ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

NANETS NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

# ENETS-NANETS Webinar:

## MiNEN – new disease or new mindset?

Tuesday, 16 June 2026
18:00 – 19:30 CEST / 12:00 – 13:30 EDT

# Disclosure Statement

**The moderators**

**Chandrikha CHANDRASEKHARAN, USA (NANETS)** reports the following potential conflicts of interest:

- Receipt of honoraria or consultation fees: Exelixis, Curium, Adcendo-Advisory/Consulting, Honoraria speaking-Real CME, Plexus, Intellisphere, Curio Science, Targeted oncology

**and**

**Mairéad McNAMARA, GBR (ENETS)** reports the following potential conflicts of interest:

- Receipt of grants/research supports: AstraZeneca, Ipsen
- Participation in a company sponsored speaker's bureau: AstraZeneca
- Other support (please specify): Travel/Accommodation: AAA/Novartis

# The Aim and Concept

- ✓ Transferring research to education and teaching is a major goal at ENETS.
- ✓ Webinars are free of charge and can be accessed by all.
- ✓ All webinars will be recorded and made available on the ENETS website after the event.
- ✓ **This webinar is intended for HCPs qualified by law to prescribe medicine.**

# CME Accreditation by UEMS-EACCME®

- ✓ This webinar is accredited by UEMS-EACCME® with **1.5 European CME Credits (ECMEC®)**.
- ✓ To receive CME credit, participants must **attend the live webinar** and complete a **feedback form**.
- ✓ Responses are anonymous.
- ✓ To obtain your **certificate with European CME credits** for this webinar, please contact the ENETS Office at office@enets.org.

# Live poll question: Getting to know the audience

**In which medical discipline are you trained or currently working?**

# Tonight's moderators

## Chandrikha CHANDRASEKHARAN

NANETS co-chair Symposium and Regional Education committee, Women in NETs SIG

University of Texas MD Anderson Cancer Center
Houston, Texas, USA
*Oncology*

## Mairéad MCNAMARA

ENETS Advisory Board Chair

University of Manchester/The Christie
Manchester, United Kingdom
*Oncology*

# Tonight's faculty

## Deyali CHATTERJEE

Vanderbilt University Medical Center
Nashville, Tennessee, USA
*Pathology*

## Clarisse DROMAIN

CHUV University Hospital of
Lausanne, Switzerland
*Radiology*

## Jessica MAXWELL

University of Texas
MD Anderson Cancer Center
Houston, Texas, USA
*Surgical Oncology*

## Massimo MILIONE

IRCCS Foundation
National Cancer Institute
Milan, Italy
*Pathology*

# Tonight's faculty

## María SAN ROMÁN GIL

Hospital Universitario 12 de Octubre, Madrid, Spain
*Oncology*

## Nikolaos TRIKALINOS

Washington University in St. Louis and Siteman Cancer Center, Missouri, USA
*Medical Oncology*

# Tonight's agenda

**Agenda:**

18:00 – 18:05 CEST / 12:00 – 12:05 EDT **Opening comments** – *Mairéad McNamara, GBR*

18:05 – 18:15 CEST / 12:05 – 12:15 EDT **Setting the scene** – *Massimo Milione, ITA*

18:15 – 18:25 CEST / 12:15 – 12:25 EDT **Case 1: Resectable MiNEN** – *Maria San Roman Gil, ESP*

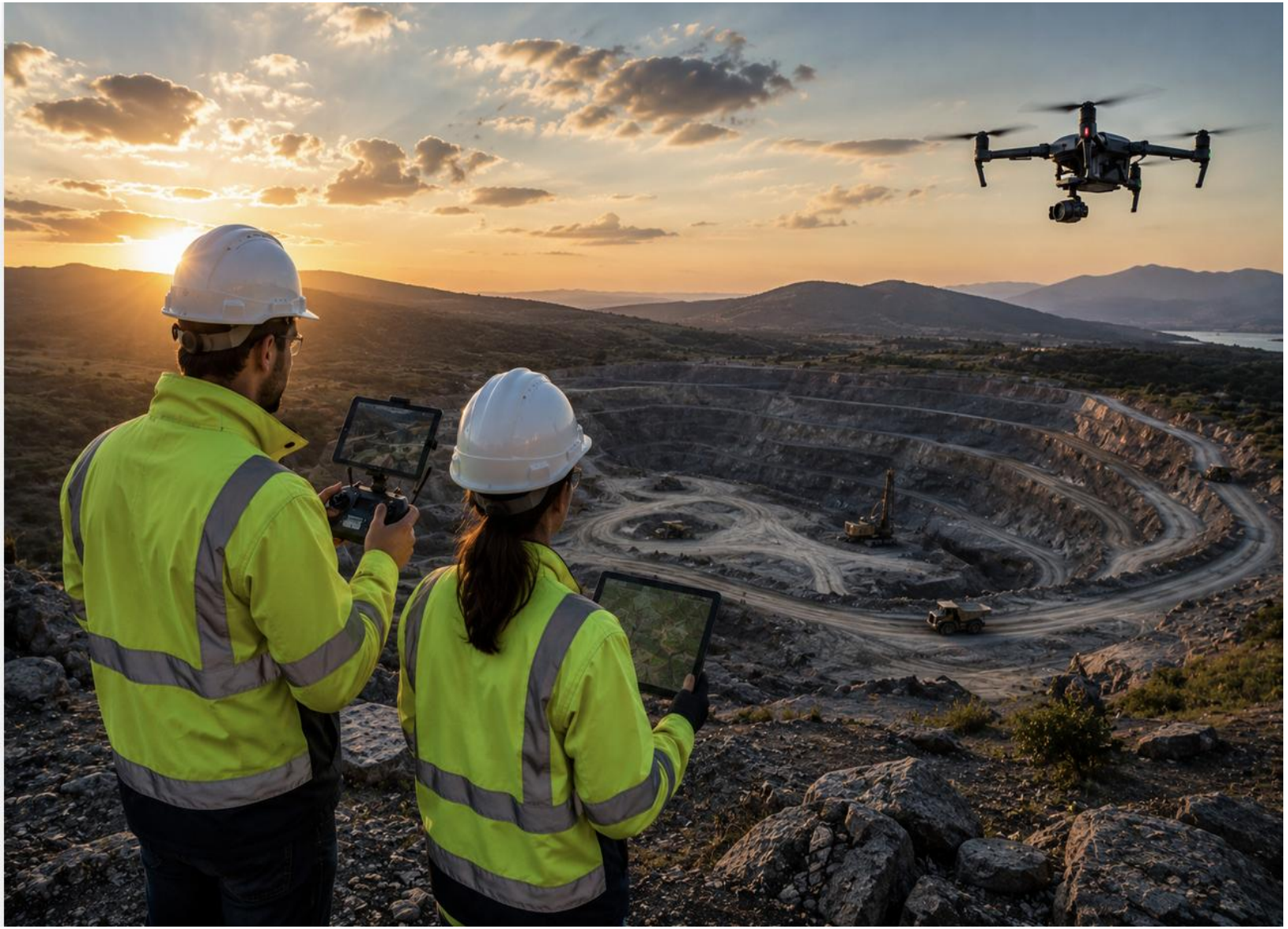
18:25 – 18:45 CEST / 12:25 – 12:45 EDT **Panel discussion**

- *Mairéad McNamara, GBR*
- *Chandrikha Chandrasekharan, USA*
- *Jessica Maxwell, USA*
- *Maria San Roman Gil, ESP*
- *Deyali Chatterjee, USA*
- *Massimo Milione, ITA*
- *Clarisse Dromain, SUI*
- *Nikolaos Trikalinos, USA*

18:45 – 19:00 CEST / 12:45 – 13:00 EDT **Case 2: Advanced MiNEN** – *Nikolaos Trikalinos, USA*

19:00 – 19:20 CEST / 13:00 – 13:20 EDT **Panel discussion**

19:20 – 19:30 CEST / 13:20 – 13:30 EDT **Wrap-up & Closing Comments** – *Chandrikha Chandrasekharan, USA*



# Setting the scene

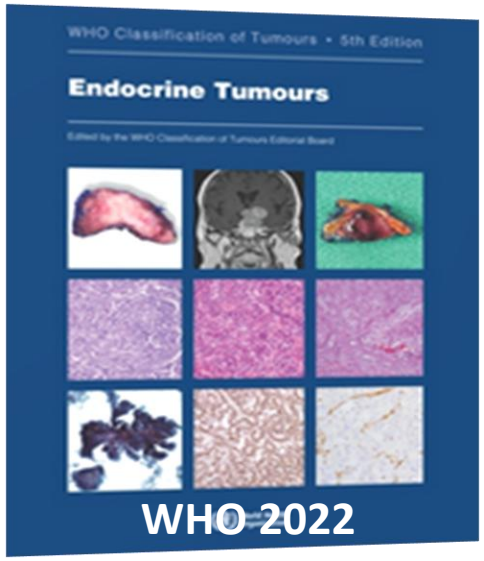
Massimo Milione
ASST Cremona-Italy

# Disclosures of Relevant Financial Relationships

✓**CONSULTING AND ADVISORY SERVICES, PUBLIC PRESENTATIONS** (3A-NOVARTIS, IPSEN, ROCHE, SAKURA FINTEK, LEICA, DIAPATH, BIOPTICA, MERCK SHARP & DHOME)

✓**FINANCIAL SUPPORT FOR CLINICAL TRIALS** (IGNYTA, ROCHE, ADOPT BBMRI-ERIC, TRANSCAN2, Fondazione IRCCS Istituto Nazionale Tumori Milano, Milan, Italy)

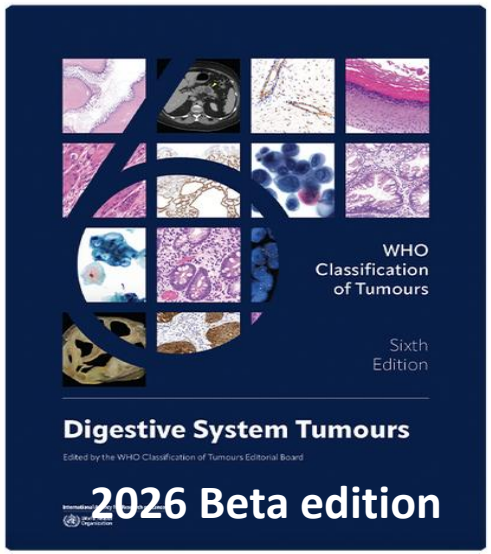
# Mixed (Neuroendocrine + non neuroendocrine) GEP Neoplasm: according to WHO




WHO 2022

In the 5° edition WHO Classification of Endocrine and Neuroendocrine Tumours, the term MiNEN has been accepted for the first time to define mixed neoplasms arising in all systems of the body.

The 30% cutoff has only been retained for digestive MiNENs.

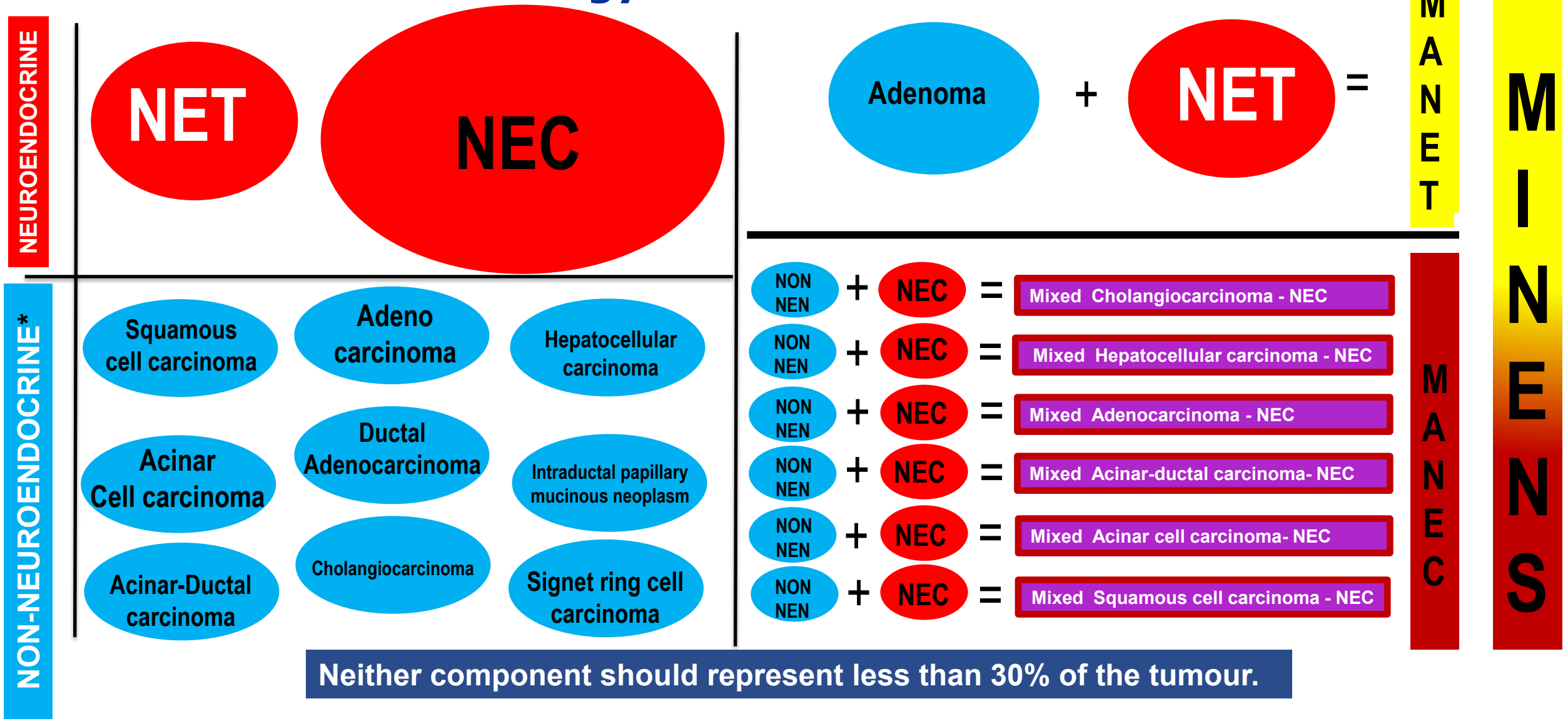



2026 Beta edition

Neither component should represent less than 30% of the tumour.

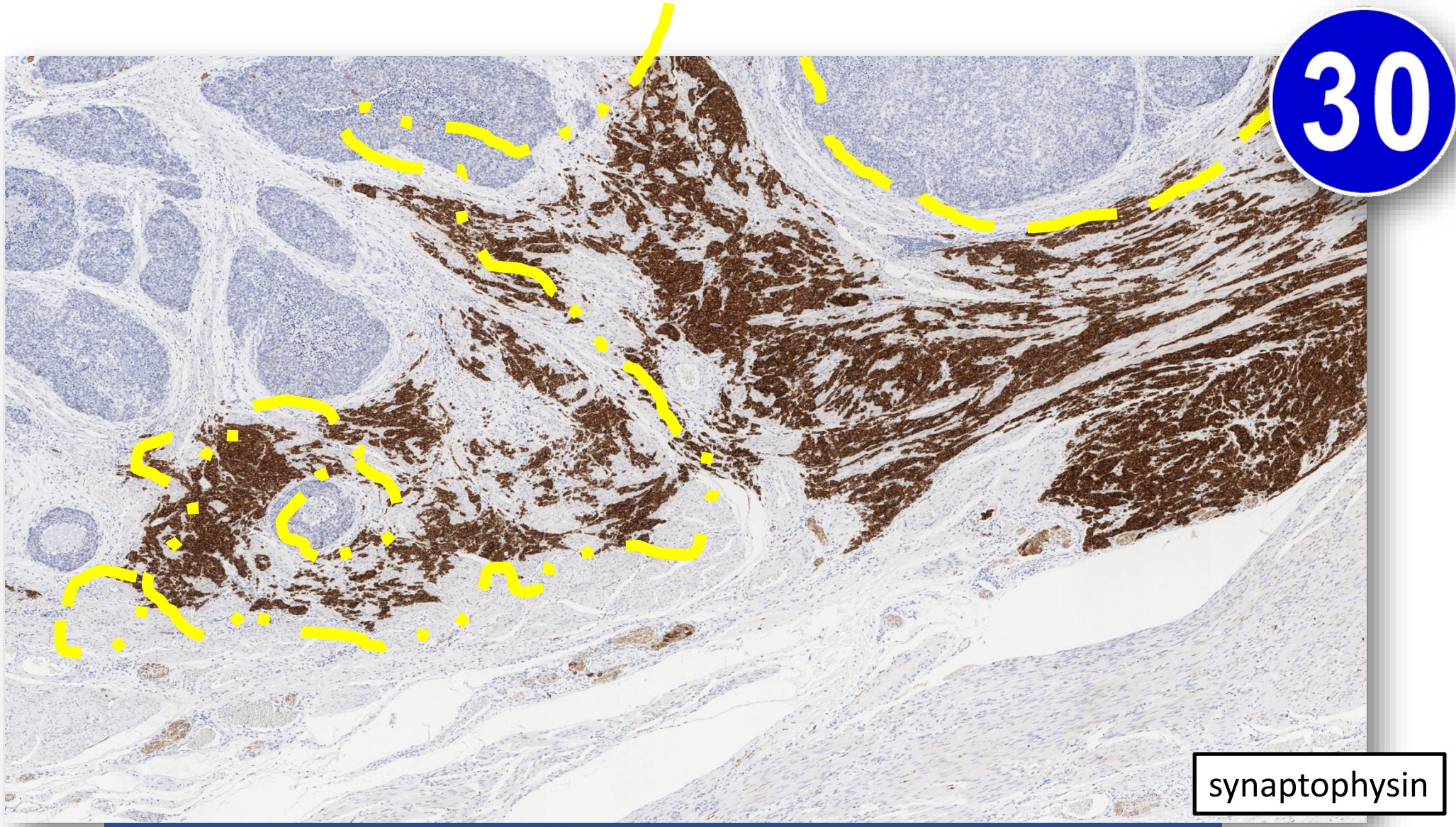
The two components must be described and graded separately.

# From Historical Terminology to WHO 2022 Classification



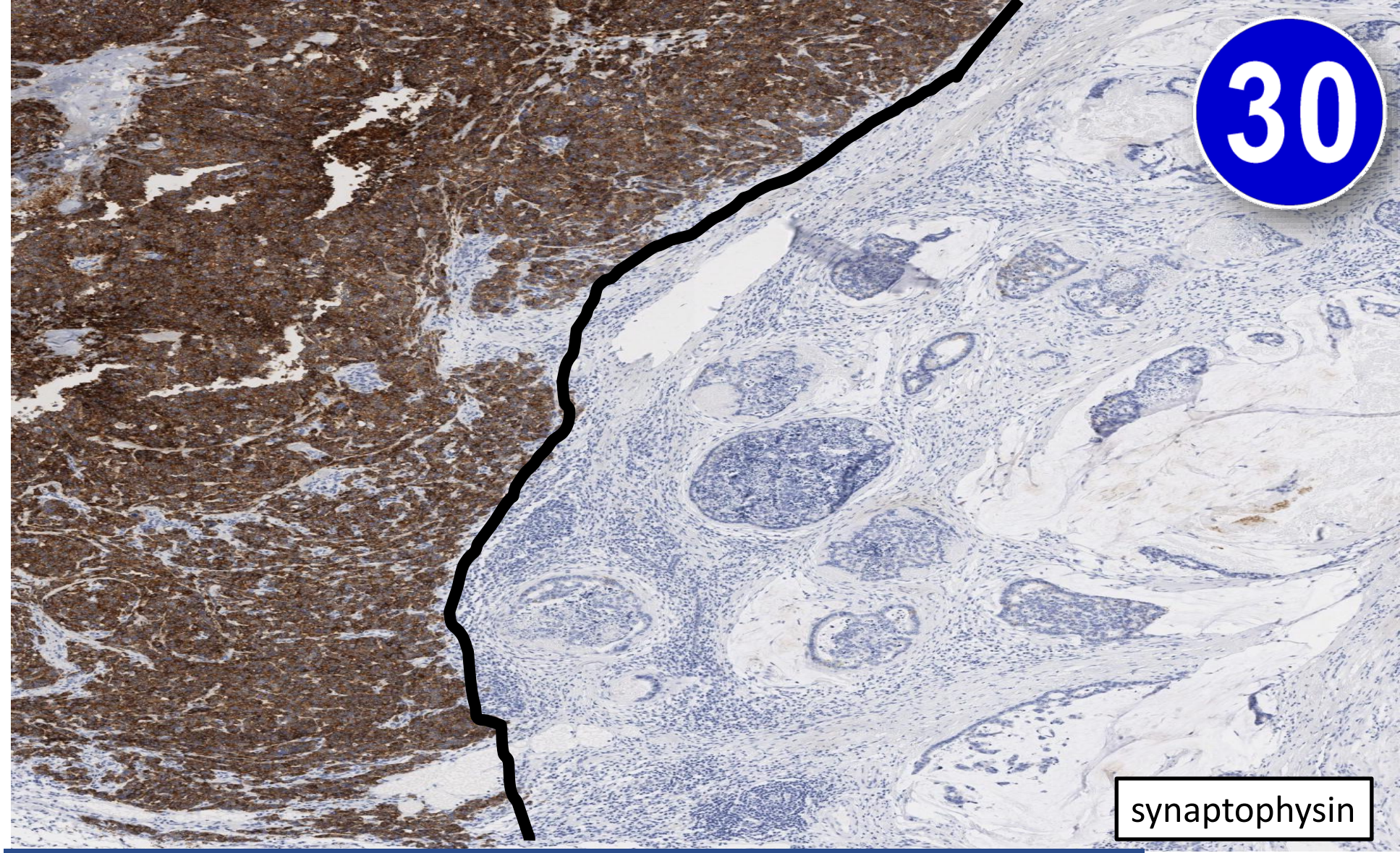

Neither component should represent less than 30% of the tumour.

**COMBINED**
**Type**



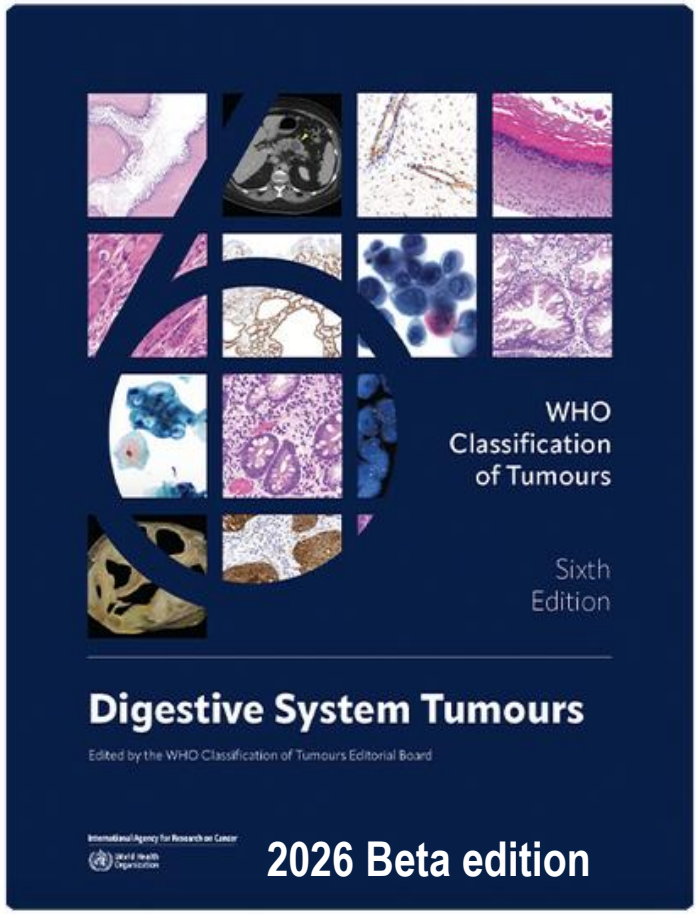

**Neither component should represent less than 30% of the tumour.**

**COLLISION**
**Type**




**Neither component should represent less than 30% of the tumour.**

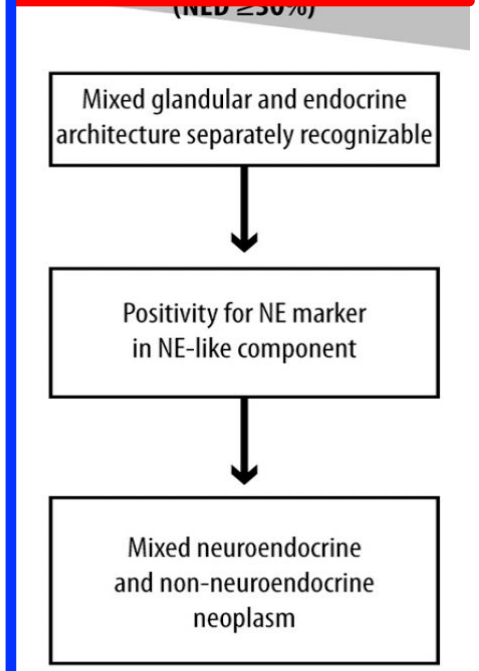
# Mixed Neoplasms beyond the 30% rule

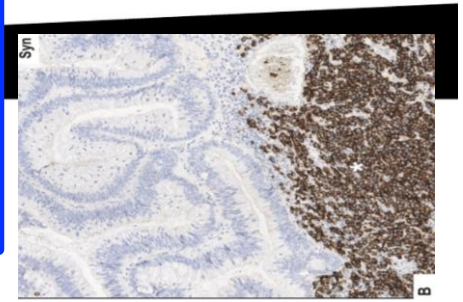



**Amphicrine Carcinomas**

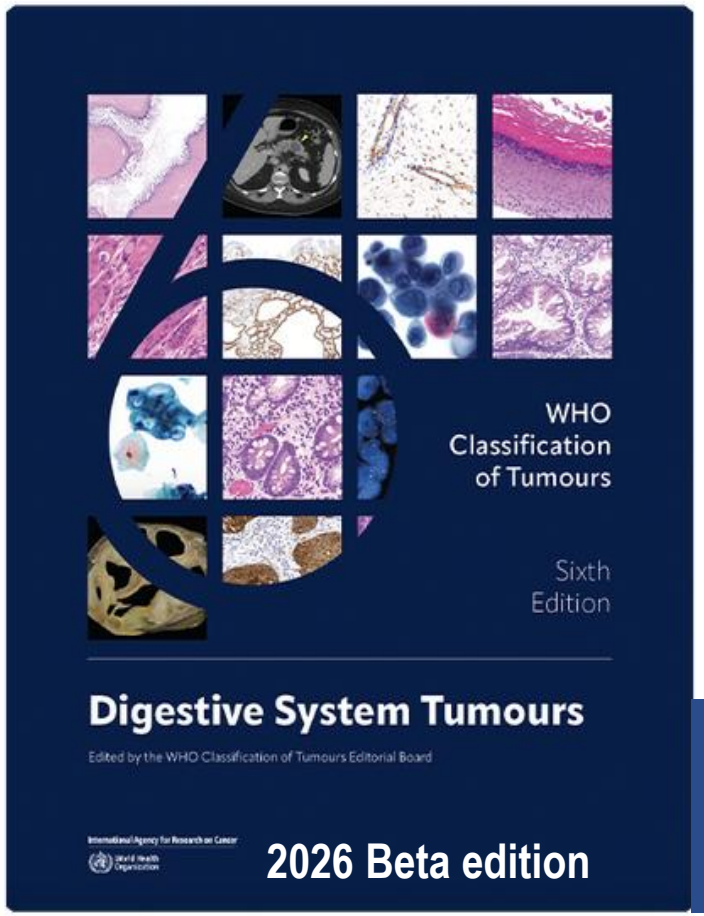
- **Ordinary Carcinoma Expressing Synaptophisyn**
- **Amphicrine Carcinomas**

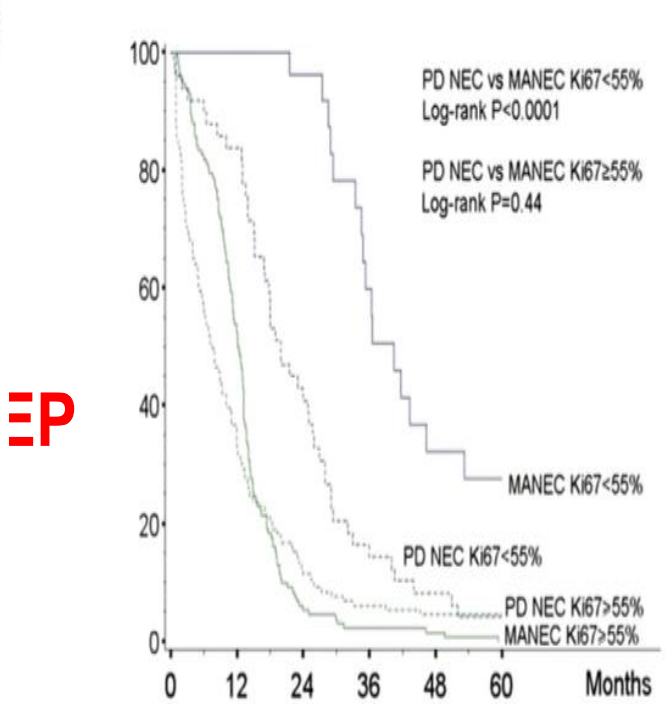
**Really MiNEN**



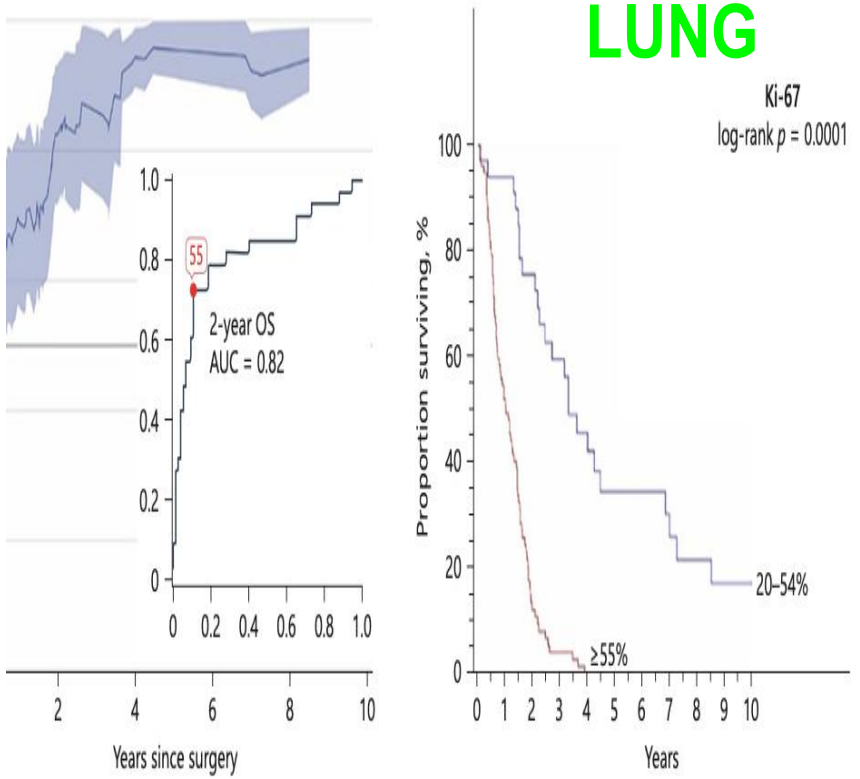

**Centonze-Sabella PMID 37268174**




EP

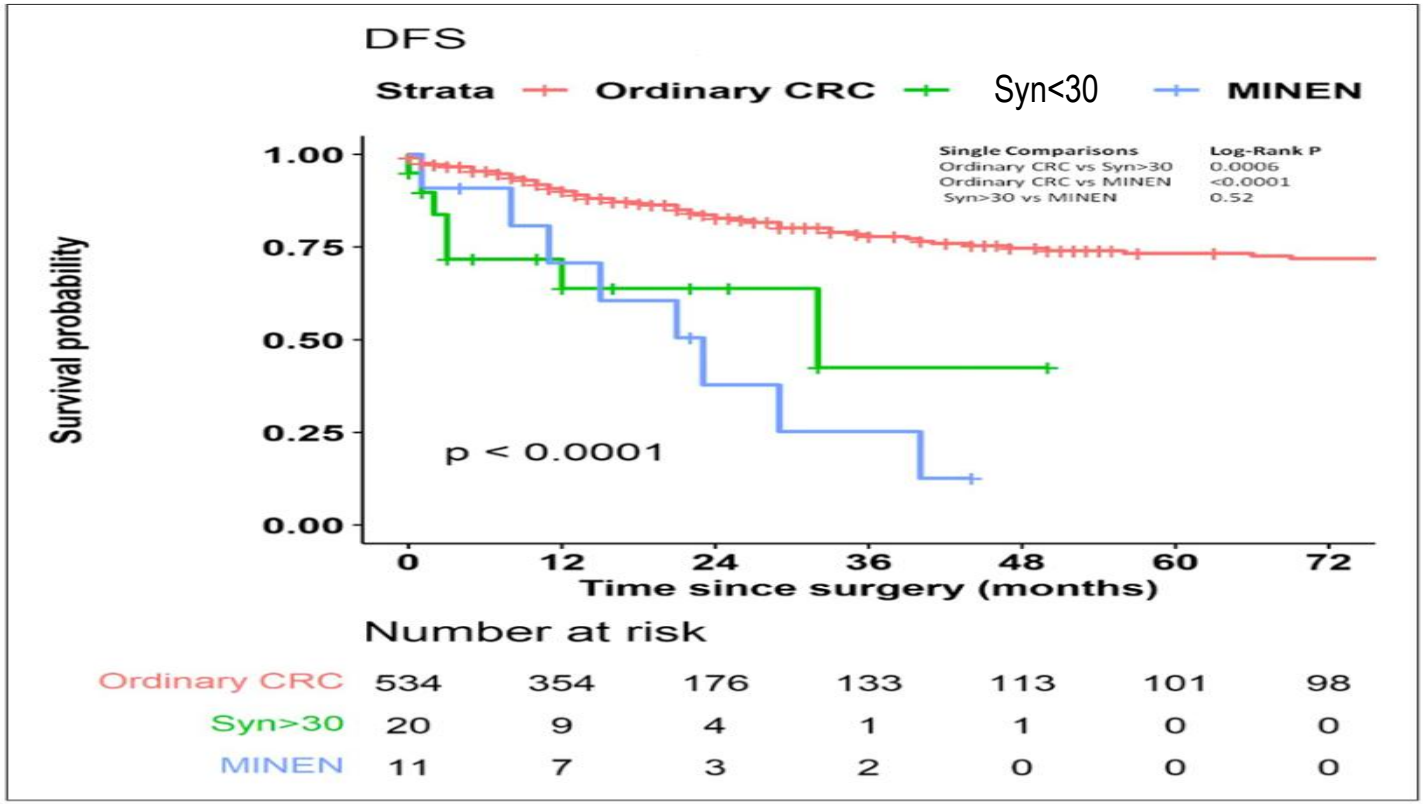
LUNG

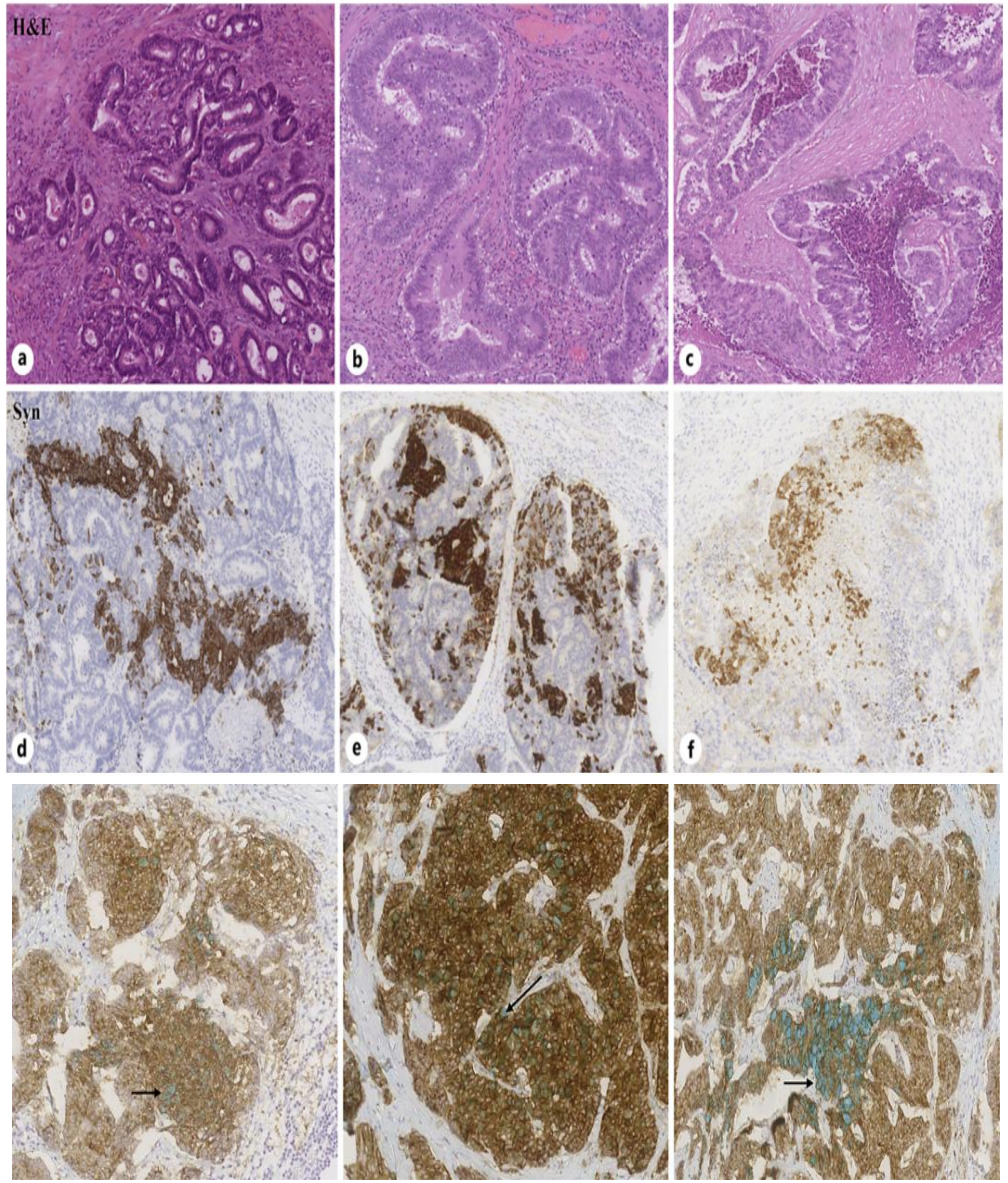



The two components must be described and graded separately, with particular attention to the evaluation of Ki-67 in the NEC component (< 55% or ≥ 55%) for prognostic stratification

*Milione PMID 32365350*

# What if the worst part isn't the bad news itself?




| | All patients | Conventional CRC | Syn-positive CRC | *p* value[1] |
|---|---|---|---|---|
| Total | 663 (100) | 636 (100) | 27 (100) | |
| *TP53* | | | | |
| WT | 22 (29.7) | 19 (30.6) | 3 (25.0) | |
| Mut | 52 (70.3) | 43 (69.4) | 9 (75.0) | 1.0 |
| *KRAS* | | | | |
| WT | 95 (53.4) | 82 (51.9) | 13 (65.0) | |
| Mut | 83 (46.6) | 76 (48.1) | 7 (35.0) | 0.3 |
| *NRAS* | | | | |
| WT | 127 (96.2) | 114 (95.8) | 13 (100.0) | |
| Mut | 5 (3.8) | 5 (4.2) | 0 (0.0) | 1.0 |
| *BRAF* | | | | |
| WT | 144 (84.7) | 132 (86.8) | 12 (66.7) | |
| Mut | 26 (15.3) | 20 (13.2) | 6 (33.3) | **0.04** |
| *APC* | | | | |
| WT | 43 (58.9) | 39 (55.7) | 9 (75.0) | |
| Mut | 30 (41.1) | 27 (44.3) | 3 (25.0) | 0.3 |

CRC, colorectal carcinoma; Syn, synaptophysin; WT, wild type; Mut, mutated.
[1]*p* value based on the Fisher's exact for categorical variables.

**Sabella PMID 40324347**


massimo.milione@istitutotumori.mi.it
grazie

# Case 1: Resectable MiNEN

María San Román, MD

Hospital Universitario 12 Octubre
Madrid, Spain

# DISCLOSURE SLIDE

- I have received support from Novartis, Merck, IPSEN, Esteve, BeOne, and Pierre Fabre for travel expenses, accommodation, and congress registration fees.
- I have not received personal honoraria, consultancy fees, advisory board fees, research funding, stock ownership, licensing fees, or royalties from these companies.

# 1. Why this case matters

- ✓ MiNEN stands for mixed neuroendocrine–non-neuroendocrine neoplasm.

- ✓ It is a rare tumour composed of **two different** malignant components:
  - ✓ A neuroendocrine component
  - ✓ A non-neuroendocrine component
    - ✓ Each of which is morphologically and IHC recognizable

**Evidence is limited to retrospective series, making treatment decisions heavily dependent on MDT assessment and tumour biology.**

| Diagnosis | Treatment | Prognosis |
|---|---|---|
| Frequently missed on biopsy | No standard perioperative strategy | Driven by the most agressive tumour |

Rindi G. et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocrine Pathology (2022) 33:115–154 / de ML, Cros J, et al Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. Neuroendocrinology (2017) 105: 412-425. Song H. et al. Comprehensive analysis of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs): A SEER database analysis of 767 cases Frontiers in Oncology. 2023

# 1. MiNEN – Why this case matters

Evidence remains limited; no randomised trials → **RETROSPECTIVE DATA**

- ✓ **Epidemiology**
  - ✓ 50-60 yo. Most common primary sites: appendix, colorectum and gastroesophageal tract
  - ✓ **Estimated an increased 10-fold between 2000 and 2017** → Difficult to estimate the actual incidence of MiNEN due to inconsistent reporting and varying nomenclature over the past several decades (amphycrine tumours…)
- ✓ **Localised disease**
  - ✓ Around 50-60% of patients present with localised disease
  - ✓ Complete surgical resection remains the cornerstone of treatment
  - ✓ Benefit of peri-operative therapy remains uncertain
- ✓ **Clinical behaviour**
  - ✓ Prognosis varies according to the **primary** site
  - ✓ **Liver** is the most common metastatic site
  - ✓ Most metastatic samples contain **poorly differentiated NEC**

Shi H, et al. Do neuroendocrine carcinomas and mixed neuroendocrine-non-neuroendocrine neoplasm of the gastrointestinal tract have the same prognosis? A SEER database analysis of 12,878 cases. Ther Adv Endocrinol Metab. 2020
Song H. et al. Comprehensive analysis of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs): A SEER database analysis of 767 cases Frontiers in Oncology. 2023
Frizziero M. et al. Retrospective study on mixed neuroendocrine non-neuroendocrine neoplasms from five European centres. World J Gastroenterol. 2019

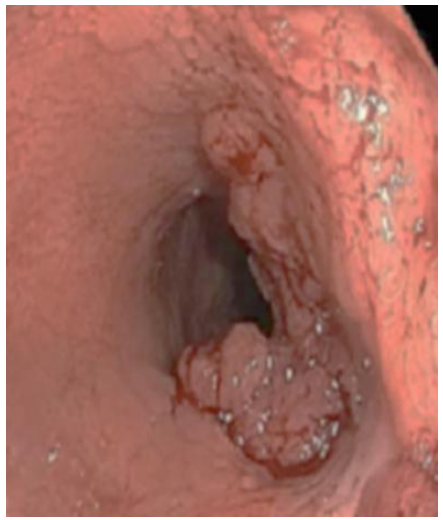
# 2. Case presentation

- ✓ 67-year-old man
- ✓ **Relevant medical history**
  - ✓ **Caustic esophageal injury at 2 years of age → Long-standing benign oesophageal stenosis, with multiple endoscopic dilatations (>10 procedures**)
  - ✓ **Gastric ulcer disease**
  - ✓ Former smoker (30 pack-years) and alcohol consumption
  - ✓ Hypertension, dyslipidemia, atrial fibrillation, glaucoma

- ✓ **Diagnostic work-up**
  - ✓ During follow-up for esophageal stenosis, a lesion involving the gastroesophageal junction was identified.

# 2. Case presentation – Initial challenge

- ✓ **April 2024 - Upper endoscopy:** Gastroesophageal lesion similar to a conventional gastroesophageal adenocarcinoma → The preoperative biopsy: *intramucosal* ***poorly-differentiated adenocarcinoma*** *of the gastroesophageal junction*



**What was missing?**
**The biopsy did not reveal the neuroendocrine component.**
No information about IHC performed

**Why does this happen?**
**Limited sampling** → Pre-operative biopsy **often misclassifies** as pure adenocarcinoma or NEC; **correct MiNEN diagnosis before surgery is achieved in only a small minority (4–14%)**

Hong *et al.* Characterizing esophageal mixed neuroendocrine–non-neuroendocrine neoplasms: insights from a retrospective multicenter study of clinical outcomes and prognostic indicators. Therapeutic Advances in Medical Oncology. 2024

# 2. Case presentation – Baseline imaging and staging

- ✓ **CT scan (May 2024)**
  - ✓ Primary tumour: Thickening of the gastric fundus wall, suspicious for malignancy
  - ✓ **Nodal disease: Enlarged lymph nodes** within the gastrohepatic ligament
  - ✓ Thoracic findings: No significant mediastinal lymphadenopathy. Small left upper lobe ground-glass infiltrates considered inflammatory/infectious

- ✓ **Clinical staging**
  - ✓ Potentially resectable gastroesophageal junction tumour
  - ✓ No evidence of distant metastatic disease

- ✓ **MDT decision**
  - ✓ Proceed to upfront surgery with curative intent.

**Initial impression**

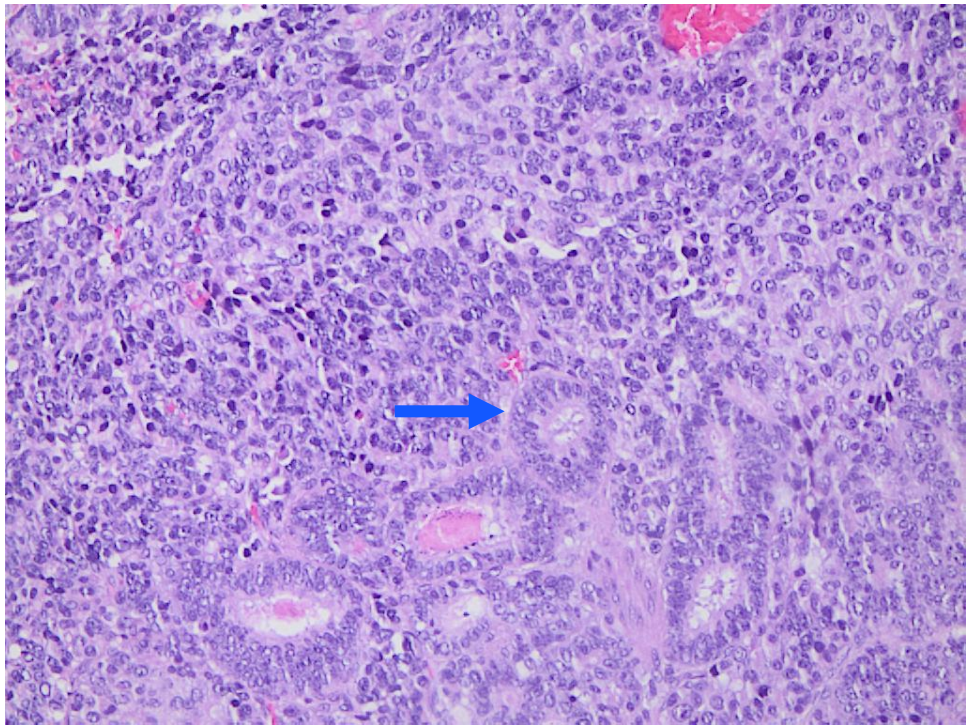
Localised gastroesophageal poorly-differentiated adenocarcinoma suitable for curative-intent treatment.

# 5. Surgery and final pathology: The diagnosis changes

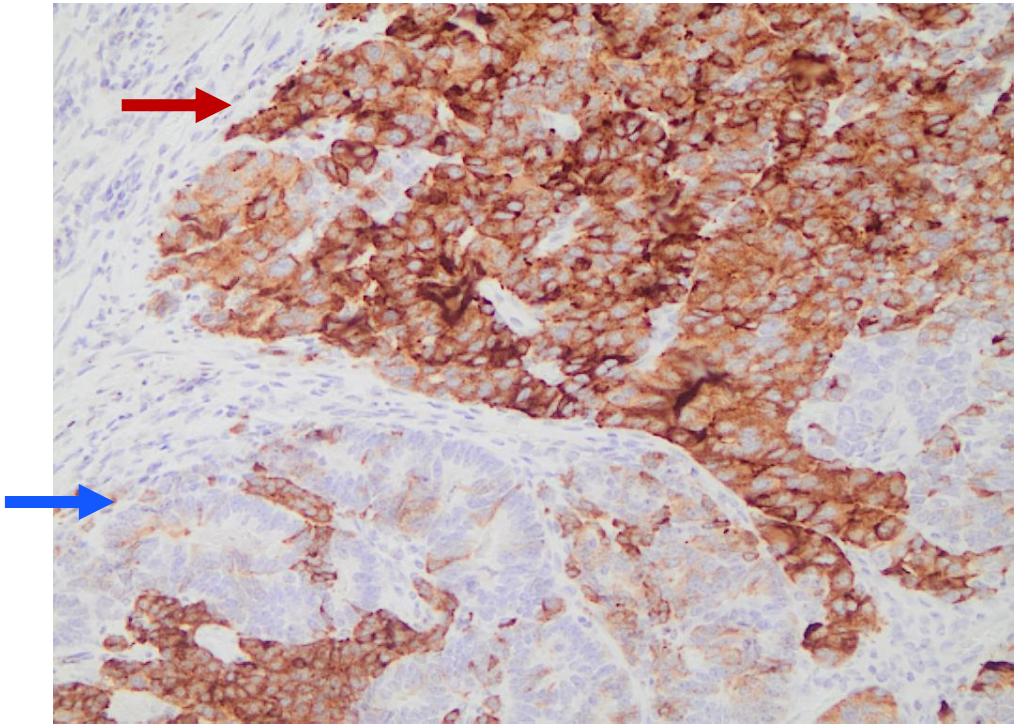
- ✓ **Surgery – 25th June 2024**
  - ✓ Esophagectomy + gastric conduit reconstruction
  - ✓ Celiac and paracardial lymphadenectomy
  - ✓ Macroscopically complete resection

| Diagnosis | GASTROESOPHAGEAL JUNCTION MiNEN |
|---|---|
| **Components** | Moderately differentiated ulcerated **adenocarcinoma** + large-cell **neuroendocrine carcinoma** |
| **Predominant biology** | High-grade neuroendocrine carcinoma component |
| **Ki-67** | 60% |
| **LVI / PNI** | Present / Present |
| **Margins** | Negative proximal esophageal and gastric margins → R0 |
| **Nodal status** | 24/42 positive lymph nodes |
| **Stage** | pT3, N3, M0 |

# 2. Case presentation – The diagnosis changes



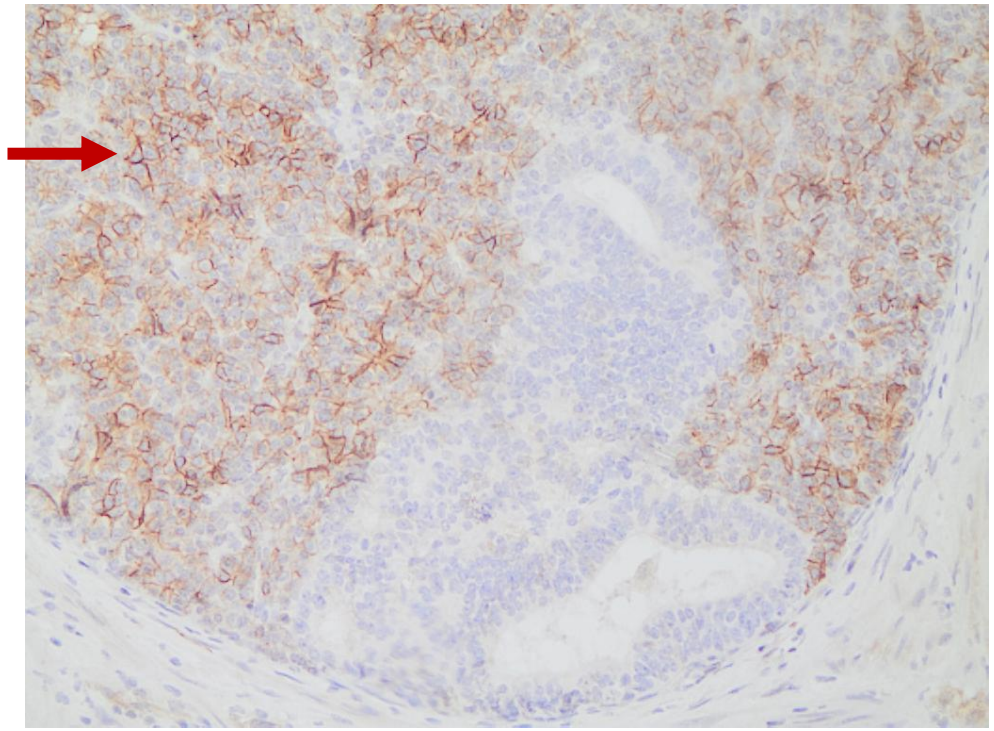
**Neuroendocrine** and **glandular** áreas (H/Ex200)



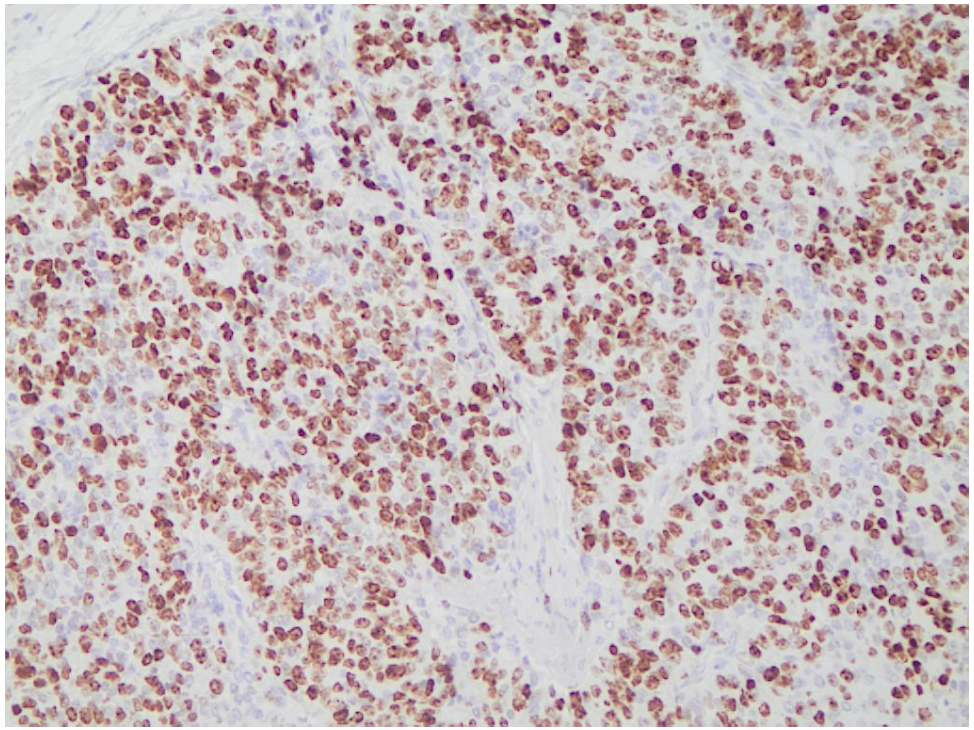
**Sinaptophysin + (neuroendocrine)** and **- (adenocarcinoma)**

*Images courtesy from Dr. Ibarrola de Andres*

# 2. Case presentation – The diagnosis changes



Membranous CD56 + (neuroendocrine)



Ki-67 (neuroendocrine) (IHCx400)

*Images courtesy from Dr. Ibarrola de Andres*

# 3. Why MiNEN matters

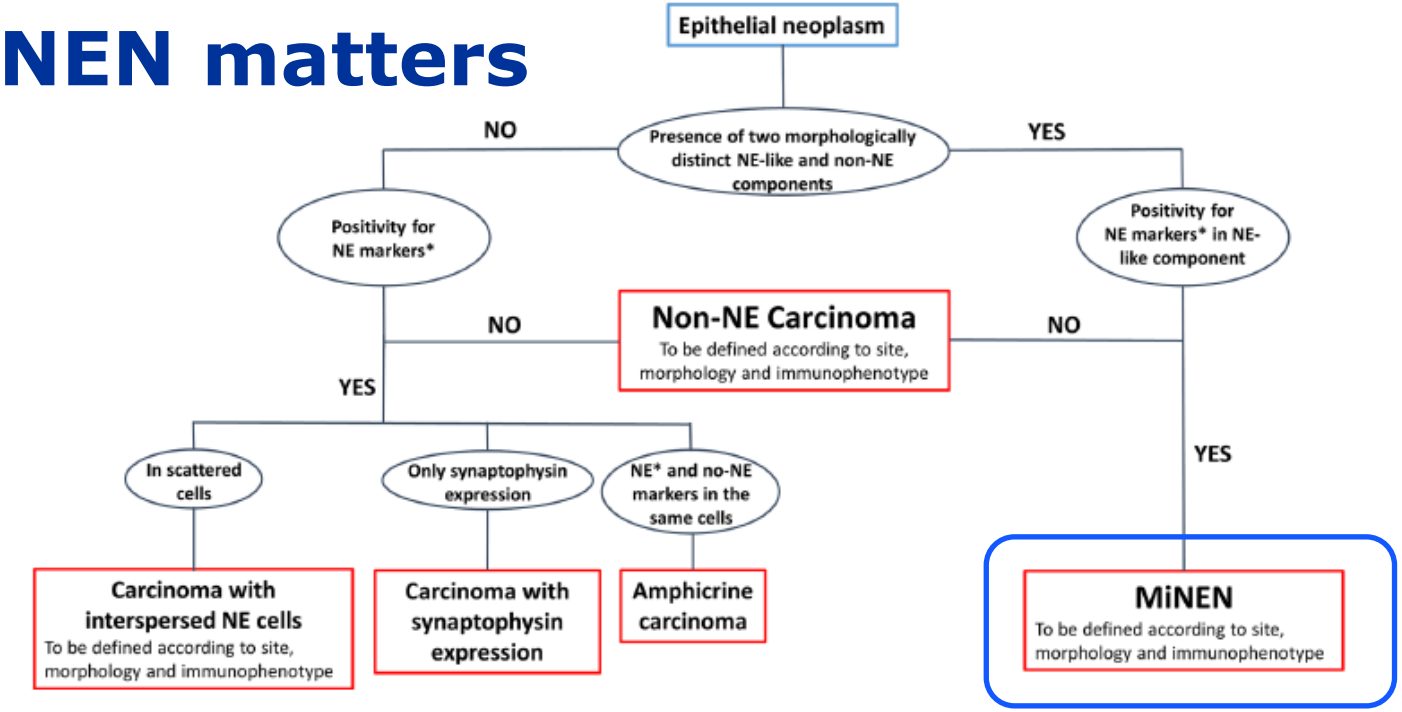
- ✓ It is a rare tumour composed of **two different** malignant components:
  - ✓ Neuroendocrine component: **NEC** >NET – synaptophysin and INSM1, chromogranin A (+/- Ki-67)
  - ✓ Non-neuroendocrine component, **adenocarcinoma** > squamous carcinoma – IHC profile of the non-NE component
    - ✓ Each of which is morphologically and IHC recognisable
      - ✓ **Histological diagnosis**

- ✓ Traditionally, each component should represent **at least 30% of the tumour**, although this threshold is sometimes debated → only retained in digestive MiNEN (WHO 2022)

  - ✓ MiNEN in non-digestive systems depends on the identification of two morphologically distinct components independent of their amount

Rindi G. et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocrine Pathology (2022) 33:115–154N / de ML, Cros J, et al Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. Neuroendocrinology (2017) 105: 412-425.

# 3. Why MiNEN matters




- ✓ **Prognosis** related to the **biologically more aggressive** component: **NEC > carcinoma > NET**
  - ✓ BUT both MiNEN components may metastasise: they need to be characterised and graded separately and considered in terms of treatment
- ✓ In metastatic cases, **a biopsy of the metastasis** is of particular importance since the **identification of the metastasising component** can influence the therapeutic choice.

Rindi G. et al. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. Endocrine Pathology (2022) 33:115–154

# 2. Case presentation – Adjuvant treatment decision

**MDT decision**

- ✓ Given the predominant LCNEC with high proliferative index and massive nodal involvement → **Adjuvant chemotherapy was recommended**.
  - ✓ Treatment administered: Paclitaxel 175 mg/m² + Cisplatin 75 mg/m² for 4 cycles (August – October 2024)

**Would you have chosen a different regimen?**

- ✓ Assessment: PET-FDG-CT (November 2024): **Complete morphologic and metabolic response**

- ✓ Close FUP with PET-FDG-CTs every 3 months

# 4. Was this really a "resectable" disease?

**Arguments for resectable disease**

- ✓ R0 resection achieved
- ✓ No distant metastases at diagnosis
- ✓ Complete metabolic response after adjuvant therapy

**Arguments for biologically systemic disease**

- ✓ Predominant LCNEC component
- ✓ Ki-67 >60%
- ✓ 24 positive lymph nodes
- ✓ Lymphovascular and perineural invasion

**Retrospective data supports surgery**

- ✓ Xu B. *et al*. In gastrointestinal MiNEN (SEER, 2000–2019), both **local and radical resection were independent protective prognostic factors** (HR 0.16 and 0.28) for cancer-specific survival
- ✓ Song H. *et al*. Large SEER MiNEN cohort: non-surgical treatment was an independent risk factor for poorer survival.

Xu B. et al. Incidence, survival, and prognostic factors for patients with gastrointestinal mixed neuroendocrine non-neuroendocrine neoplasms: a SEER population-based study. Journal of Cancer Research and Clinical Oncology (2023)
Song H. et al. Comprehensive analysis of mixed neuroendocrine non-neuroendocrine neoplasms (MiNENs): A SEER database analysis of 767 cases Frontiers in Oncology. 2023

# 5. Why surgery matters

**Retrospective data supports surgery**

- Multiple retrospective studies and systematic reviews consistently report that **curative-intent surgical resection offers the best chance for prolonged survival** in patients with **localised MiNEN**
  - Median OS after curative surgery ranges from 24 to 68 months, depending on tumour site and biology
  - Radical resection (R0) is particularly important for optimal outcome
  - **Recurrence rates remain high**, especially within the first 2 years post-surgery

**Surgery remains the cornerstone of treatment for localised MiNEN when an R0 resection is feasible.**

Frizziero M. et al. Mixed Neuroendocrine Non-Neuroendocrine Neoplasms: A Systematic Review of a Controversial and Underestimated Diagnosis. Journal of Clinical Medicine.2020. Pommergaard HC. et al. Surgery of the primary tumour in 201 patients with high-grade gastroenteropancreatic neuroendocrine and mixed neuroendocrine-non-neuroendocrine neoplasms. Journal of Neuroendocrinology. 2021 Wen L et al. The clinical profiles, management, and prognostic factors of biliary mixed neuroendocrine non neuroendocrine neoplasms. Medicine, 2020. Amin M. et al. Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) of gastrointestinal (GI) tract: A single institution experience. Journal of Clinical Oncology. 2020. Iwasaki K. et al. Long-term surgical outcomes of gastric neuroendocrine carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasms. World Journal of Surgical Oncology. 2022. Zheng M. et al. Survival Profile and Prognostic Factors for Appendiceal Mixed Neuroendocrine Non-neuroendocrine Neoplasms: A SEER Population-Based Study. Frontiers in Oncology. 2020

# 6. Perioperative treatment

**Evidence remains controversial** → No randomised trials available

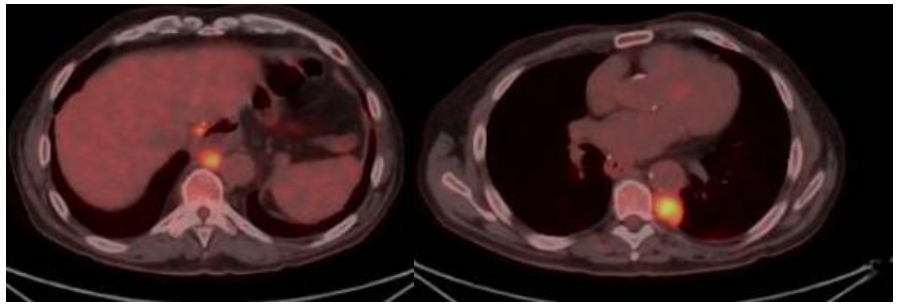
- **NEC-dominant MiNEN**: Usually treated with platinum-based regimens (etoposide or irinotecan)
- **Adenocarcinoma-dominant MiNEN**: Often managed according to adenocarcinoma protocols (FOLFOX/CAPOX)

- <u>Retrospective evidence</u>
  - Some series suggest **benefit from neoadjuvant/adjuvant chemotherapy**
    - *Neoadjuvant*: The strongest **gastric** MiNEN series (n=69; Ma F, et al.): Better OS with neoadjuvant chemotherapy before surgery: 3-year OS:68.8% with NA vs 43.8% with upfront surgery
    - *Adjuvant* chemotherapy improves outcomes in some series: Largest retrospective series of gastric NEC/MiNEN (777 patients), omission of adjuvant chemotherapy was associated with a higher risk of recurrence after curative resection (multivariate HR 1.43)
  - Other studies show **no significant survival advantage**
    - *Neoadjuvant*: **gastric** MiNEN series – Not significant differences (n=49; van der Veen A, et al.)
    - *Adjuvant*: Frizziero et al; n=69: 53% received perioperative treatment → Receipt of perioperative treatment (vs surgery alone) did not improve RFS (P = 0.375), or OS (P = 0.240) – However usually adenocarcinoma-driven

Jacob A. et al. An Update on the Management of Mixed NeuroendocrineNon-neuroendocrine Neoplasms (MiNEN) Curr. Treat. Options in Oncol. (2022). Ma F, et al. Neoadjuvant chemotherapy improves the survival of patients with neuroendocrine carcinoma and mixed adenoneuroendocrine carcinoma of the stomach. J Cancer Res Clin Oncol.2020. van der Veen A, et al. Management of resectable esophageal and gastric (mixed adeno)neuroendocrine carcinoma: A nationwide cohort study. European Journal of Surgical Oncology. 2018. Zheng H, et al. Multi-institutional development and validation of a nomogram to predict recurrence after curative resection of gastric neuroendocrine/mixed adenoneuroendocrine carcinoma. Gastric Cancer. 2021

# 2. Case presentation: Follow-up strategy

- ✓ PET-FDG-CT June 2025: Findings consistent with **metastatic recurrence**:
  - ✓ Pleural mass (SUVmax 9.9)
  - ✓ Diaphragmatic implants
  - ✓ Retrocrural disease
  - ✓ Retropancreatic adenopathy
  - ✓ Suspicious pulmonary nodules
  - ✓ Hypermetabolic focus in surgical bed



- ✓ Disease-free interval: Approximately **8 months** after completion of adjuvant chemotherapy.

**June 2024 surgery** → Oct 2024 adjuvant completed → Nov 2024 complete metabolic response → **June 2025 metastatic relapse**

# 7. Follow-up strategy

## Live poll question:

**What would be your preferred next step?**

- ✓ A. Platinum re-challenge
- ✓ B. FOLFIRI
- ✓ C. FOLFOX/CAPOX
- ✓ D. FOLFIRINOX
- ✓ E. Clinical trial (if available)

# 7. Follow-up strategy

**What would be your preferred next step?**

- ✓ A. Platinum re-challenge
- ✓ B. FOLFIRI
- ✓ C. FOLFOX/CAPOX
- ✓ D. FOLFIRINOX
- ✓ **E. Clinical trial (if available) → DAREON™-7: *A study to test how well different doses of BI 764532 in addition to chemotherapy are tolerated by people with advanced neuroendocrine cancers***

**Referral to our centre**

# 10. Evolution in our centre (metastatic disease)

**Jul 2025**

- Carboplatin–etoposide initiated.
  - Pleural biopsy: metastatic NEC component.
  - DLL3 positive (pre-screening DAREON-7).
- Febrile neutropenia/sepsis requiring CT adjustments and G-CSF support

**Aug 2025**

- Enrolled in DAREON-7 (CT+Obrixtamig [bispecific antibody DLL3/CD3]).
- Treatment course: Poor tolerance requiring further dose reductions, delays and G-CSF support.

**Response assessment**

- Initial CT: mixed response (non-RECIST PD).
- Subsequent CT: stable disease (+3.5%).

**Outcome:** Progressive clinical deterioration despite radiological stability.

Despite **DLL3-positive** disease and trial enrolment, the patient experienced limited clinical benefit and ultimately died 6 months after metastatic relapse (December 2025).

# 12. Discussion points

- ✓ Should **neuroendocrine markers be routinely performed** in poorly differentiated gastroesophageal carcinomas?
- ✓ **Would it have been considered resectable** if MiNEN diagnosis was made at first biopsy?
- ✓ Should **therapy** in potentially resectable MiNEN follow: adenocarcinoma paradigm OR NEC paradigms when they co-exist
  - ✓ **What is the optimal perioperative strategy**?

# 13. Take-home messages

- ✓ MiNEN is often diagnosed **only after surgery.**
- ✓ Although evidence is limited and retrospective, **radical surgery remains the cornerstone of localised disease** (R0 resection).
- ✓ Pathology must **report both components separately** + consider biopsy at relapse to guide systemic treatment
- ✓ The **most aggressive or the metastatic component** often **guides treatment**.
- ✓ **Perioperative treatment** must be **individualised** in expert MDTs.

| What we know | What we don't know |
|---|---|
| Rare disease | Optimal peri-operative treatment |
| Frequently underdiagnosed | Which component should drive therapy (carcinoma and NEC) |
| Often presents with advanced disease (34 – 46%) | Best perioperative strategy |
| Surgery is standard in localised disease | Who truly benefits from surgery |

# Panel Discussion

# Case 2: Patient with metastatic MiNEN

Nikolaos A Trikalinos, MD, MS

Washington University in St Louis,
St Louis, MO, USA

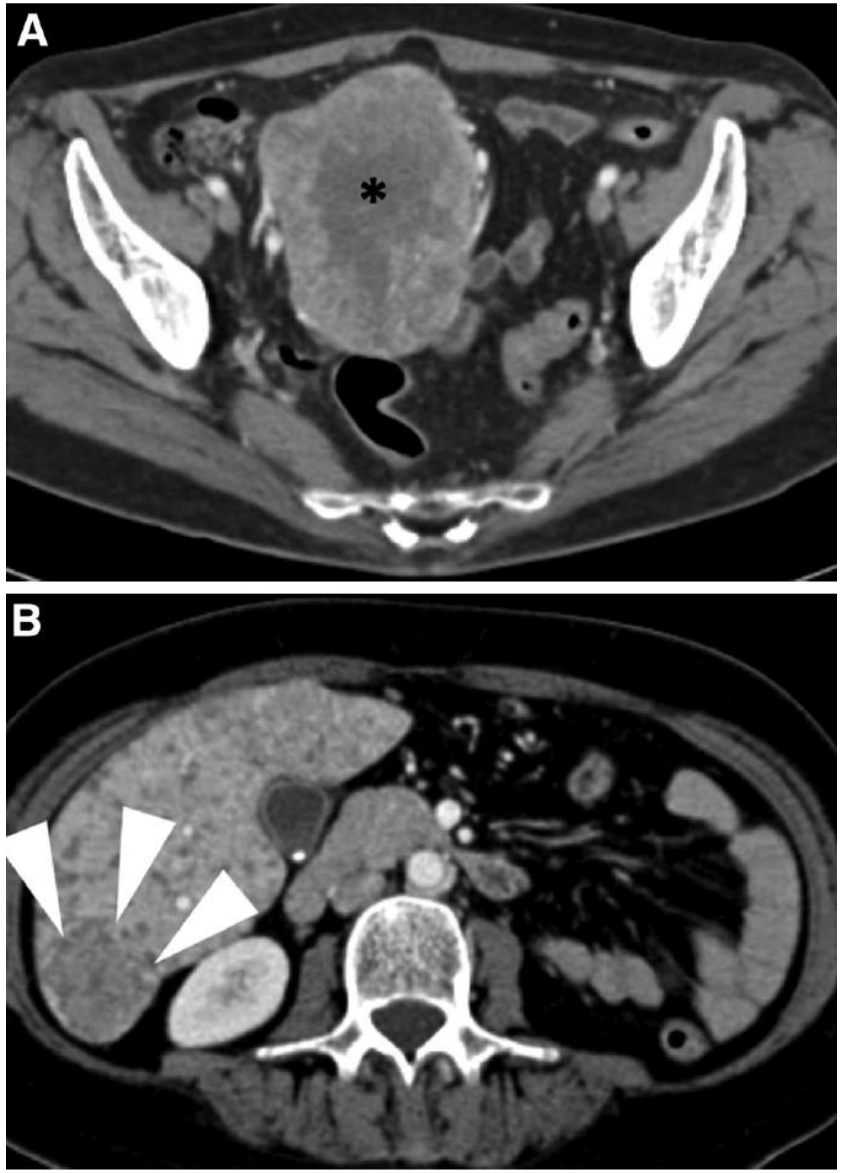
# DISCLOSURE SLIDE

- Sub-PI or PI for multiple institutional studies funded under Exelixis, Curium, Novartis, BMS, Nykode Therapeutics, Elevar Therapeutics, Jazz Pharmaceuticals, Pharma Mar

- No financial interests related to this presentation

# Clinical presentation

- ✓ A 51-year-old patient with sarcoidosis was evaluated for new onset abdominal pain.
- ✓ Six years before she had been diagnosed with FIGO stage Ia endometrial adenocarcinoma and synchronous ovarian endometrioid adenocarcinoma FIGO stage Ic. MMR deficiency was shown in tumour (Loss of MSH2/MSH6) but not in germline testing. She had received curative resection followed by adjuvant carboplatin and paclitaxel, then taxotere.
- ✓ Now imaging showed a right hemipelvic mass (A) and presumed liver metastasis (B)

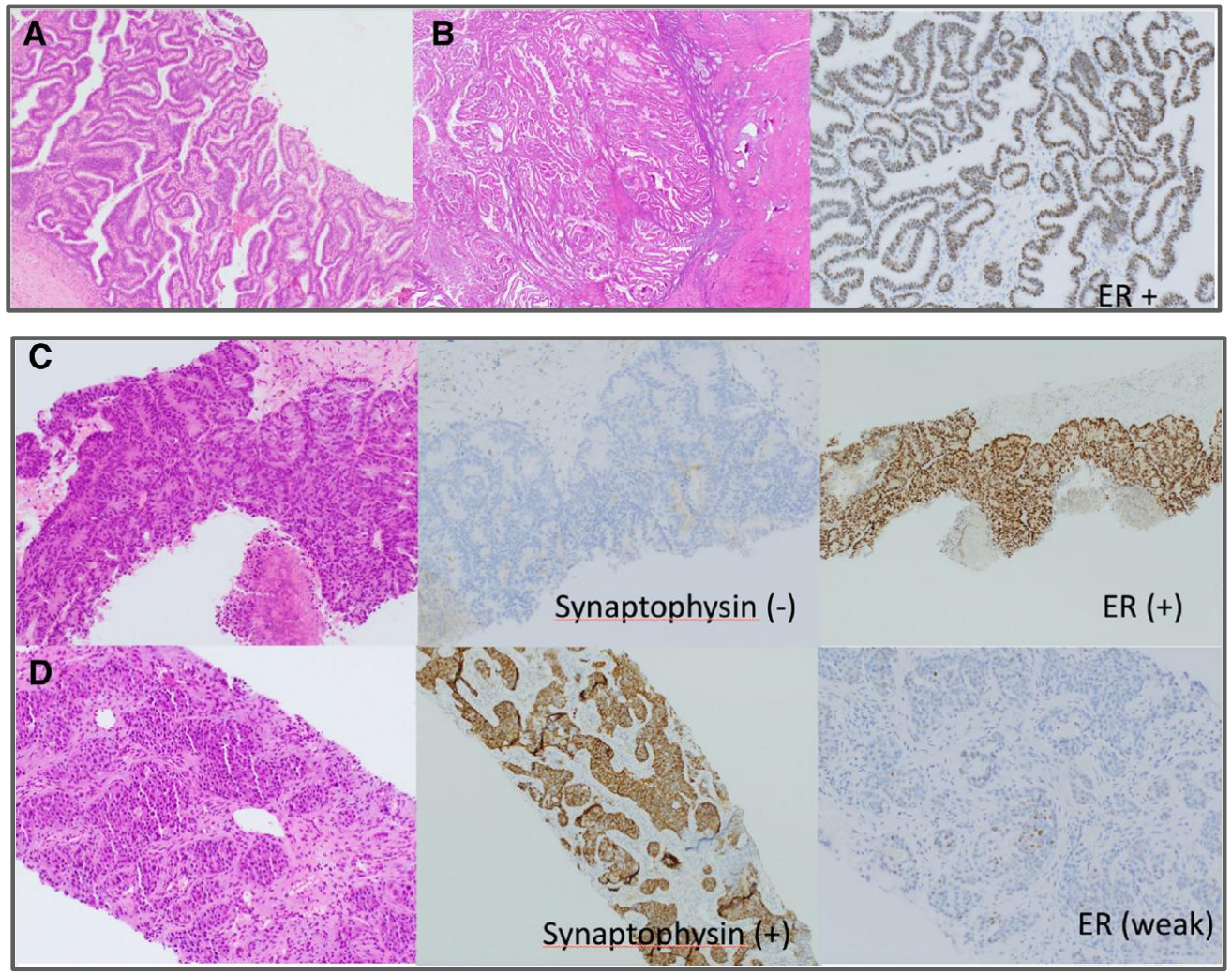


# Pathology

Original Ovarian / Endometrial
CDX2 weak, ER/PR positive, negative for chromogranin and synaptophysin

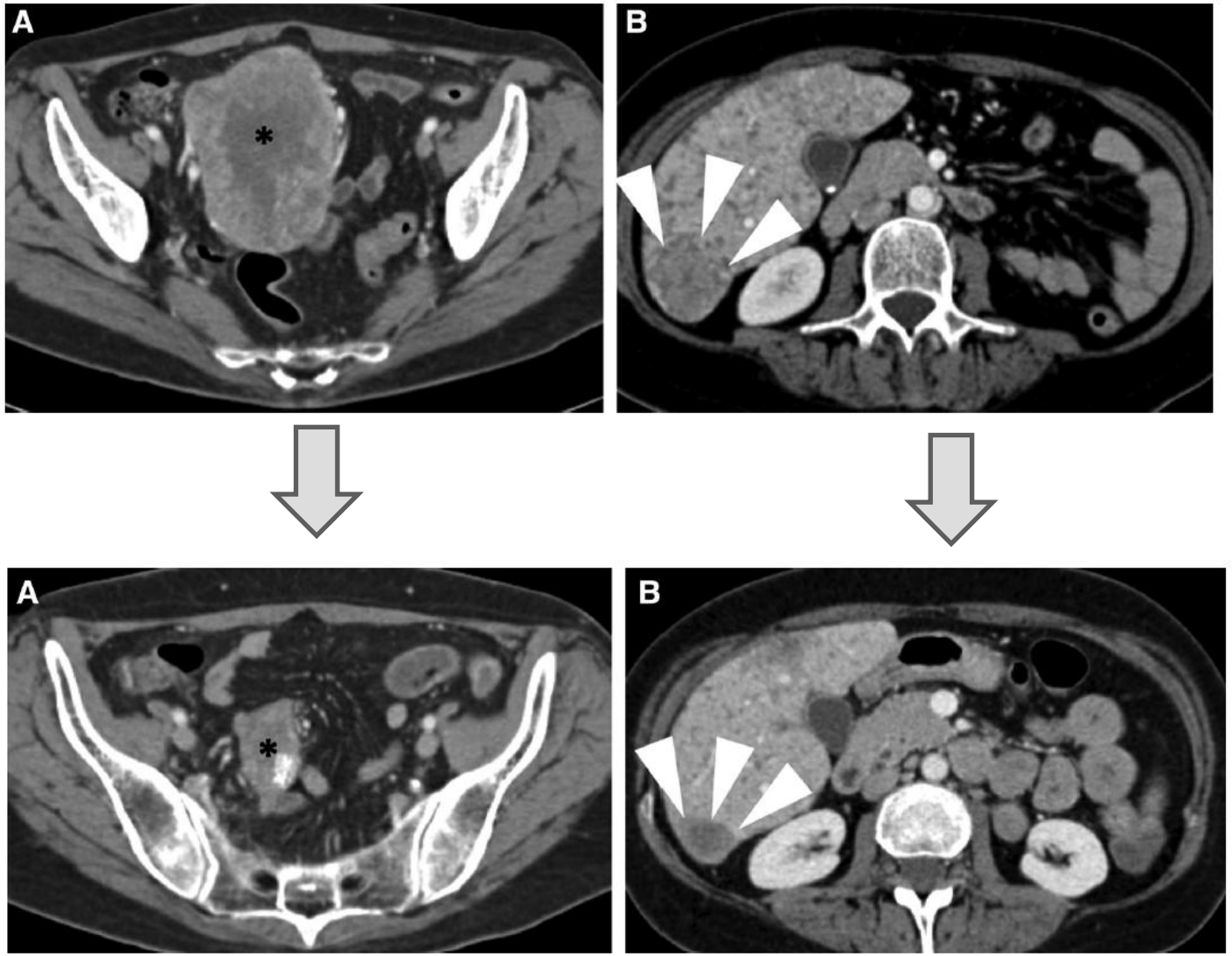
Recurrent Pelvic (endometrioid carcinoma)
ER positive, negative for chromogranin / synaptophysin

Recurrent Liver
Well differentiated NET G3!
Ki-67 of 40%, focal ER positive, strong chromogranin and patchy synaptophysin



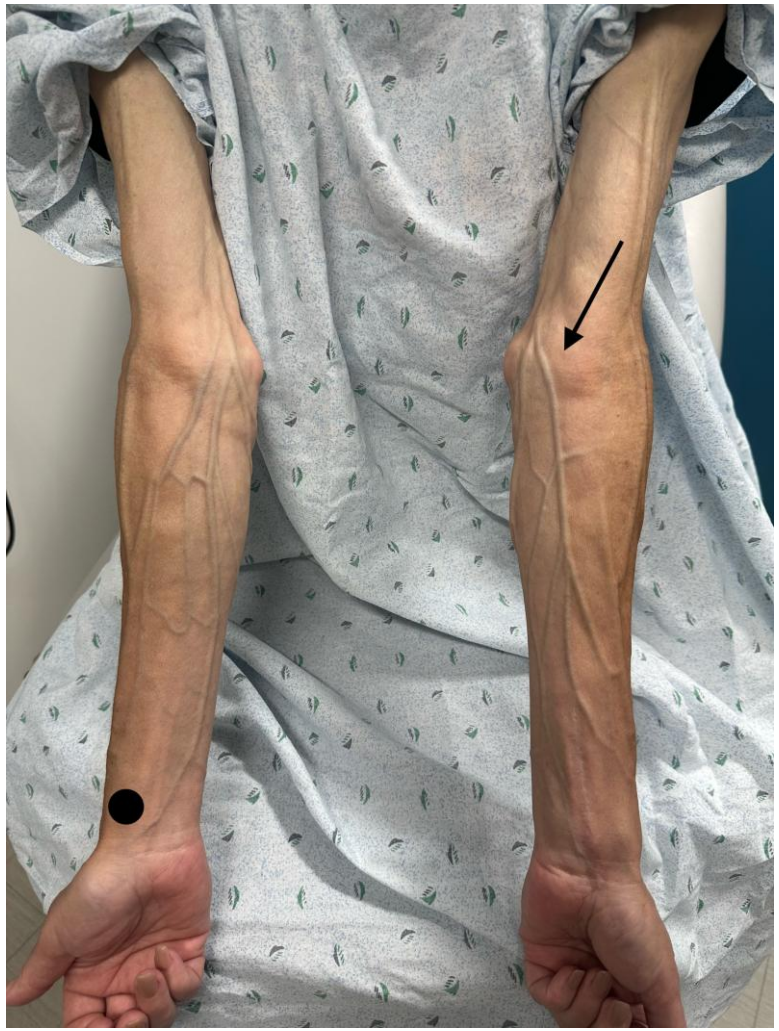
# Treatment

- ✓ Collaboration with gynecological oncology re: regimens that could treat both an endometrial and high-grade neuroendocrine neoplasm
- ✓ Carboplatin + etoposide x 5 cycles, with interim response and ultimate progression
- ✓ Genetics on liver and endometrial lesion confirmed high tumour mutational burden (44) and patient was placed on pembrolizumab, with significant response



# Treatment

- ✓ Tolerated pembrolizumab
- ✓ Sarcoidosis waxed and waned on pembrolizumab
- ✓ Lipodystrophy appeared
- ✓ After about 2 years of treatment, she was placed on a break
- ✓ FDG PET/CT has shown metabolic response and she remains without disease progression 5 years after end of treatment

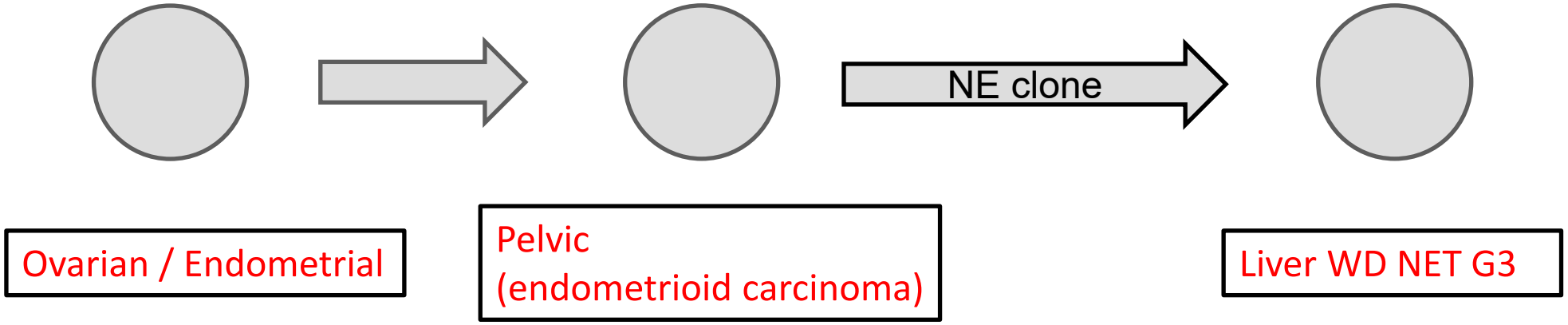


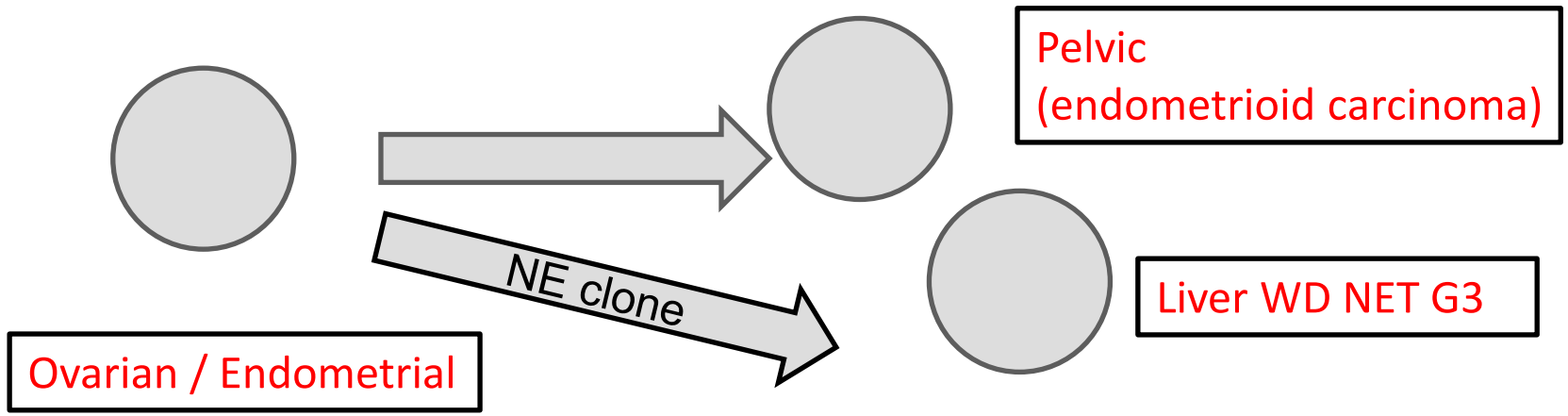
# Genetics

- ✓ Somatic variant testing was very similar (94%) between all instances of the tumour
- ✓ Common lineage suggestion instead of three distinct cancers

| Specimen (all MSI-high) | Original ovarian and uterine tumor | Adenocarcinoma recurrence | NEN recurrence |
|---|---|---|---|
| VAF | | | |
| PD-L1 expression (%) | 0 | 5 | 30 |
| TMB | 32 | 44 | 44 |
| APC R232* | 36.4 | 29.1 | 30.2 |
| APC splice site 423-2A>G | 38.2 | 31.7 | 30.2 |
| APC T1556fs*9 | 32.4 | 23.4 | 23.2 |
| ARID1A G276fs*87 | 33.8 | 30.9 | 24.2 |
| ARID1A Q1327fs*11 | | | 24.3 |
| BCORL1 P1681fs*20 | 35.5 | 25.3 | 26 |
| ERBB2 R678Q | 39.9 | 25.3 | 25.9 |
| ESR1 Y52H | 16.4 | | |
| FBXW7 R13* | 37.2 | 27.3 | 26.8 |
| FUBP1 Y505fs*20 | 65.3 | 50.5 | 48.3 |
| MLL2 P647fs*283 | | 24 | |
| MSH2 splice site 942 + 1G>T | 38.8 | 26.7 | 27.4 |
| MSH2 C778fs*9 | 34.4 | 26.9 | 23 |
| MSH6 F1088fs*5 | 28.5 | 19.8 | |
| PBRM1 G677fs*9 | 34.9 | 28.7 | 24.5 |
| PBRM1 L1349fs*35 | | | 27.4 |
| PPP2R1A R258C | 39 | 27.9 | 25.9 |
| PRKAR1A R368* | | | 26 |
| PTEN N323fs*21 | 30.9 | 27.5 | 26.9 |
| PTEN R233* | 36.4 | 27.5 | 28.2 |
| QKI K134fs*14 | 33.7 | 23.3 | 22.9 |
| SDHA Q176H | | 3 | |
| JAK1 K860fs*16 | | | 24.3 |
| VHL F136V | 1.4 | | |
| SOX9 V306fs*77 | | | 8.7 |

# Evolution process



# Questions for discussion

- ✓ Are MiNENs one tumour in different life stages or separate tumours that grew together?

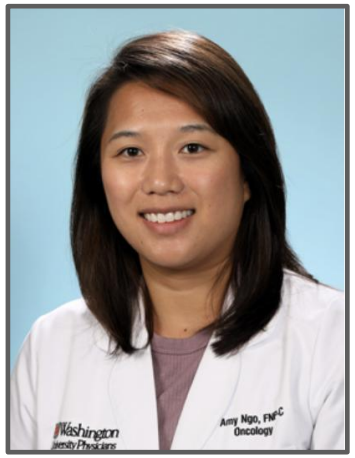
- ✓ How does one prioritise treatment for MiNENs based on their individual components?

# “Prince”

A male Grevy’s zebra foal was born at the Saint Louis Zoo on May 26, 2026. The foal, Prince, weighed approximately 95 lbs. at birth. He is doing well and bonding with his mother, Amira, in the public Grevy’s zebra habitat at Red Rocks at the Zoo.

# Thank you

NEURO ENDOCRINE
TUMOR BOARD, WASHINGTON UNIVERSITY ST.LOUIS, MO

# Panel Discussion

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

NANETS NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

# Closing comments

# Take-home messages

1. Pathology is key in treatment decisions- report all components including Ki-67 in NEN component

2. Biology is driven by the aggressive component-often neuroendocrine carcinoma

3. Surgery for localized disease in a multidisciplinary discussion

4. Molecular profiling may aid treatment options in some

# A BIG "Thank You" to

- ✓ Our speakers and moderators
- ✓ The ENETS Office team: Martina FLESCHEN, Ulrike KNELL, Anna MALDRYK & Leah MATTHEWS
- ✓ The NANETS Office Team: Cassandra CLEARE
- ✓ YOU, our valued participants

# Open Call: NextGEN ENETS Scientific Workshop 2026

- ✓ **Dates:** 1 – 3 October 2026
- ✓ **Location:** Capolago, Lago di Varese, Italy
- ✓ **Target group:** Early-career NEN researchers (PhD/post-docs)
- ✓ **Capacity:** Limited to 20 participants
- ✓ **Deadline:** 18 June 2026 (23:59 CEST)
- ✓ **Apply now:** https://www.enets.org/grant/nextgen-enets-scientific-workshop-2026.html

# Stay connected with

## ENETS & NANETS

| ENETS | | NANETS |
|---|---|---|
| https://www.linkedin.com/company/european-neuroendocrine-tumor-society-ev | LinkedIn | https://www.linkedin.com/company/nanets |
| @ENETS_ORG | X | @NANETS1 |
| @enets.org | Bluesky | @nanets.bsky.social |
| www.facebook.com/european.neuroendocrine.tumor.society | facebook | https://www.facebook.com/NANETS/ |
| ----- | Instagram | @nanetsmed |

# Sponsor acknowledgements

The ENETS Webinar Series 2026 is supported by Bioscientifica, Camurus and ITM with an unrestricted educational grant.

# Thank you for attending this webinar!

**We hope you enjoyed the session and would greatly appreciate your feedback.**

Please take a moment to complete the **feedback form**,

which will appear automatically when you leave this Zoom room.

To receive **CME credits** for this webinar, please complete the following steps:

1. **Complete the feedback form**.
2. Contact the ENETS Office at office@enets.org **to request your CME certificate**.

## Interested in upcoming webinars?

Visit the ENETS website for all the details!