- Tanımlama
- Tanı
- Tedavi
- takip

Gep-net

- Nöroendokrin tümörleri oluşturan en büyük grup (>%50)
- Gis tümörlerinin %2'si.
- 1997-2012 yılları arasında 6 kat artış.
- 3.56 /100.000 / yıl (SER)
- Çoğu iyi differansiye ve sporadik.
- MEN1 , VHL, tuberoz skleroz , NF

Cellular pleomorphism per se is not a useful feature for grading NETs. The following grading scheme has been proposed for gastrointestinal NETs.

Grade	Definition
GX	Grade cannot be assessed
G1	Mitotic count (per 10 HPF)* <2 and Ki-67 index (%)¶ <3
G2	Mitotic count (per 10 HPF) = 2 to 20 or Ki-67 index (%)¶ = 3 to 20
G3	Mitotic count (per 10 HPF) >20 or Ki-67 index (%)¶ >20

* 10 HPF = 2 mm^2; at least 50 HPFs (at 40 times magnification) must be evaluated in areas of highest mitotic density in order to adhere to WHO 2010 and 2017 criteria.

¶ MIB1 antibody; % of 500 to 2000 tumor cells in areas of highest nuclear labeling.

WHO/ENET 2010

Differentiation	Grade	Mitotic count*	Ki-67 index¶	Traditional	ENETS, WHO
Well differentiated	Low grade (G1)	<2 per 10 HPF	<3%	Carcinoid, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G1
	Intermediate grade (G2)	2 to 20 per 10 HPF	3 to 20%	Carcinoid, atypical carcinoid$^{\Delta}$, islet cell, pancreatic (neuro)endocrine tumor	Neuroendocrine tumor, G2
Poorly differentiated	High grade (G3)	>20 per 10 HPF	>20%	Small cell carcinoma	Neuroendocrine carcinoma, G3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, G3, large cell

		Moran[1] (2000)	WHO[2] (2004) WHO[3] (2015)	WHO[4] (2000)	Hochwald[5] (2002) AFIP[6] (2007)	WHO[7] (2004)	ENETS[8,9] (2006) AJCC[10] (2009) WHO[11] (2010)	WHO[12] (2019)
Organ system		Thymus	Lung, thymus	GI	Pancreas	Pancreas	GI, pancreas	GI, pancreas, hepatobiliary
Mitotic index	G1	<3/10 HPF	<2/2 mm^2	NA	<2/50 HPF	<2/2 mm^2	<2/2 mm^2	<2/2 mm^2
	G2	4 to 9/10 HPF	2 to 10/2 mm^2	NA	2 to 10/50 HPF	2 to 10/2 mm^2	2 to 20/2 mm^2	2 to 20/2 mm^2
	G3	NA	NA	NA	NA	NA	>20/2 mm^2	>20/2 mm^2
Ki-67	G1	NA	NA	NA	NA	<2%	≤2% (<3%)	<3%
	G2	NA	NA	NA	NA	>2%	3 to 20%	3 to 20%
	G3	NA	NA	NA	NA	NA	>20%	>20%
Other parameters		Necrosis	Necrosis	Size, invasion, metastasis	Necrosis	Size, invasion, metastasis	None	Assessment of morphology and marker expression helps to differentiate from poorly differentiated neuroendocrine carcinoma

WHO 2019 Gis and HPB net

Terminology	Differentiation	Grade	Mitotic rate* (mitoses/2 mm²)	Ki-67 index* (percent)
NET, G1	Well differentiated	Low	<2	<3
NET, G2	Well differentiated	Intermediate	2 to 20	3 to 20
NET, G3	Well differentiated	High	>20	>20
NEC, small cell type (SCNEC)	Poorly differentiated	High$^{\Delta}$	>20	>20
NEC, large cell type (LCNEC)	Poorly differentiated	High$^{\Delta}$	>20	>20
MiNEN	Well or poorly differentiated¶	Variable¶	Variable¶	Variable¶

NET rol oyanayan genetik değişiklikler:

death-domain- associated protein (DAXX)
alpha-thalassemia/intellectual disability syndrome X-linked(ATRX)

NEC rol oynayan genetik değişiklikler:

TP53, RB1

Neuroendocrine neoplasms (NEN)	Classification and molecular pathology	The general principles of the new classification of neuroendocrine tumours (NET) will be applied to the entire 5th series, based on a consensus meeting in Lyon (1), dividing NEN into NET and neuroendocrine carcinomas (NEC) based on their molecular differences. Mutations in MEN1, DAXX and ATRX are entity-defining for well-differentiated NETs, while NECs usually have *TP53* or *RB1* mutations

Summary of Selected Updates in 5th Edition of World Health Organization Classification of Digestive System Tumors

Summary of Selected Updates
G3 neuroendocrine tumor (NET) – New category formed for the grading of neuroendocrine neoplasms (NENs)
New Terminology for Mixed Neoplasms – Mixed neuroendocrine-non-neuroendocrine tumors – MiNENs (previously mixed adenoneuroendocrine carcinoma [MANEC])
Terminology for appendiceal goblet cell carcinoma/carcinoid altered to appendiceal goblet cell adenocarcinoma
Category of hyperplastic and preneoplastic lesions has been abolished in the classification of neuroendocrine tumors (NETs) of the pancreas

Clinical Differences: NETs and NECs

From a clinical perspective, the key distinction is between grade 3 (G3) NETs and NECs with respect to platinum-containing chemotherapy. Patients with NECs respond well to platinum-containing chemotherapy while patients with G3 NETs fail to respond to this therapy.[6,7]

Tanı

- NET çoğunlukla KC metastazı yaparlar. Bu lezyonlar çoğunlukla hipervasküler dir. Uygun hastalarda mutlaka arteryal ve portal venöz faz incelenmelidir.
- Uygun olduğunda SSR-Pet/ct kontrastlı BT ya da MRI ile birlikte uygulanmalı.
- SPECT/CT , SSR-Pet'e göre daha az invaziftir.
- High grade net ve NEC'lerde hızlı progrese olan hastalıkta FDG-Pet/ct aktif hastalığı gösterme açısından uygundur.

Tanı

	Sensitivity	Specifitiy
CT	61-93 %	71-100 %
MRI(DW-MRI)	54-100%	98%
EUS(pan-net)	86%	92%
SSR based imaging SSR- Pet-CT	92%	95%
SSR – Pet.MRı		
Spect/ct		

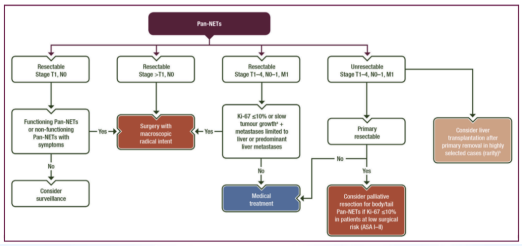
Tanı

	Location	Clinical Symptoms	Testing
NETs of Gastrointestinal Tract, Lung, and Thymus	Primary tumors in GI tract (ileum, appendix, rectum), lung, or thymus	• Primary tumors in the GI tract usually are not associated with symptoms of hormone secretion unless extensive metastasis. • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction. • Bronchial/thymic tumors may be associated with classic carcinoid syndrome as well as Cushing syndrome.	• 24-hour urine or plasma 5-HIAA › Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts. • Test for Cushing syndrome (NE-C, 2 of 3)
PanNET: PPoma	Pancreas	Clinically silent	• Serum pancreatic polypeptide (category 3)
PanNET: Insulinoma	Pancreas	Hypoglycemia	• While hypoglycemic: › Serum insulin › Pro-insulin › C-peptide • See Workup for insulinoma (PanNET-3)
PanNET: VIPoma	Most common in pancreas, can be extra pancreatic	Diarrhea, hypokalemia	Serum VIP
PanNET: Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoagulable state	Serum glucagon
PanNET: Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin[a]

	Location	Symptoms	Testing
Pheochromocytoma/ Paraganglioma	Adrenal or extra-adrenal sympathetic or parasympathetic chain	Hypertension, tachycardia, sweating, syncope	• Plasma free or 24-hour urine fractionated metanephrines[c] • Cervical paragangliomas: consider serum and urine catecholamines or methoxytyramine (the metabolite of dopamine)[c]
Pituitary Tumor	Pituitary (part of MEN1)	May be asymptomatic, depends on the hormone secreted	• Serum IGF-1 (category 2B) • Serum prolactin • LH/FSH • Alpha subunits • TSH (free T4) • Screen for Cushing syndrome
Cushing Syndrome[b]	Adrenal, pituitary, or ectopic (often bronchial or thymic)	Central weight gain, striae, hypertension, hyperglycemia, depression, hirsutism	• Screen for hypercortisolemia with 1 of the following tests[d]: › 1 mg overnight dexamethasone suppression test › 2–3 midnight salivary cortisols › 24-hour urinary free cortisol • Confirmatory testing if positive • Plasma ACTH
Hyperaldosteronism	Adrenal	Hypertension, hypokalemia	• Screening: Suppressed renin/renin activity in association with an elevated plasma aldosterone level (> 15 ng/dL)[11] • Confirmatory testing if positive[e]
Suspected or Confirmed Adrenocortical Carcinoma	Adrenal	Symptoms of Cushing syndrome or hyperaldosteronism (see above) Androgen excess symptoms	• See workup above for Cushing syndrome or hyperaldosteronism • Testosterone • DHEA-S

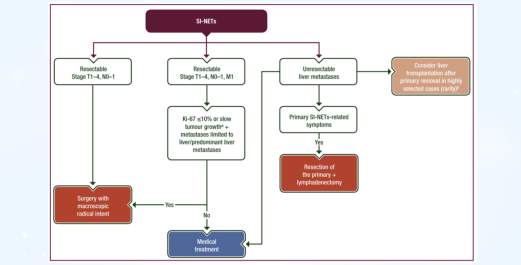
Tedavi (lokorejyonel hastalık)

- G1-G2 NET : Cerrahi ilk tercih.
- NF- pan-Nets < 2 cm - takip?? (yaşlı , morbidite)
- NF-pan-net, 2 cm> , genç hasta, inv bulguları(ana kanal genişlemesi ,sarılık). = cerrahi
- Uzun dönem sağ kalım beklentisi olan hastalar lnd ile beraber pankreatikoduodenektomi
- F-pan-net = cerrahi , eğer 2 cm > ise enuklasyon olabilir.
- Lokalize NEC için cerrahi OS açısından tartışmalı.



Lokorejyonel (SI-net)

- Makroskopik radikal rezeksiyon ilk tercih.
- LND (en az 8 ln) öneriliyor.
- Lokal ileri tümörlerde de kr intestinal obstrüksiyon, akut iskemi gibi komplikasyonlara yol açabileceğinde cerrahi önerilir.



Metastatik

- Seçilmiş hastalarda cerrahi
- Ancak: nec (high grade net) ve extraabdominal met kontraindikasyon
- Kc met GEP-Net küratif cerrahi sonrası 5-year OS: yaklaşık %85

- Evre 4 hastalıkta palyatif primer tm cerrahisi herhangi bir katkısı yok
- NF Net debulking cerrahi yeri yok ancak F Net yarar sağlayabilir
- KC tx? – extraabdominal met yok ,G1-g2 (Ki-67<10 %), primer tm R0 rez, kc met < total kc volumunun %50 , 60>yaş ,

Medikal tedavi(semptom kontrol)

- F-net ilk basamak semptomatik tedavi : SSA(octreotide,lanreotide)
- Rutin uygulanım: uzun etkili octreotide: 30 mg I.M(1 ad/ay); lanreotide 120 mg S.C
- Geçmeyen semptomlarda 2 adet/ay kadar uygulanabilir.

- If-a (3-5 million IU s.c 3 kez/ week)
- Telotristat ethyl (250-500 mg 3 times/day) (TELESTAR study) (diarede azalma)
- Diazoxide(insulinoma)

Medikal tedavi (antiproliferatif tedavi)

- SSAs
  - İlk basamak
  - Cevap oranları düşük < 5%
  - Advanced SSTR-pos , yavaş ilerleyen GEP-net, Ki 67 < 10% (ESMO IA)
- IFN-a:
  - Özellikle midgut tm lerde.
- Everolimus:
  - 10 mg/d
  - Median PFS 9.7 ay ➔ 16.6 ay (RADIANT-1 study)
- Sunitinib
  - Pan-Net için EMA onaylı tek TKI
  - PFS: 5.5 ay ➔ 11.4 ay

Sistemik KT

- Advanced Pan-Net ve NEN G3.
  - İrrezektabl KC met G1/G2 Pan-Net.
  - Temozolomide (TEM) ya da TEM + Capesitabine(CAP). Pan-Net alternatif tdv
  - Cisplatin ya da carpoplatin + etoposide ilk basamak : NEC G3

Takip

- R0/R1 rez sonrası
  - NET G1/G2 (ki 67<5%) : 6 ay
  - Net G2 (Ki-67 > 5%): 3 ay
  - NET G3: 2-3 ay
- Biyokimyasal marker: CgA, NSE, LDH (NEC)
- Ömür boyu
- NET G1 (< 1cm) apendiks ve rektum kökenli R0 rezeke edilmişse ve histolojik parameterler iyi ise takip gerekli değil.

Teşekkürler…

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