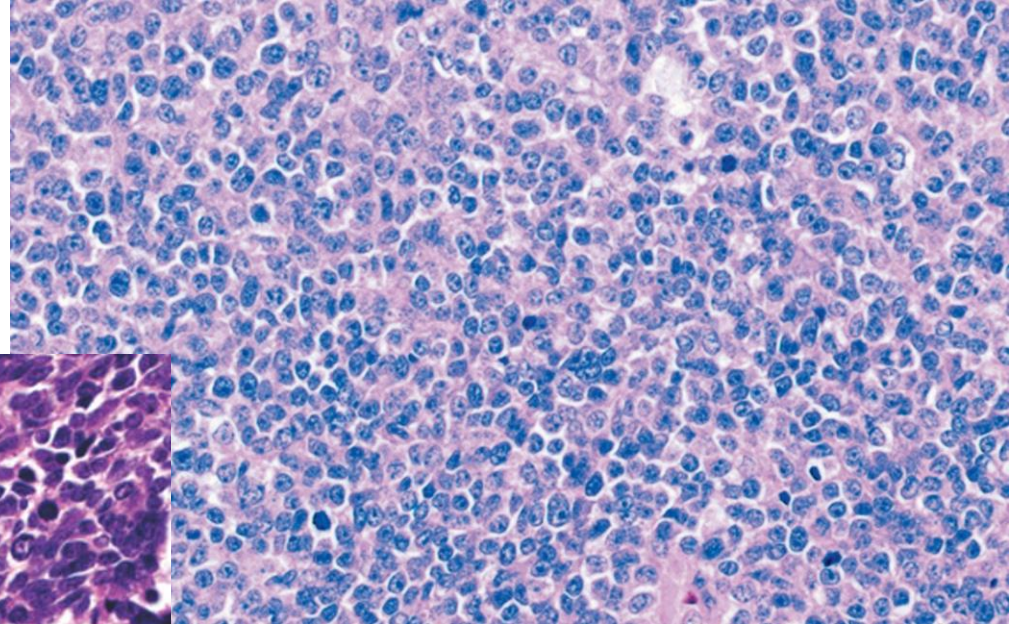
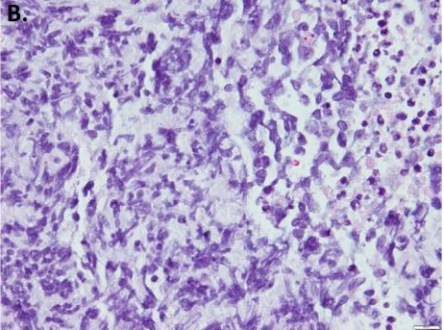
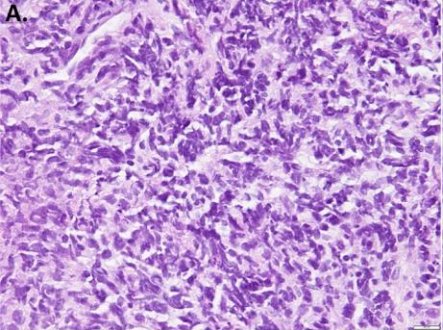


Small cell transformatie

- Verworven resistentie mechanisme
- 5-14% EGFR-mutated longadenocarcinoma onder TKI
- 1ste, 2de als 3de lijn generatie EGFR- inhibitoren
- ALK-inhibitie
- Predispositie adenoca met Rb1 en TP53 alteraties

DD SCLC - mimickers

- SMARCA-4 deficiënte ongedifferentiëerde tumoren
 - Verlies SMARCA4/ BRG1 en SMARCA2/BRM, expressie SALL4, CD34 en SOX2
- Basaloid plaveiselcelcarcinoma
 - P40/P63
- Weinig rokers
 - Lymfoma
 - (Ewing) sarcoma
 - NUT
 - Merkel cell carcinoma
- Nooit roker
 - meta kleincellig NEC andere lokalisatie
 - combi SCLC-adenoca



Pathologie NEN long

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Hooggradige neuro-endocriene carcinomen met carcinoïde morfologie

- >10 mitosen/ 2mm² (KI67 >20-30%)
- MAAR: 'Carcinoïde' morfologie:
 - nesten, geen palissadering, geen prominente nucleoli
- LCNEC variant??? > genomisch analyse: eerder AC!!!
- Biologisch gedrag vermoedelijk intermediair
- Literatuur:
 - "LCNEC, carcinoïde variant"
 - "hooggradig atypisch carcinoid"

Long versus GI tractus

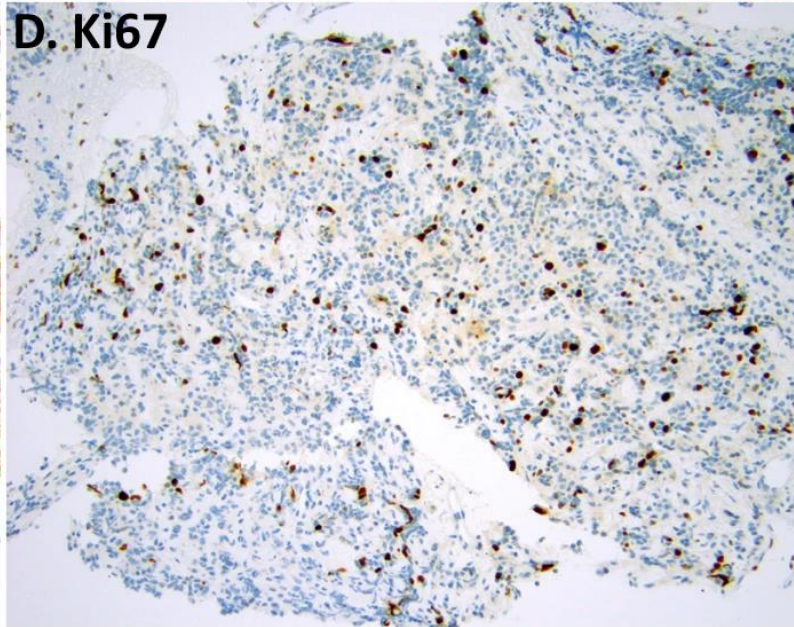
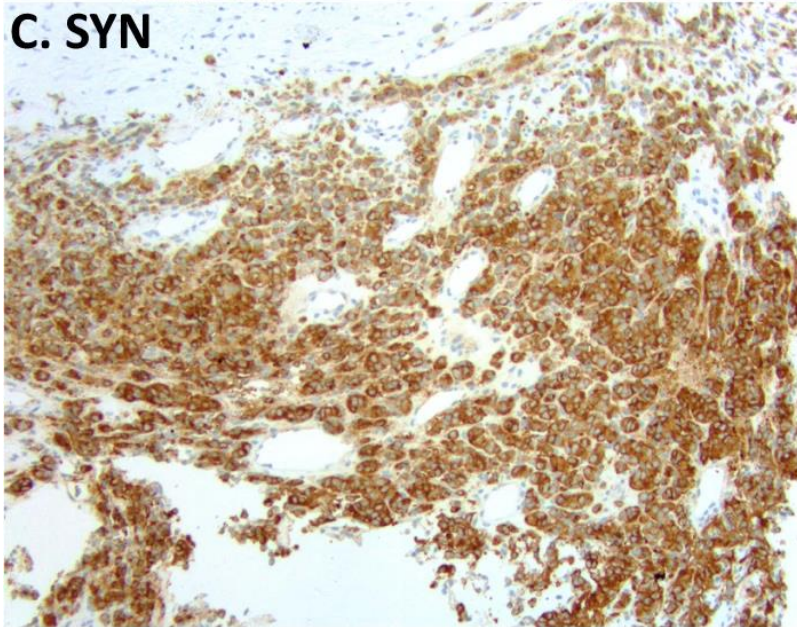
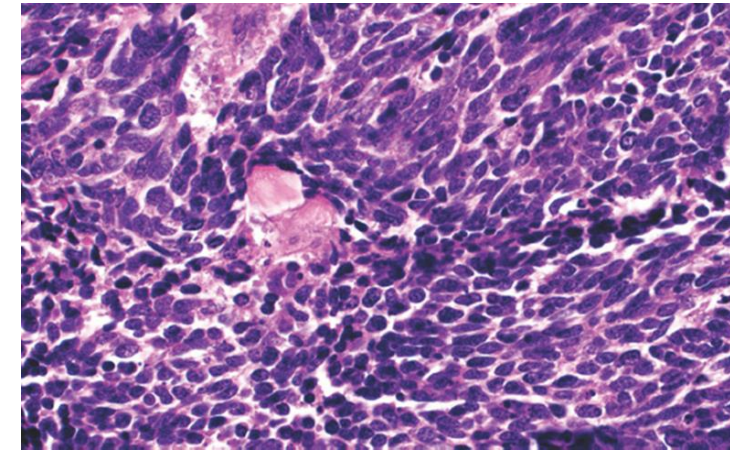
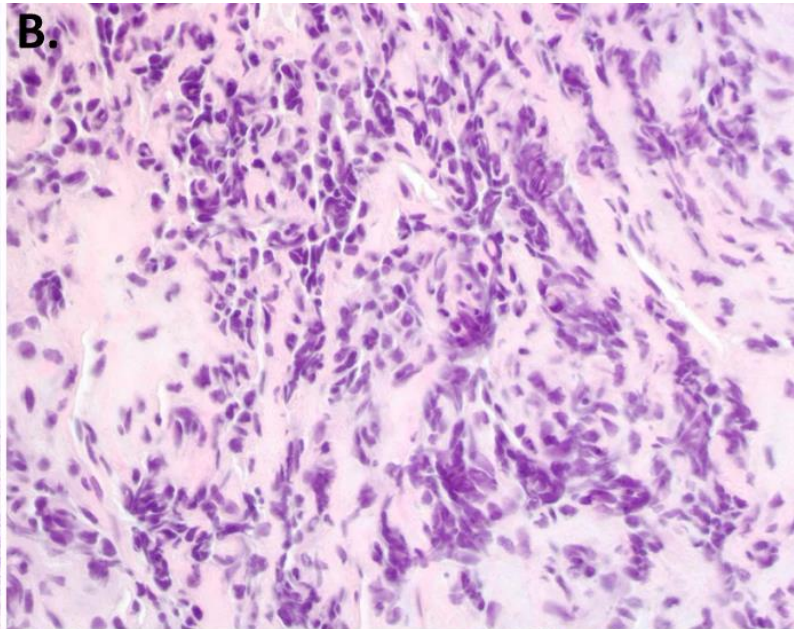
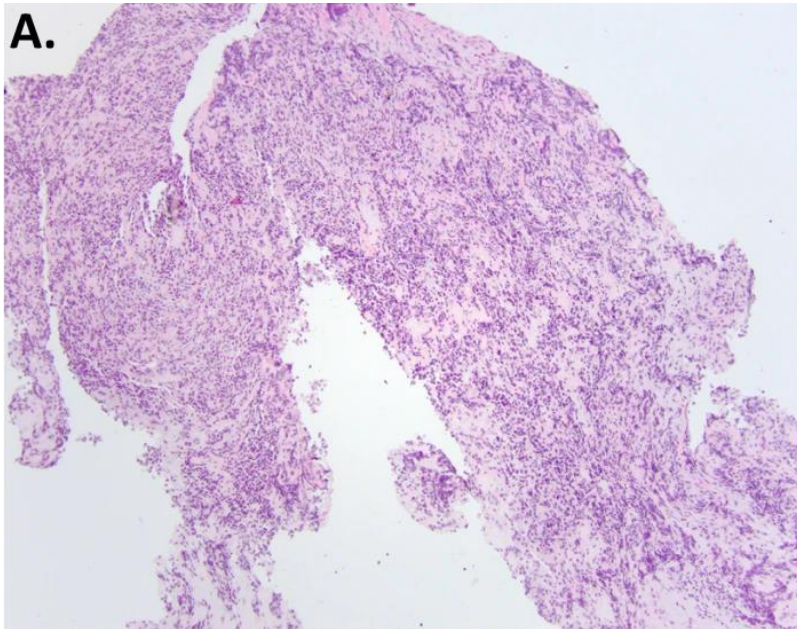
Thoracic WHO 5th Ed, 2021

Digestive WHO 5th Ed, 2019

Terminology	Criteria: Mitotic counts per 2 mm ²	Terminology	Criteria: Mitotic counts per 2 mm ²	Ki67 index
Typical carcinoid	<2	NET, grade 1	<2	<3%
Atypical carcinoid	2–10 (or necrosis)	NET, grade 2	2–20	3–20%
–	–	NET, grade 3	>20	>20%
SCLC and LCNEC (NEC)	>10	NEC (small cell or large cell)	>20	>20%
Combined NEC and NSCLC				

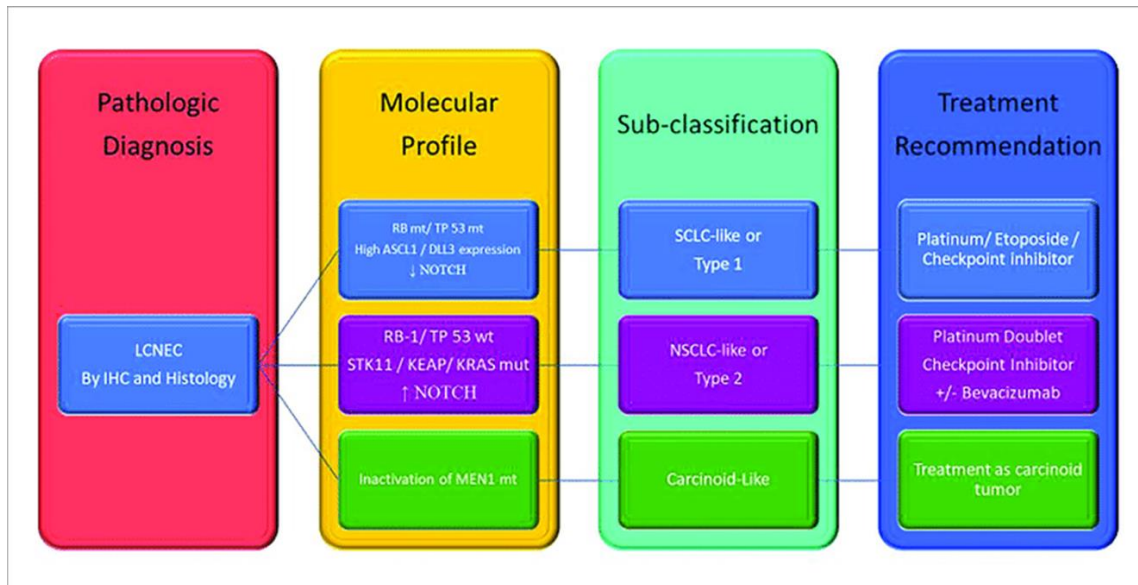
Rol van KI67?

- WHO 5th ed: “desirable” >> 6th ed Routinemerker?
 - Beter reproduceerbaar dan mitosen tellen
 - Minder weefsel nodig
 - Minder tijdrovend 😊
- Tot op heden geen consensus over cut-off points
 - TC <5%
 - AC 5-30%
 - LCNEC 20-60%
 - SCLC 70-100%
- Mogelijks nuttig om type resectie te bepalen van carcinoid
- Bepalen van gebieden om mitosen te tellen
- DD carcinoid vs SCLC/LCNEC in gecrushte kleine biopten

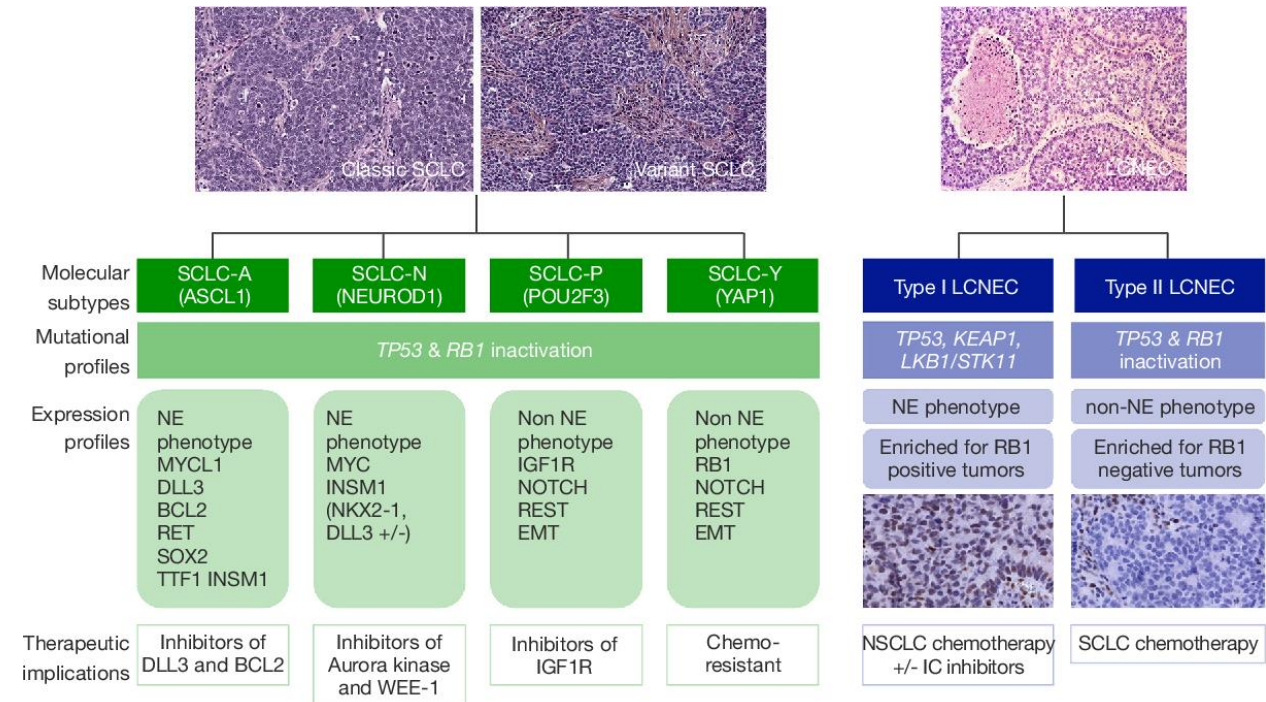


Genomische subtypering

- Grote vooruitgang in het ontrafelen van genomische profielen en herkennen van biologische subtypes.
- Nieuwe diagnostische/prognostische/predicatieve hulpmiddelen en nieuwe therapeutische opties!



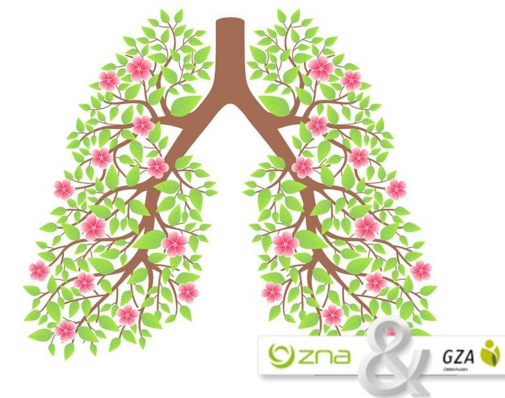
Atieh, Tahani & Huang, Chao. (2021). Treatment of Advanced-Stage Large Cell Neuroendocrine Cancer (LCNEC) of the Lung: A Tale of Two Diseases. *Frontiers in Oncology*. 11.



Dank voor uw aandacht,
vragen?



Literatuur



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- Wang Q, Gümüş ZH, Colarossi C, Memeo L, Wang X, Kong CY, Boffetta P. SCLC: Epidemiology, Risk Factors, Genetic Susceptibility, Molecular Pathology, Screening, and Early Detection. *J Thorac Oncol.* 2023 Jan;18(1):31-46.
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- Pelosi G, Travis WD. The Ki-67 antigen in the new 2021 World Health Organization classification of lung neuroendocrine neoplasms. *Pathologica.* 2021 Oct;113(5):377-387.
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