

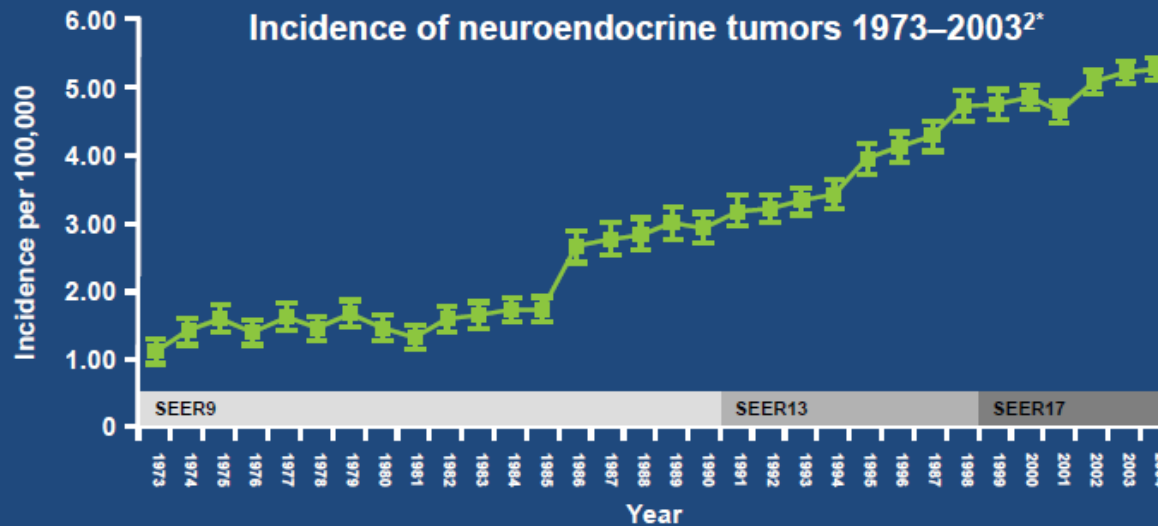
Vaka Sunumu

Metastatik Nöroendokrin Tümörü

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Tıbbi Onkoloji

NET insidans ve Prevalans

- Early estimates of incidence 1–2 per 100,000 population¹
- Diagnosed incidence increasing, likely due to improved awareness, classification, and diagnostic modalities²
- Prevalence estimated to be >100,000 in United States²



*Cases selected from SEER database using International Classification of Disease for Oncology histology codes 8150–8157, 8240–8246, and 8249; adapted from Yao JC, et al. 2008

1. Modlin IM, et al. Cancer 2003;97:934–959
2. Yao JC, et al. J Clin Oncol 2008;26:3063–3072

Özgeçmiş ve Başvuru Semptomları

- ❑ 67 yaşında, erkek hasta
- ❑ 4 yıldır bilinen Tip2 DM ve HT mevcut
- ❑ Oral anti-diyabetik ve ACE inhibitörü kullanıyor
- ❑ BPH bağlı olarak operasyon öyküsü var
- ❑ **12/2015** tarihinde şiddetli, geçmeyen sırt ağrısı, kilo kaybı ve halsizlik ile doktora başvuruyor

Lomber Spinal MR; Primeri Bilinmeyen Metastaz

KONTRASTLI LOMBER SPİNAL MR TETKİKİ

FSE T2 Sagittal, SE T1 Aksiyel ve Sagittal, Postkontrast Aksiyel, Sagittal planda alınan görüntülerin incelenmesinde;

Lomber lordoz normaldir.

Torakolomber bileşke düzeyinde açıklığı sola bakan hafif skolyoz mevcuttur.

Lomber disk sinyalleri dejenerasyona sekonder T2 AG'lerde azalmıştır.

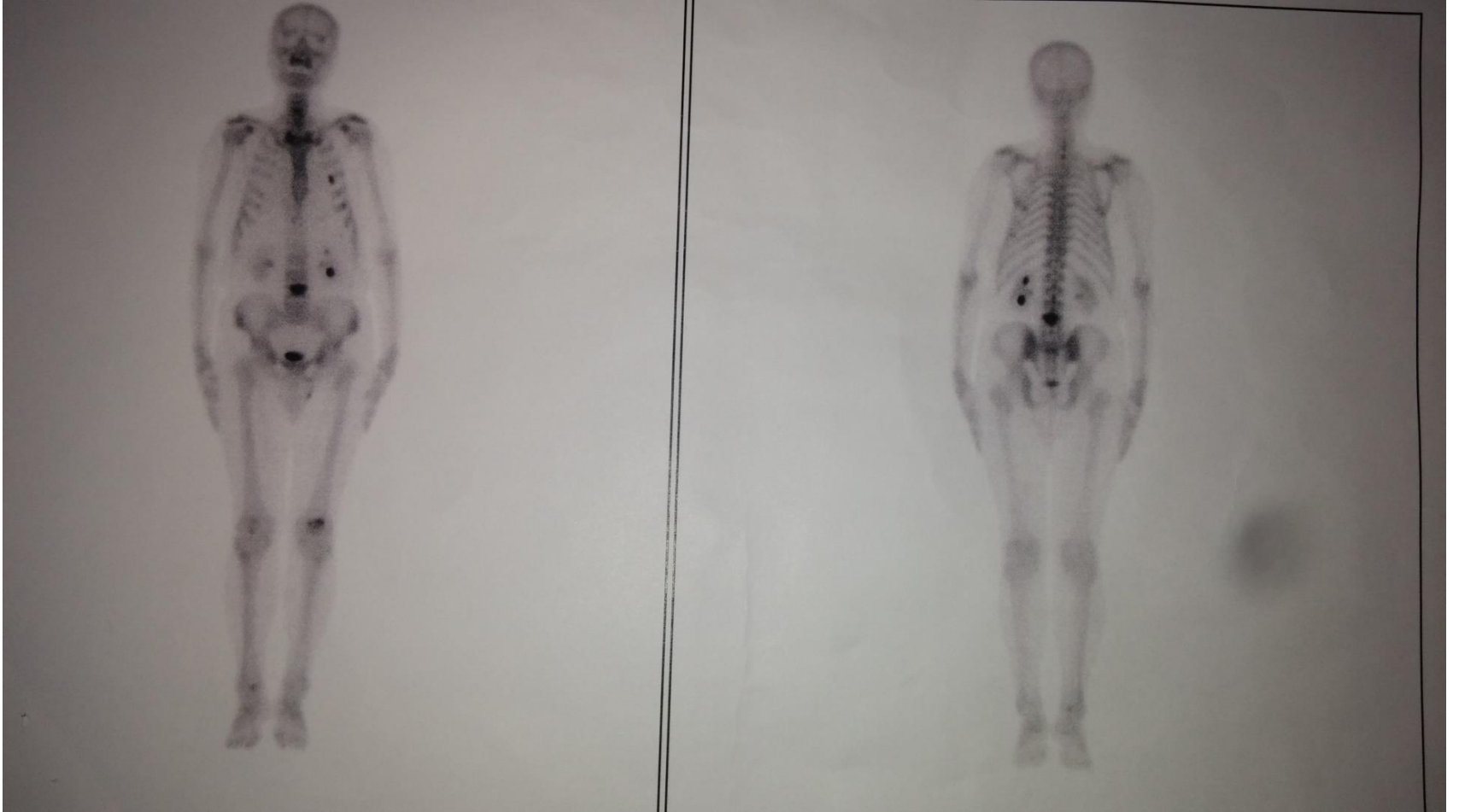
Vertebra korpus köşelerinde minimal sivrileşmeler mevcuttur.

L4 vertebra korpus sol posterolateralde kanal içerisine uzanım gösteren ve epidural komponenti bulunan, yaklaşık 3x3,5 cm ebadında, T1 AG'lerde hipointens, T2 AG'lerde vertebra korpusunda göre hipointens sinyal özelliğinde, IVKM sonrasında epidural komponentinde daha belirgin olmak üzere heterojen yoğun kontrastlanma gösteren ve epidural komponentinin kanal içerisinde sol L4 köküne bası oluşturduğu kitlesel lezyon mevcuttur (Met? Primer osseoz kitle?). Klinik ile birlikte değerlendirilmesi ve klinik gereklilik halinde histopatolojik verifikasyon önerilir.

L4-5 düzeyinde disk posterior konturunda düzleşme mevcuttur.

Görüntü alanına giren üst batın kesitlerinde sağ böbrek orta zonda 1,5 cm çaplı bir adet kortikal kist mevcuttur.

Tüm Vücut Kemik Sintirafisi



Tüm Vücut Kemik Sintirafisi

RAPOR

Sintigrafik Bulgular: 20 mCi Tc-99m HDP enjeksiyonundan sonra hastanın lomber bölgesinden alınan kan akımı, kan havuzu görüntüleri ve 3 saat sonra anterior - posterior tüm vücut tarama görüntüleri ile spot görüntüler alındı.

Erken görüntülerde kan akımı ve kan havuzu görüntülerinde; L4 vertebraya uyan alanda hiperemi izlenmektedir.

Geç görüntülerde; L4 vertebrada izlenen yoğun artmış aktivite tutulumu alınan SPECT görüntüler ile birlikte değerlendirildiğinde vertebra korpusunda ve sağda posterior elemanlara uzanım göstermektedir.

Sol 4. kostakondral bileşkede artmış aktivite tutulumu izlenmektedir.

Sol dizde patellaya uyan alanda ve sağ tibia alt ucuna uyan alanda hafif odaksal artmış aktivite tutulumu izlenmektedir.

Diğer vücut kemiklerinde aktivite dağılımı hasta yaşıyla uyumludur.

Sonuç:

- L4 vertebra korpusunda ve sağda posterior elemanlara uzanım gösteren diffüz yoğun artmış aktivite tutulumu ve sol 4. kostakondral bileşkede izlenen aktivite için radyolojik korelasyon önerilir.
- Sol dizde patellaya uyan alanda ve sağ tibia alt ucuna uyan alanda odaksal izlenen artmış aktivite tutulumu dejeneratif veya diğer benign kemik patolojileri ile ilgili olabilir.

Thoraks-Batın BT



Thoraks-Batın BT

YÖNTEM : İnceleme Oral ve IV kontrast madde (1.5-2 ml/kg) uygulamasını takiben aksiyel planda 1.5 mm kesitler alınarak multipl anar reformat görüntüleri eşliğinde değerlendirilmiştir.

BULGULAR :

Karaciğerin boyutları, konturları ve parankim yapısı tabiidir. **Karaciğerde büyüğü 7. segmentte 29 mm çapında olmak üzere hemen tüm segmentlerde izlenen, erken arteriyal fazda periferik belirgin kontrast tutulumu gösteren, venöz fazda hipodens karakterde izlenen multipl sayıda kitlesel lezyonlar izlenmektedir (metastaz ile uyumlu).**

İntra ve ekstrahepatik safra yollarında genişleme gözlenmemiştir.

Safra kesesi boyutları, duvar kalınlığı tabiidir. Lümende kalkül saptanmamıştır.

Dalağın boyutları, konturları ve parankim yapısı tabiidir.

Pankreas kuyruğu lokalizasyonunda boyutları yaklaşık 54 x 50 mm ölçülen hipodens nekrotik alanlar içeren, düzensiz sınırlı, heterojen kontrastlanan kitlesel lezyon izlenmektedir (pankreas tm?). Superiorda kitlesel lezyon ile mide fundus arasındaki yağlı planlar silinmiştir. Kitlesel lezyon sol lateral duvarı dalak ile belirgin yakın komşuluk göstermekte olup bu alanda dalak parankimi içerisinde lezyona komşu bölümde boyutları 33 x 25 mm ölçülen düzensiz sınırlı hipodens lezyon dikkati çekmektedir (direkt invazyon?, dalak met?). Lezyon çevresindeki yağlı planlarda dansite artımı ve kirlenme dikkati çekmektedir.

Sürrenal glandlara ait patoloji saptanmamıştır.

Böbreklerin boyutları, konturları ve parankim yapısı tabiidir. **Sol böbrekte büyüğü 1 cm çapında birkaç adet kalkül görünüm izlenmektedir. Her iki böbrekte büyüğü 15 mm çapında birkaç adet kortikal kist mevcuttur.**

Mesane homojen görünümde olup, muntazam konturludur.

Prostat boyutu artmıştır. Median lobu mesaneye protrüdedir.

Sigmoid kolonda ve inen kolonda divertikül görünümleri dikkati çekmektedir.

Batın ve pelviste serbest sıvı saptanmamıştır.

L4 vertebra korpusunda diğer vertebralara oranla hiperdens görünümüdür (metastaz?).

SONUÇ

: - Pankreas kuyruk tm
- Karaciğer, dalak ve kemik metastazları

Karaciğer Tru-cut Biyopsi

>> GÖRÜNTÜLEME EŞLİĞİNDE BİOPSI (KALIN YA DA İNCE İĞN : PERKÜTAN KC KİTLE BİOPSI

Klinik Bilgi: Kc'de büyüğü sağ lobda 34x28 mm boyutunda olan multipl kitleler mevcuttur (metastaz ?).

İşlem: Standart steril şartlarda, lokal anestezi altında US eşliğinde Kc sağ lobda tanımlanan kitleden 18 G iğne ile kalın iğne biopsisi yapıldı. İşleme bağlı komplikasyon gelişmedi. Örnekler patolojiye gönderildi.

4 saat mutlak yatak istirahati
Kanama ve vital bulgu takibi

NET Histolojik Sınıflandırma

Differentiation and grade	Mitotic count*	Ki-67 index [†] (%)	Traditional classification	ENETS/WHO classification ²	Moran et al ³
Well differentiated					
Low grade (grade 1)	<2	≤2	Carcinoid, islet cell, pancreatic (neuro) endocrine tumor	NET, grade 1	NEC, grade 1
Intermediate grade (grade 2)	2–20	3–20	Carcinoid, atypical carcinoid, [‡] islet cell, pancreatic (neuro) endocrine tumor	NET, grade 2	NEC, grade 2
Poorly differentiated					
High grade (grade 3)	>20	>20	Small-cell carcinoma	NEC, grade 3, small cell	NEC, grade 3, small cell
			Large-cell NEC	NEC, grade 3, large cell	NEC, grade 3, large cell

NEC = neuroendocrine carcinoma

*Per 10 high-power fields

[†]Cellular proliferation marker

[‡]Applies only to intermediate-grade NET of the lung

1. Kulke MH, et al. *J Clin Oncol* 2011;29:934–943

2. WHO Classification of Tumours of the Digestive System, 4th ed., 2010

3. Moran CA, et al. *Am J Clin Pathol* 2009;131:206–221

NET Histolojik Sınıflandırma



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PRINCIPLES OF PATHOLOGY FOR DIAGNOSIS AND REPORTING OF NEUROENDOCRINE TUMORS

Required information:

- Anatomic site of tumor
- Diagnosis
- Grade (See Table 1)
- Mitotic rate and/or Ki-67
- Size of tumor
- Presence of multicentric disease
- Presence of vascular invasion
- Presence of perineural invasion
- Presence of other pathologic components (eg, non-neuroendocrine components)
- Lymph node metastases to include the number of positive nodes and total number of nodes examined
- Margin status (report as positive or negative)
- Assign TNM stage per the AJCC TNM system ([See Staging](#))

Optional information:

- Immunohistochemical staining for general neuroendocrine markers
- Immunohistochemical staining for specific peptide markers
- Presence of nonischemic tumor necrosis
- Presence of unusual histologic features (eg, oncocytic, clear cell, gland forming)
- Exact distance of tumor to margin(s) if less than 0.5 cm
- Background pathology of organ (ie, PanIN, ECL cell hyperplasia)

Table 1

Grade	Gastroenteropancreatic (GEP) NETs	Lung and Thymus	Differentiation
Low Grade (G1)	<2 mitoses/10 HPF AND/OR <3% Ki-67 index	<2 mitoses/10 HPF AND no necrosis	Well-differentiated NET
Intermediate Grade (G2)	2–20 mitoses/10 HPF AND/OR 3–20% Ki-67 index	2–10 mitoses/10 HPF AND/OR foci of necrosis	Well-differentiated NET
High Grade (G3)	>20 mitoses/10 HPF AND/OR >20% Ki-67 index	>10 mitoses/10 HPF	Poorly differentiated neuroendocrine carcinoma

Adapted from Bosman FT, Carneiro F, Hruban RH, Theise ND. World Health Organization Classification of Tumours of the Digestive System. IARC, Lyon, 2010; and Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. IARC, Lyon, 2015.

Table 1 should be used as a general guide. Definitions vary between lung, thymus, and GEP-NETs in some classification systems. It is recognized that occasionally a morphologically “well-differentiated” NET may have a proliferation index by Ki-67, which technically falls into the “high-grade” category by this measure alone. Clinical judgment should be used in such discordant cases. In general, this discordance should not cause a reclassification of a well-differentiated NET as a “poorly differentiated NEC.” In these cases, the tumor should be reported as a well-differentiated NET (so-called “atypical carcinoid” terminology in lung and thymus) with the specific mitotic rate and Ki-67 proliferation index included in the report as additional information ([See NE-A 3 of 4](#)).

Patoloji

MAKROSKOPİK BULGULAR :

EN BÜYÜĞÜ 1.5 CM UZUNLUĞUNDA 0.1 CM ÇAPINDA 4 ADET TRU-CUT BİOPSİ
MATERYELİ. TTA 4P/1BL

TANI :

KARACİĞER, SAĞ LOB, TRU-CUT BİOPSİ;
NÖROENDOKRİN KARSİNOM (WHO; 2010)

İMMUNHİSTOKİMYASAL BULGULAR:

CK 7: NEGATİF

CK20: NEGATİF

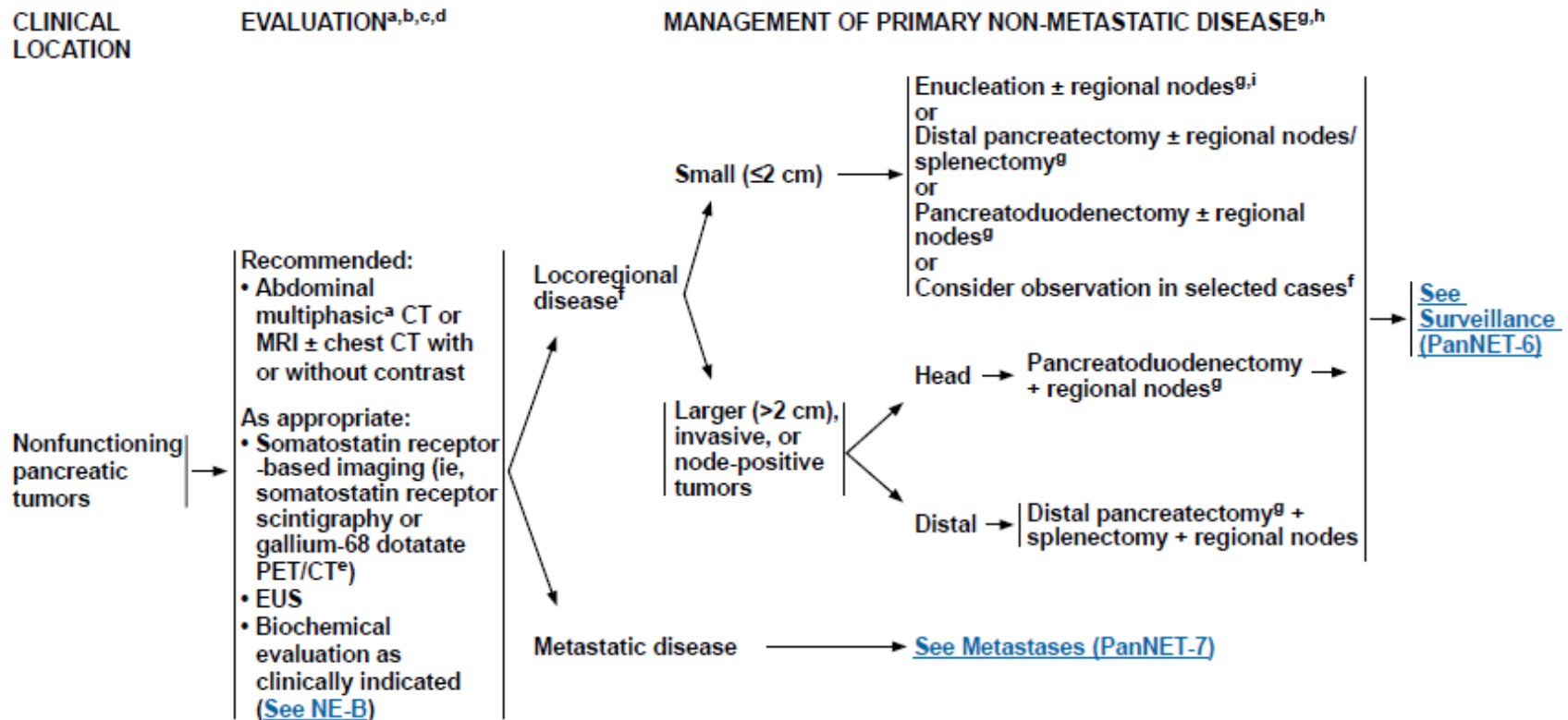
KROMOGRANİN: POZİTİF

SİNAPTOFİSİN: POZİTİF

Ki 67: >%20

MİTOZ: <20 (10 BBA)

NET Tedavi Seçenekleri



NET Evreleme



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Neuroendocrine Tumors

Advanced NET (Imaging)

GASTROINTESTINAL TRACT MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

EVALUATION

Locoregional unresectable
disease of the GI tract and/or
distant metastases

- Multiphasic abdominal/pelvic CT or MRI
- Chest CT (± contrast) as clinically indicated
- Somatostatin receptor-based imaging (ie, somatostatin receptor scintigraphy or gallium-68 dotatate PET/CT)
- Biochemical evaluation as clinically indicated

If complete resection possible →

Asymptomatic, low tumor burden →

Locally symptomatic from primary tumor →

Clinically significant tumor burden →

Carcinoid syndrome →

NET-9

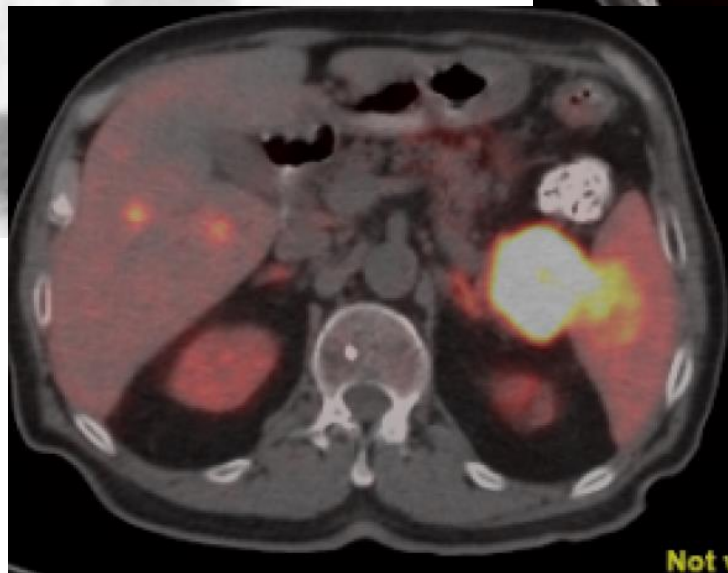
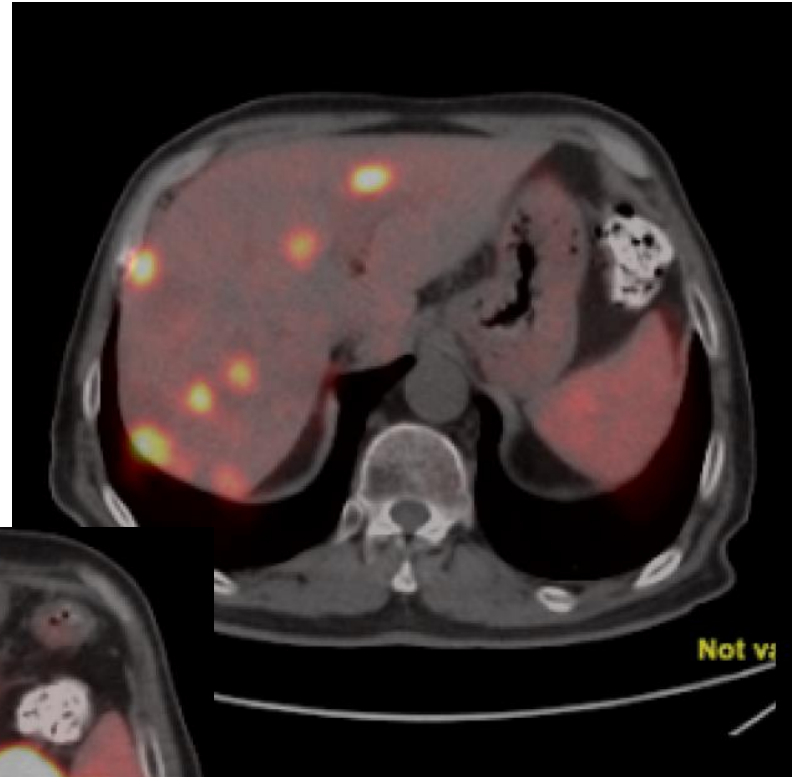
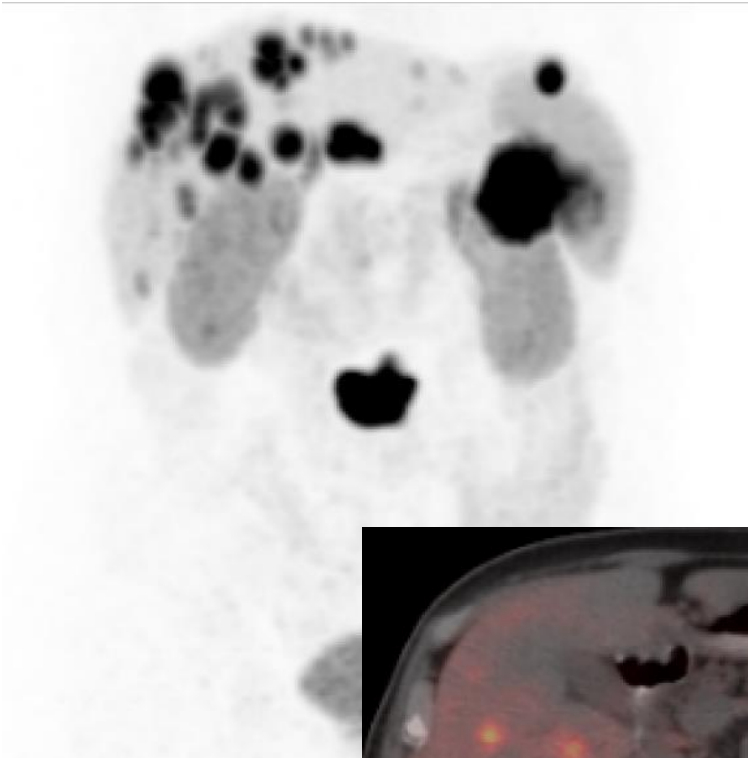
NET Semptomlara Göre İleri Tetkik Gerekir

PRINCIPLES OF BIOCHEMICAL TESTING (1 OF 3)¹⁻¹⁰

- Some neuroendocrine tumors can secrete specific neuroendocrine hormones. Hormonal workup should be guided by the presence of symptoms of the excess hormone. Screening for hormones in asymptomatic individuals is not routinely required.
- Proton pump inhibitors are known to cause false elevations in serum gastrin and chromogranin A.
- If Multiple endocrine neoplasia type 2 (MEN2) is suspected, then patients should be evaluated for pheochromocytoma/paraganglioma prior to any procedures.⁹

	Location	Clinical Symptoms	Testing
Neuroendocrine Tumors of Gastrointestinal Tract, Lung, and Thymus (carcinoid tumors)	Primary tumors in GI tract (ileum, appendix, rectum)	<ul style="list-style-type: none"> • 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's syndrome. 	<ul style="list-style-type: none"> • Chromogranin A (category 3) • 24-hour urine 5-HIAA <ul style="list-style-type: none"> ▶ 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's syndrome (NE-B, 2 of 3)
Pancreatic NET (see subtypes below)	Pancreas	Depends on hormone secreted, can be clinically silent	<ul style="list-style-type: none"> • Serum pancreatic polypeptide (category 3) • Chromogranin A (category 3)
Insulinoma	Pancreas	Hypoglycemia	<ul style="list-style-type: none"> • Serum insulin • Pro-insulin • C-peptide • See Workup for insulinoma (PanNET-3)
VIPoma	Most common in pancreas, can be extra pancreatic	Diarrhea, hypokalemia	Serum VIP
Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoagulable state	Serum glucagon
Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin*

01/2016; Ga-68 PET-CT



Ga-68 PET-CT

TEKNİK PROSÜDÜR ve GÖRÜNTÜLEME PROTOKOLÜ
RADYOFARMASÖTİK Ga-68 DOTA Tyr-3 Octreotate
TARAYICI MODELİ SİMENS Biograph LSO HI-REZ entegre PET/CT

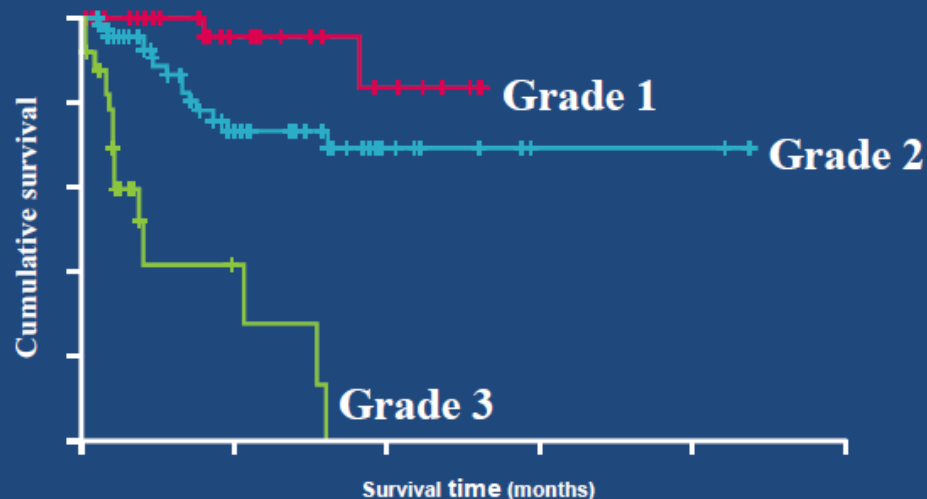
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Çekim saati:12:53:, Pozisyon sayısı: 9Pozisyon süresi:2 Dk, BT parametreleri:
mAs,Çekim kapsama alanı: verteks üst uyuk

SONUÇ:

- Batın sol üst kadranda **pankreas başı** düzeyinde yerleşimli lateralde dalak hilusuna uzanımı olan anteriorda mide korpusu ile yakın komşuluk gösteren yoğun karakterde artmış aktivite tutulumu olan somatostatin reseptörü ihtiva eden kitle lezyon.
- **Dalak hilusu** düzeyinde parankimde yerleşimli metastaz lehine değerlendirilen artmış aktivite tutulumu.
- **Karaciğer her iki lobunda** oldukça yoğun karakterde artmış aktivite tutulumları ile iskelet sisteminde **lomber 4. vertebra korpusunda** yoğun karakterde artmış aktivite tutulumları izlenen Ga-68 DOTA TATE PET/BT çalışması.
- NOT: FDG PET/BT çalışması ile karşılaştırıldığında lezyonların tutulum yoğunluğunda belirgin artış olması nedeniyle bu bulgular ön planda iyi diferansiyel NET düşündürmektedir. Ayrıca Lu-177 DOTA TATE tedavisi için uygun olduğu gözlenmektedir.

NET Histolojik Grade Bağlı Sağkalım

- Survival in an institutional series of pancreatic (n=131), duodenal (n=23), and gastric (n=48) NETs
- Proportion alive at 5 years:
 - Grade 1: 96%
 - Grade 2: 73%
 - Grade 3: 28%



NET Tedavi Seçenekleri

Definition of Poorly Differentiated Neuroendocrine Carcinoma: Role of Ki-67

Retrospective review of 252 patients with poorly differentiated neuroendocrine carcinomas (G3) treated with platinum/etoposide

```
graph TD; A[Retrospective review of 252 patients with poorly differentiated neuroendocrine carcinomas (G3) treated with platinum/etoposide] --> B[Ki-67 < 55%]; A --> C[Ki-67 > 55%]; B --> D[Response rate: 15%  
Overall survival: 14 months]; C --> E[Response rate: 42%  
Overall survival: 10 months];
```

Ki-67<55%:

Response rate: 15%
Overall survival: 14 months

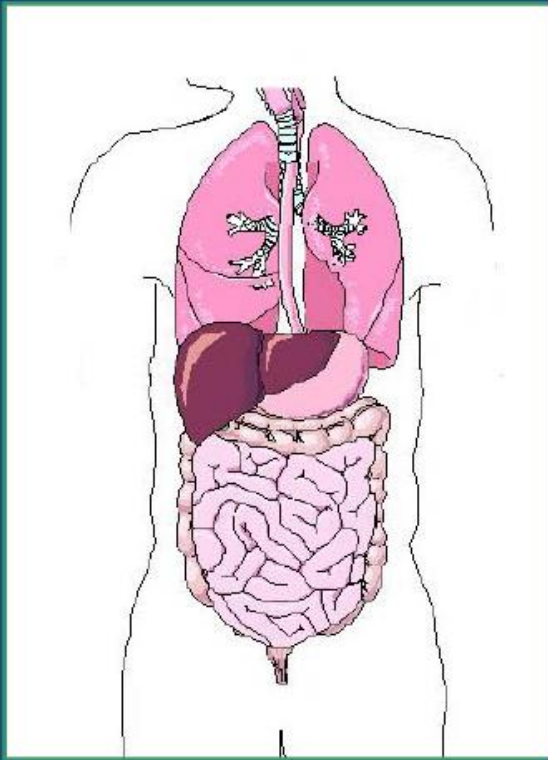
Ki-67>55%:

Response rate: 42%
Overall survival: 10 months

Ki-67 of 55% may be a more appropriate cutoff to determine treatment of poorly differentiated neuroendocrine carcinoma

NET Yerleşim Yerine Göre Sınıflandırılması

Carcinoid Tumors

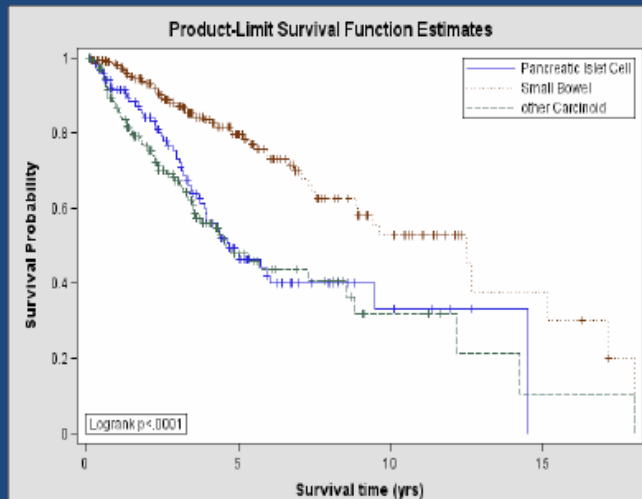


- **Foregut (33%):**
lungs and bronchi, stomach
- **Midgut (34%):**
small intestine, appendix,
proximal large bowel
- **Hindgut (14%):**
distal large bowel, rectum

NET Tumor Alt Tipine göre Sağkalım

Metastatic Neuroendocrine Tumors: Survival by Tumor Subtype

Single Institution Database (N=677)



Pancreatic NET: 5.9 yrs
 Small Bowel Carcinoid: 10.1 years

SEER Database

Site	Median Survival (months)		
	Localized	Regional	Distant
Appendix	>360	>360	27
Cecum	135	107	41
Colon	261	36	5
Duodenum	107	101	57
Gastric	154	71	13
Liver	50	14	12
Lung	227	154	16
Pancreas	136	77	24
Rectum	290	90	22
Small bowel	111	105	56
Thymus	110	68	40

Pancreatic NET: 2 years
 Small Bowel Carcinoid: 4.6 years

Pankreas Yerleşimli NET

NEUROENDOCRINE TUMORS

```
graph TD; A[NEUROENDOCRINE TUMORS] --> B[Pancreatic Neuroendocrine Tumors* (Islet cell tumors)]; A --> C[Carcinoid Tumors]
```

Pancreatic
Neuroendocrine Tumors*
(Islet cell tumors)

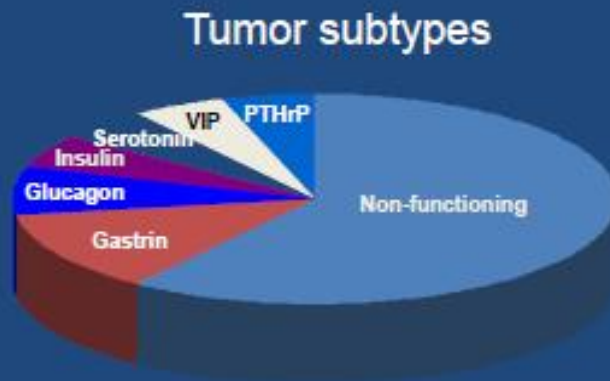
Carcinoid Tumors

*Pancreatic NET comprise 5-8% of all NET in SEER; 22-28% in institutional databases

1. Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072
2. Page UF et al. *Endocrine-Related Cancer* 2009; 15: 1063-97
3. Ter-Minassian et al. *Proc ASCO* 2010

Pankreas Yerleşimli NET

- 60–70% 'non-functional'
- 30–40% associated with symptoms of hormone hypersecretion



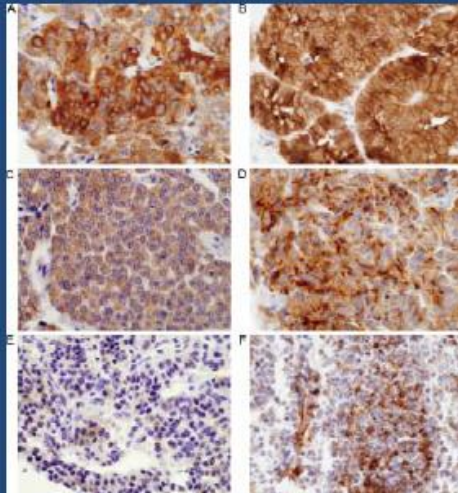
PTHrP = parathyroid hormone-related protein



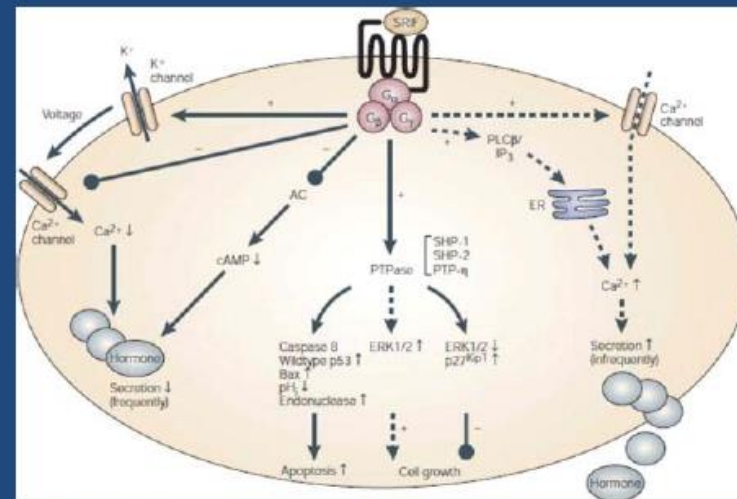
Necrolytic migratory erythema associated with glucagonoma

NET Somatostatin Reseptörleri

Somatostatin Receptors in Neuroendocrine Tumors



Expression of SSTR 1, 2A, 2B, 3, 4 and 5 in Pulmonary NET



Somatostatin receptor signaling pathways

NET Tedavi Seçenekleri

- Somatostatin Analogs
- Liver Directed Therapy
- Cytotoxic Chemotherapy
- “Targeted” Therapies

NET Tedavi Seçenekleri



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PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY

Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

- Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for neuroendocrine tumors.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms for GI tumors, see [NET-9](#).

Options for Unresectable and/or Metastatic NET of the Gastrointestinal Tract	<ul style="list-style-type: none"> • Octreotide^{a,b} LAR 20–30 mg intramuscular injection, monthly¹ • Lanreotide^a 120 mg deep subcutaneous injection, monthly² • Consider (listed in alphabetical order): <ul style="list-style-type: none"> ▶ Cytotoxic chemotherapy (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.) ▶ Everolimus³ ▶ Interferon alfa-2b⁴ (category 3)
Options for Unresectable and/or Metastatic NET of the Lung/Thymus	<ul style="list-style-type: none"> • See NET-8. Depending on tumor burden and grade, options may include: <ul style="list-style-type: none"> ▶ Octreotide^b LAR 20–30 mg intramuscular injection, monthly¹ ▶ Lanreotide 120 mg deep subcutaneous injection, monthly² ▶ Everolimus ± octreotide or lanreotide ▶ Temozolomide ± octreotide or lanreotide ▶ Cisplatin + etoposide^c ± octreotide or lanreotide ▶ Carboplatin + etoposide^c ± octreotide or lanreotide
Options for Carcinoid Syndrome	<ul style="list-style-type: none"> • Octreotide^{b,1} or lanreotide² ± therapy for poorly controlled carcinoid syndrome, including: <ul style="list-style-type: none"> ▶ Telotristat 250 mg orally, three times daily (for persistent diarrhea)⁵, and/or ▶ Additional therapy for disease control (for any persistent symptoms [ie. flushing, diarrhea])

^aSomatostatin analog dosing also applicable for locoregional disease.

^bFor symptom control, octreotide 150–250 mcg SC TID or octreotide LAR 20–30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10–14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

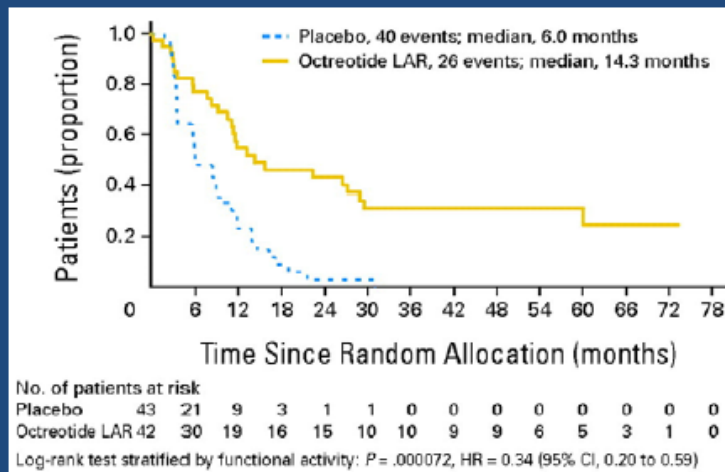
^cCisplatin/etoposide or carboplatin/etoposide can be considered for intermediate grade/atypical tumors with Ki-67 proliferative index and mitotic index in the higher end of the defined spectrum.

[Continued](#)

[See References on NE-D \(3 of 3\)](#)

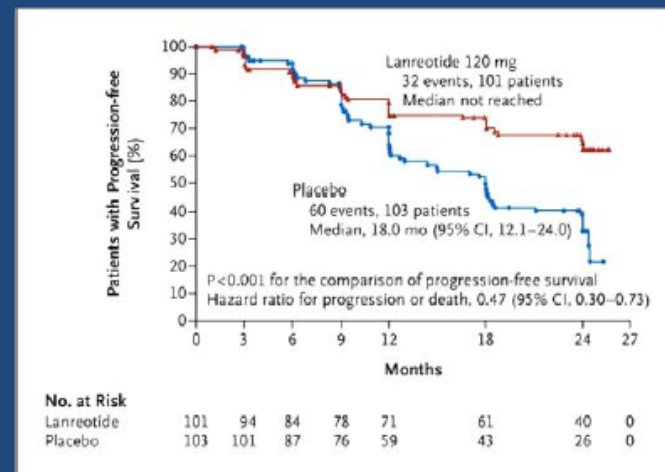
NET Tedavi Seçenekleri

Octreotide and Lanreotide for the Treatment of Advanced NET



PROMID:

Rinke A et al, J Clin Oncol 2009; 27: 4656-63



CLARINET:

Caplin ME et al. N Engl J Med 2014;371:224-233.

CLARINET Çalışması

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

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Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D.,
Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D.,
Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc.,
Séverine Martinez, B.Sc., Joëlle Blumberg, M.D.,
and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

ABSTRACT

BACKGROUND

Somatostatin analogues are commonly used to treat symptoms associated with hormone hypersecretion in neuroendocrine tumors; however, data on their antitumor effects are limited.

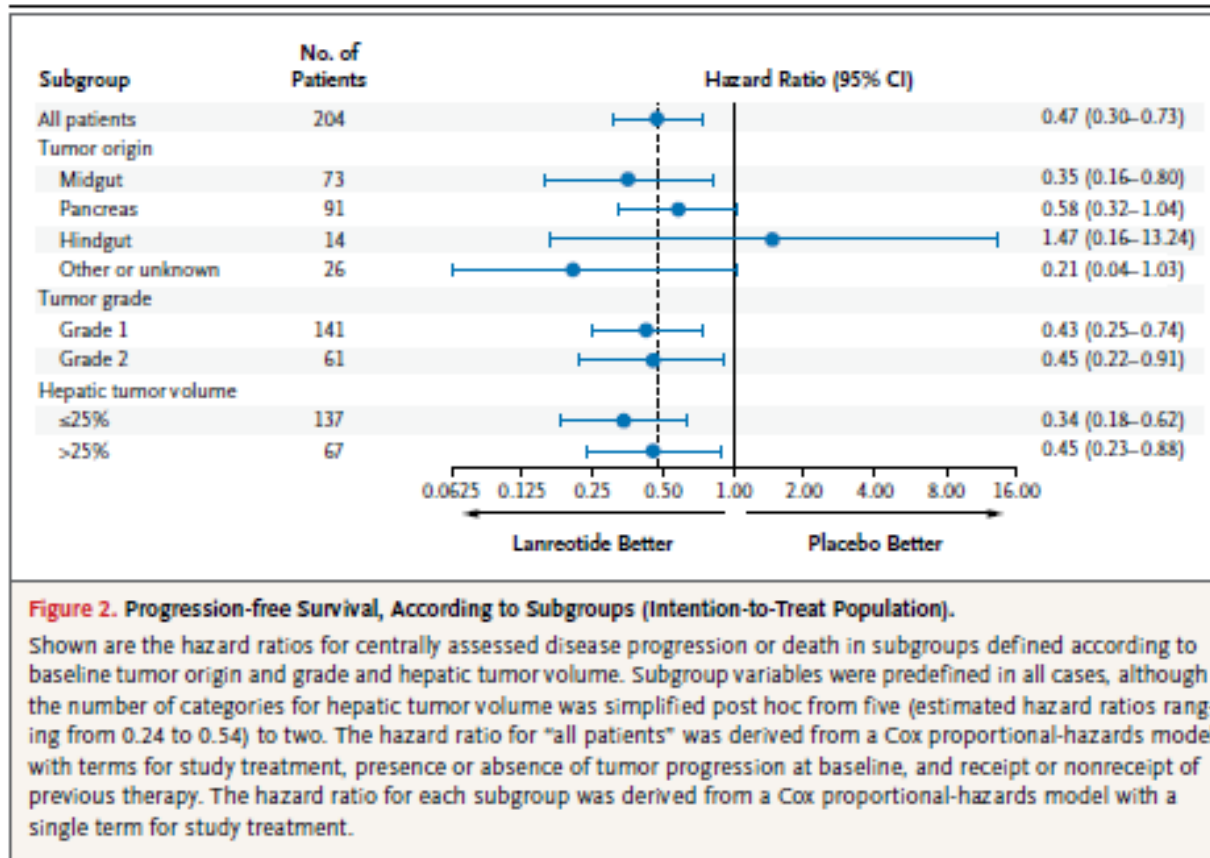
METHODS

We conducted a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor-positive neuroendocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of <10%) and documented disease-progression status. The tumors originated in the pancreas, midgut, or hindgut or were of unknown origin. Patients were randomly assigned to receive an extended-release aqueous-gel formulation of lanreotide (Autogel [known in the United States as Depot], Ipsen) at a dose of 120 mg (101 patients) or placebo (103 patients) once every 28 days for 96 weeks. The primary

From Royal Free Hospital, London (M.E.C.); Charité University Medicine Berlin, Berlin (M.P.); University of Warmia and Mazury, Olsztyn, Poland (J.B.Ć.); University of Texas M.D. Anderson Cancer Center, Houston (A.T.P.); University Hospital, Vienna (M.R.); Department of Oncology of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic (E.S.); Robert-Debré Hospital, Reims (G.C.); Ipsen, Les Ulis, (A.L., S.M., J.B.), Beaujon Hospital, Clichy (P.R.), and Paris Diderot University, Paris (P.R.) — all in France; Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles (E.M.W.); Vall d'Hebron University Hospital, Barcelona (J.C.); Western

CLARINET Çalışması

LANREOTIDE IN ENTEROPANCREATIC NEUROENDOCRINE TUMORS



PROMID Çalışması

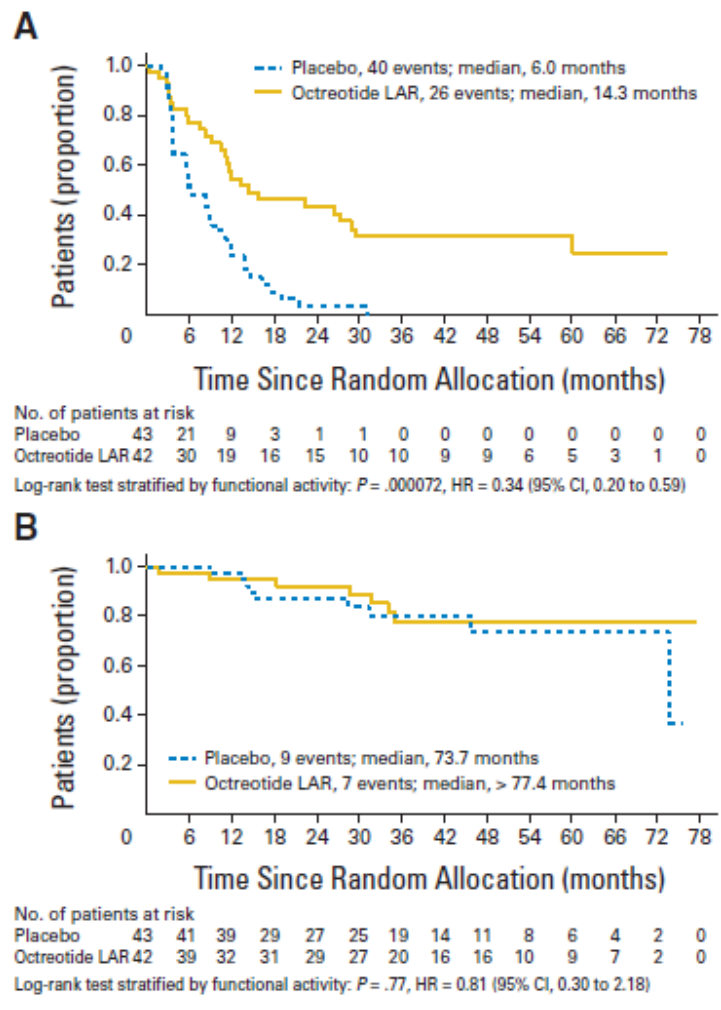


Fig 2. (A) Conservative intent-to-treat analysis of time to progression or tumor-related death. (B) Intent-to-treat analysis of overall survival. HR, hazard ratio.

Table 2. Per-Protocol Subgroup Analyses of Treatment Effects for Time to Progression or Tumor-Related Death

Factor	No. of Patients	Per-Protocol Analysis			
		Octreotide LAR	Placebo	HR	95% CI
Carcinoid syndrome	33	14.3	5.5	0.23	0.09 to 0.57
Inactive tumor	52	28.8	5.9	0.25	0.10 to 0.59
Liver involvement					
0%	12	13.1	8.2	0.55	0.10 to 3.09
0%-10%	52	29.4	6.1	0.17	0.08 to 0.40
10%-50%	14	11.2	5.5	0.40	0.10 to 1.67
> 50%	7	4.6	2.8	0.71	0.11 to 4.45
Chromogranin A*					
Elevated	56	14.3	5.6	0.26	0.13 to 0.54
Not elevated	27	28.8	8.5	0.26	0.08 to 0.85
Karnofsky performance status					
≤ 80%	12	11.5	6.1	0.32	0.05 to 1.98
> 80%	73	27.1	5.8	0.23	0.12 to 0.45
Age, years					
< 63	43	28.8	8.3	0.23	0.08 to 0.63
≥ 63	42	14.3	5.7	0.23	0.10 to 0.53
Primary tumor resection					
Yes	56	29.4	5.9	0.16	0.07 to 0.36
No	29	10.3	5.6	0.84	0.35 to 2.06
Time since diagnosis, months					
< 4.3	43	11.5	5.6	0.34	0.15 to 0.76
≥ 4.3	42	28.8	8.3	0.22	0.09 to 0.56

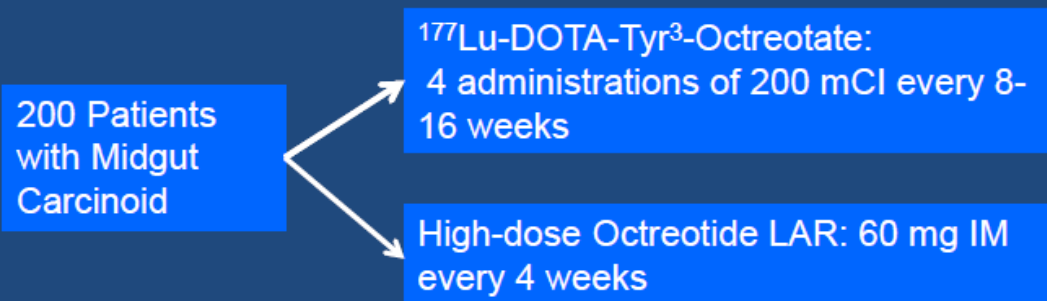
Abbreviation: HR, hazard ratio.

*Plasma chromogranin A levels were determined at the participating study centers. Because assay conditions varied between centers, the respective absolute values were transformed. Levels were considered elevated if greater than the upper limit of normal controls.

NET Tedavi Seçenekleri

NETTER-1: Phase III Study of ^{177}Lu -DOTA,Tyr³-Octreotate vs. Octreotide LAR in Patients with Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors

*Strosberg et al, Presented at ECCO/ESMO 2015

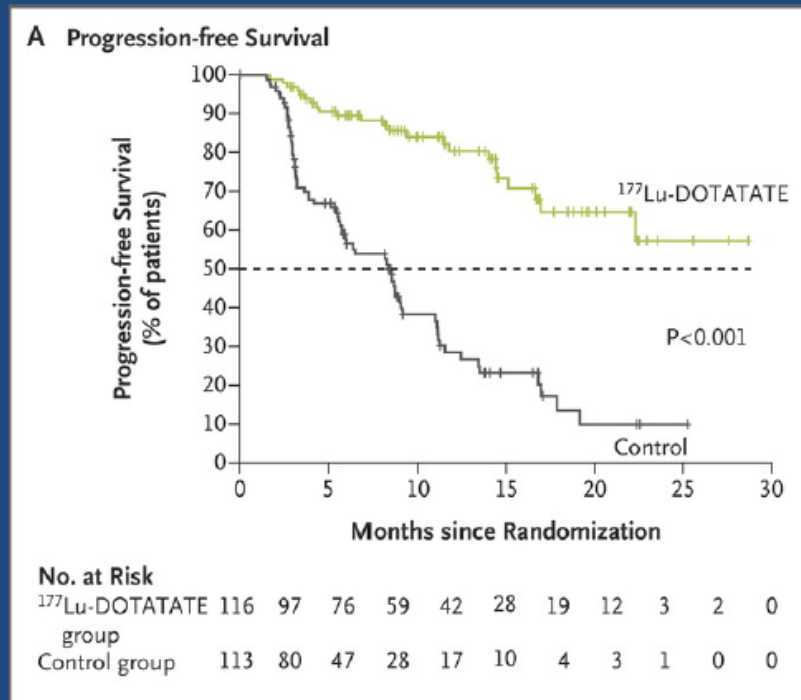


Primary endpoint: Progression-Free Survival

Secondary endpoints: Response rate, TTP, Overall Survival

NET Tedavi Seçenekleri

Progression Free Survival: 177 Lu Dotatate vs. placebo

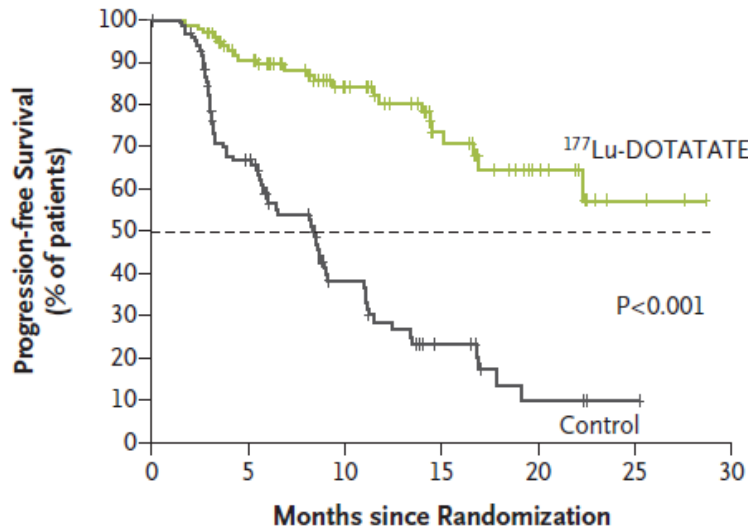


Median PFS not reached ($^{177}\text{Lu Dotatate}$) vs 8.4 mos (placebo)

NET Tedavi Seçenekleri

The NEW ENGLAND JOURNAL of MEDICINE

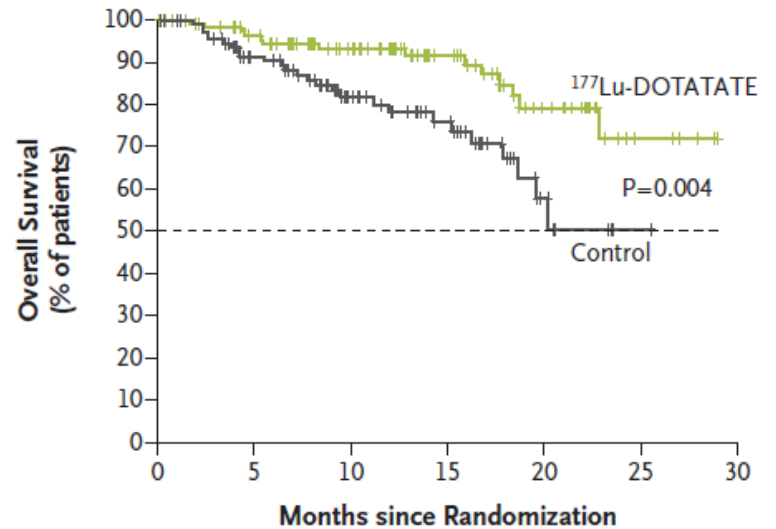
A Progression-free Survival



No. at Risk

¹⁷⁷ Lu-DOTATATE group	116	97	76	59	42	28	19	12	3	2	0
Control group	113	80	47	28	17	10	4	3	1	0	0

B Overall Survival (Interim Analysis)



No. at Risk

¹⁷⁷ Lu-DOTATATE group	116	108	96	79	64	47	31	21	8	3	0
Control group	113	103	83	64	41	32	17	5	1	0	0

NET Tedavi Seçenekleri

C Prespecified Subgroup Analysis of Progression-free Survival

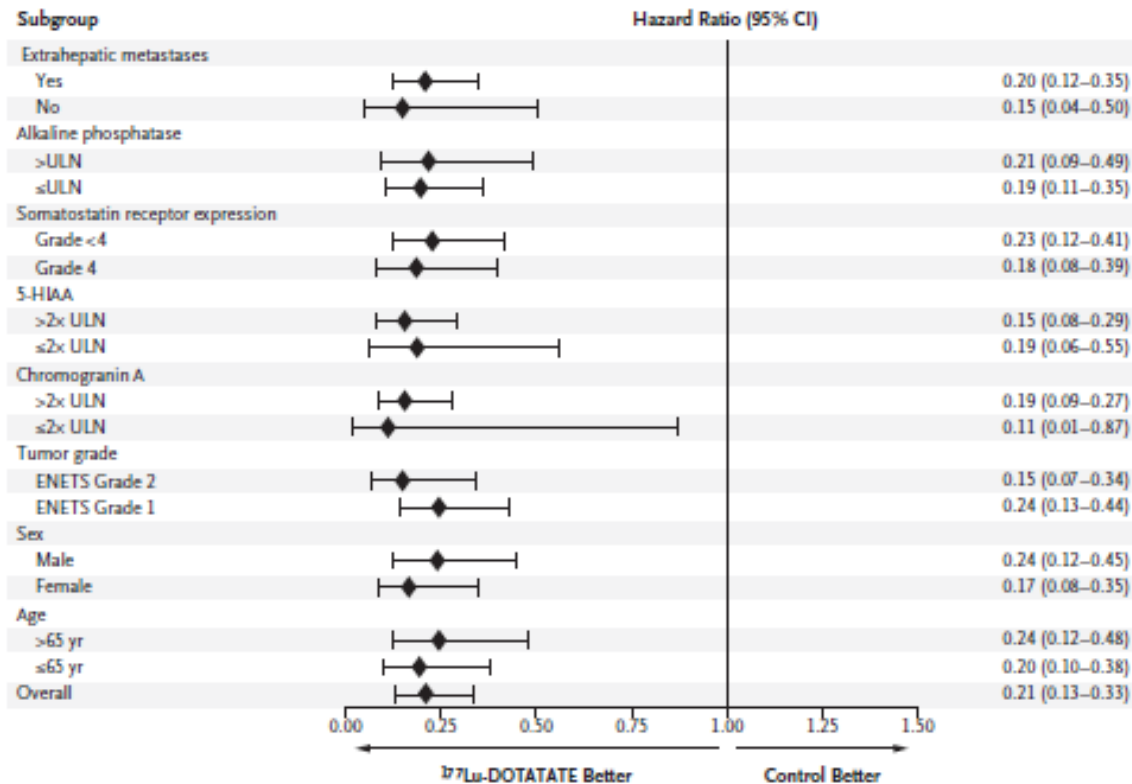


Figure 1. Progression-free Survival and Overall Survival.

Panel A shows the results of the Kaplan–Meier analysis of progression-free survival as assessed by independent central reviewers who were unaware of the treatment assignments, and Panel B the results of the planned interim analysis of overall survival. Tick marks in Panel A represent data censored at the last time the patient was known to be alive and without disease progression and tick marks in Panel B represent data censored at the last time the patient was known to be alive. Panel C shows the effect of trial treatment on progression-free survival in prespecified subgroups. European Neuroendocrine Tumor Society (ENETS) grade 1 indicates a low-grade tumor, and ENETS grade 2 indicates an intermediate-grade tumor. The ^{177}Lu -Dotatate group received ^{177}Lu -Dotatate at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg). The control group received octreotide LAR alone administered intramuscularly at a dose of 60 mg every 4 weeks. 5-HIAA denotes 5-hydroxyindoleacetic acid, CI confidence interval, and ULN upper limit of the normal range.

NET Tedavi Seçenekleri

¹⁷⁷LU-DOTATATE FOR MIDGUT NEUROENDOCRINE TUMORS

Table 2. Objective Tumor Response.*

Response Category	¹⁷⁷ Lu-Dotatate Group (N=101)	Control Group (N=100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

* The objective response rate was defined as the percentage of patients who had a response according to Response Evaluation Criteria in Solid Tumors (RECIST) (sum of partial responses and complete responses). Patients for whom no post-baseline computed tomography (CT) or magnetic resonance imaging (MRI) scans or central response data were available (15 patients in the ¹⁷⁷Lu-Dotatate group and 13 patients in the control group) were excluded from this analysis (trial is still ongoing).

† The P value was calculated with the use of Fisher's exact test.

Table 3. Overview of Adverse Events (Safety Population).*

Event	¹⁷⁷ Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	<i>number of patients (percent)</i>		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.

† P values were calculated with the use of Fisher's exact test.

NET Tedavi Seçenekleri

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Table 4. Adverse Events (Safety Population).*

Event	¹⁷⁷ Lu-Dotatate Group (N=111)		Control Group (N=110)		P Value†
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	
	<i>number of patients (percent)</i>				
Any adverse event	105 (95)	46 (41)	92 (84)	36 (33)	0.01
Gastrointestinal disorders					
Nausea	65 (59)	4 (4)	13 (12)	2 (2)	<0.001
Vomiting	52 (47)	8 (7)	11 (10)	1 (1)	<0.001
Abdominal pain	29 (26)	3 (3)	29 (26)	6 (5)	1.00
Diarrhea	32 (29)	3 (3)	21 (19)	2 (2)	0.11
Distension	14 (13)	0	15 (14)	0	0.84
General disorders					
Fatigue or asthenia	44 (40)	2 (2)	28 (25)	2 (2)	0.03
Edema peripheral	16 (14)	0	8 (7)	0	0.13
Blood disorders					
Thrombocytopenia	28 (25)	2 (2)	1 (1)	0	<0.001
Anemia	16 (14)	0	6 (5)	0	0.04
Lymphopenia	20 (18)	10 (9)	2 (2)	0	<0.001
Leukopenia	11 (10)	1 (1)	1 (1)	0	0.005
Neutropenia	6 (5)	1 (1)	1 (1)	0	0.12
Musculoskeletal disorders					
Musculoskeletal pain	32 (29)	2 (2)	22 (20)	1 (1)	0.16
Nutrition disorders					
Decreased appetite	20 (18)	0	9 (8)	3 (3)	0.04
Nervous system disorders					
Headache	18 (16)	0	5 (5)	0	0.007
Dizziness	12 (11)	0	6 (5)	0	0.22
Vascular disorders					
Flushing	14 (13)	1 (1)	10 (9)	0	0.52
Skin disorders					
Alopecia	12 (11)	0	2 (2)	0	0.01
Respiratory disorders					
Cough	12 (11)	0	6 (5)	0	0.22

* Shown are all adverse events that were reported in at least 10% of the patients in the ¹⁷⁷Lu-Dotatate group, with the exception of neutropenia, which was reported in less than 10% of the patients in the ¹⁷⁷Lu-Dotatate group. For the individual events, the system organ classes in the *Medical Dictionary for Regulatory Activities (MedDRA)* hierarchy are shown in bold and are followed by the MedDRA preferred terms (not bold). The safety population included all patients who underwent randomization and received at least one dose of trial treatment.

† P values were calculated with the use of Fisher's exact test.

01/2016 Tarihinde Uygulanan Tedavi

- Somatuline 120 mg(Lanreotide) 28 günde bir
- Lumbal 4 vertebraya 30Gy Radioterapi
- Zolendronik asid 4 mg iV 28 günde bir

01/2016 Tarihinde Uygulanan Tedaviye Klinik Yanıt Deęerlendirilmesi

Tedavi bařlandıktan 1 ay sonra

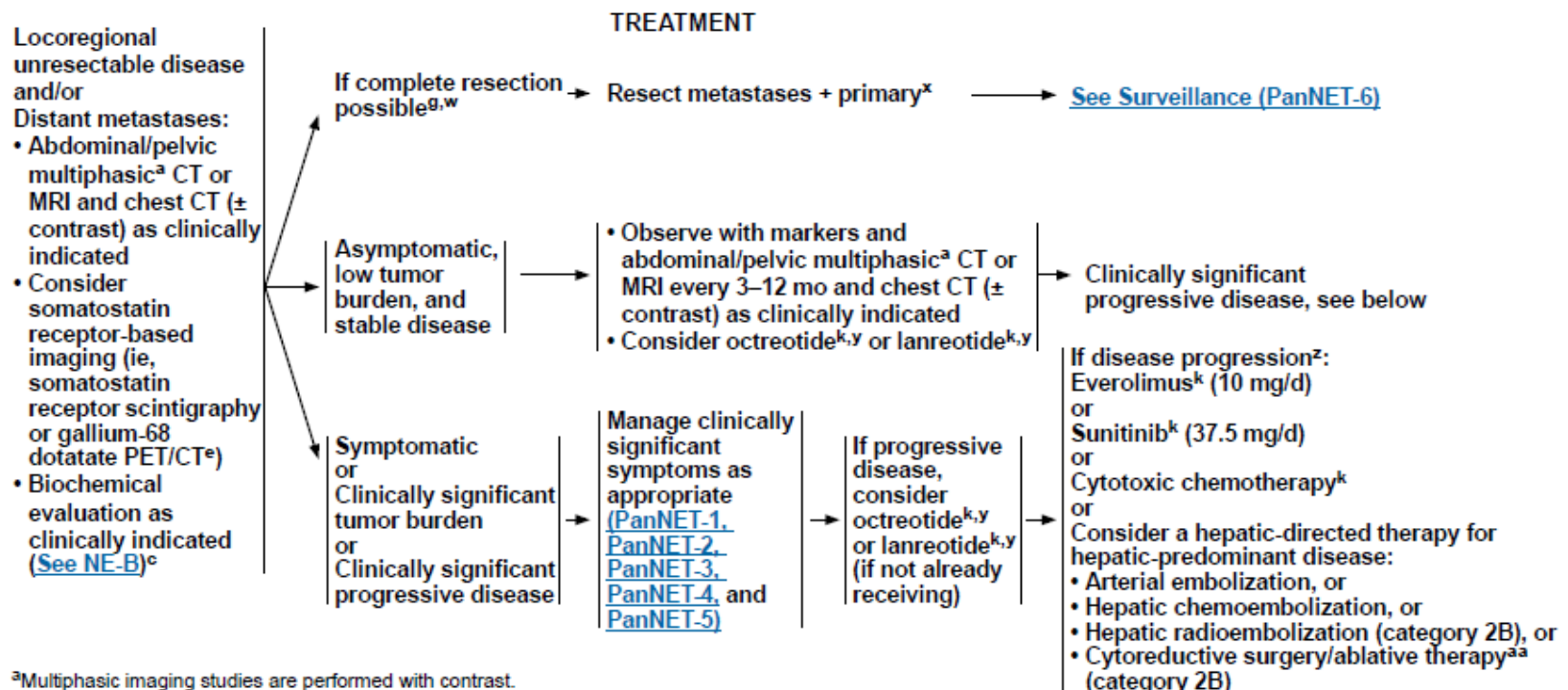
- Hastanın sırt bölgesinde ki ağrı tamamen geriledi
- Kilo kaybı, halsizlik semptomları tama yakın geriledi

03/2017 Tarihinde Ga-68 PET-CT yanıt Değerlendirilmesi

- Hastanın şikayet ve semptomu yok,
- Genel durumu iyi
- Biyokimya, hemogram değerleri normal
- Somatuline 120 mg tedavisinin 12 ayında yanıt değerlendirilmesine gönderildi

İyi diferansiye NET'lerde Yanıt Değerlendirilmesi Nasıl ve Ne zaman olmalıdır?

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES^g



^aMultiphasic imaging studies are performed with contrast.

^cSee Principles of Biochemical Testing (NE-B).

^ePET/CT of skull base to mid-thigh.

^gSee Surgical Principles for Management of Neuroendocrine Tumors (NE-C).

^kSee Principles of Systemic Anti-Tumor Therapy (NE-D).

^wNoncurative debulking surgery might be considered in select cases.

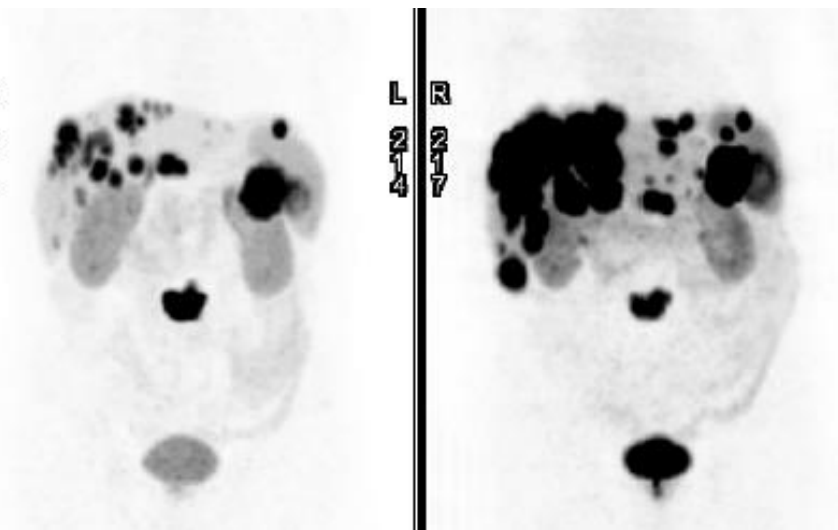
^xStaged or synchronous resection when possible. When performing staged pancreatoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreatoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.

^yFor patients with insulinoma, octreotide or lanreotide should be used only if somatostatin scintigraphy is positive. If used, they should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).

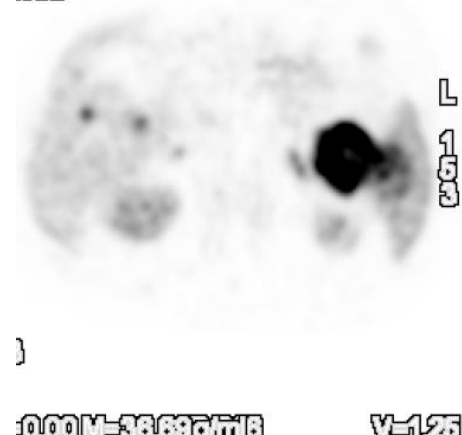
^zIf disease progression, treatment with octreotide or lanreotide may be continued in combination with any of the subsequent options.

^{aa}Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited, but data on their use are emerging.

01/2016-03/2017 Ga-68 PET-CT



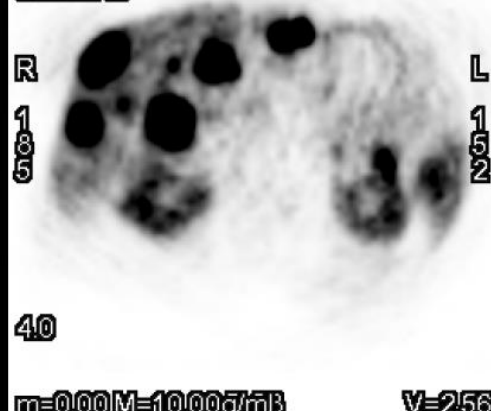
183



0.00 M=38.89g/mB

V=125

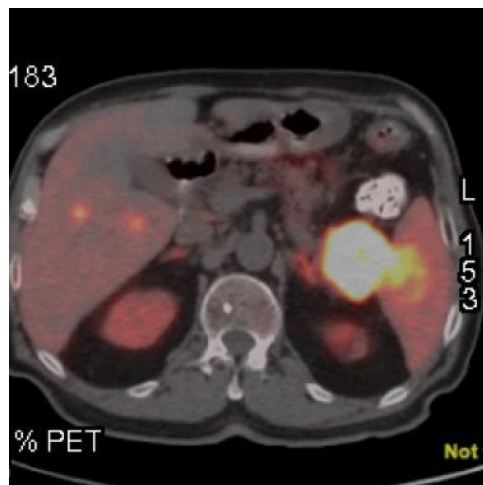
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SIEMENS



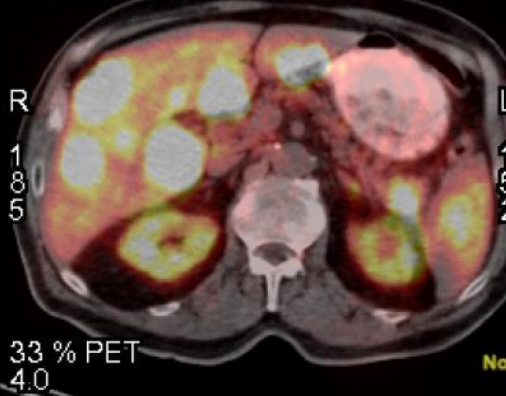
40

m=0.00 M=10.00g/mB

V=256



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01/2016-03/2017 Ga-68 PET-CT

Tetkik : Y-90 veya Lu-177 işaretli terapötik bileşikler

Endikasyon: Pankreas NET tanı hasta

Yüksek doz Lu-177 Somatostatin Reseptör tedavisinden sonra yapılan Tüm vücut sintigrafisinde ve SPECT/BT görüntülerinde;

Alınan tüm vücut planar ve SPECT-CT imajlarında karaciğerde bilateral lobda yaygın görüntüde yoğun artmış aktivite tutulumu gösteren lezyonlar dikkati çekmiştir. Pankreas kuyruk düzeyinde yoğun artmış aktivite tutulumlarının izlendiği olguda ayrıca dalakta medialde belirgin dalağın genelini kaplamış görüntüde yoğun artmış aktivite tutulumları da izlenmiştir. L4 vertebra korpusunda skleroz olarak izlenen lezyonda hafifçe artmış aktivite tutulumu dikkati çekmiştir.

Sonuç:

Karaciğerde, pankreas kuyruk kesiminde ve dalakta izlenen lezyonlarda yoğun L4 vertebra korpusunda izlenen sklerotik lezyonda ise hafifçe artmış aktivite tutulumunun izlendiği Lu-177 DOTA TATE tüm vücut sintigrafisi.

01/2016-03/2017 Ga-68 PET-CT

Bulgular:

Güncel çalışma Ocak 2016 tarihli Ga-68 DOTA TATE PET/BT çalışması ile karşılaştırılarak değerlendirilmiştir. Buna göre;

Pankreas kuyruk düzeyinde yerleşimli dalak hilusu ve mide büyük kurvatürü ile yakın komşuluk halinde, dalak parankimine doğru invazyon şüphesi uyandıran kitle lezyon güncel çalışmada yaklaşık 4.5 cm boyutlarında ölçülmüş olup boyutlarında ve aktivite tutulumunda önceki çalışmaya kıyasla kısmen regresyon saptanmakla birlikte halen yoğun artmış aktivite tutulumu göstermektedir. Önceki çalışmada dalak hilusu düzeyinde parankim içerisinde yerleşimli kitle lezyonda ise boyutlarında ve santral nekrotik komponentinde artış izlenirken aktivite tutulumunda belirgin regresyon saptanmıştır.

Karaciğer her iki lobunda multipl odaklar halinde izlenen yoğun artmış aktivite tutulumunun gözlendiği metastatik nodüler - kitlesel lezyonlarda boyut ve aktivite tutulumunda artış saptanmıştır. Önceki çalışmada sol gastrik, hepatogastrik ve çölyak alanlarda izlenen hafifçe artmış aktivite tutulumu gösteren lenf nodlarında ise aktivite tutulumunda regresyon mevcuttur.

Akciğer parankimlerinde, mediastende, her iki supraklaviküler fossada patolojik düzeyde artmış aktivite tutulum odağı saptanmamıştır.

İskelet sisteminde lomber 4. vertebra korpusunda izlenen yoğun aktivite tutulumunun gözlendiği sklerotik görünümlü lezyonda aktivite tutulumunda kısmen regresyon saptanmıştır. İskelet sisteminin diğer kısımlarında patolojik düzeyde artmış aktivite tutulum odağı saptanmamıştır. Sol 3. kosta posteriorunda önceki çalışmaya benzer görünümde sklerotik lezyon alanında kaydadeğer aktivite tutulumu seçilmemiştir.

Sonuç:

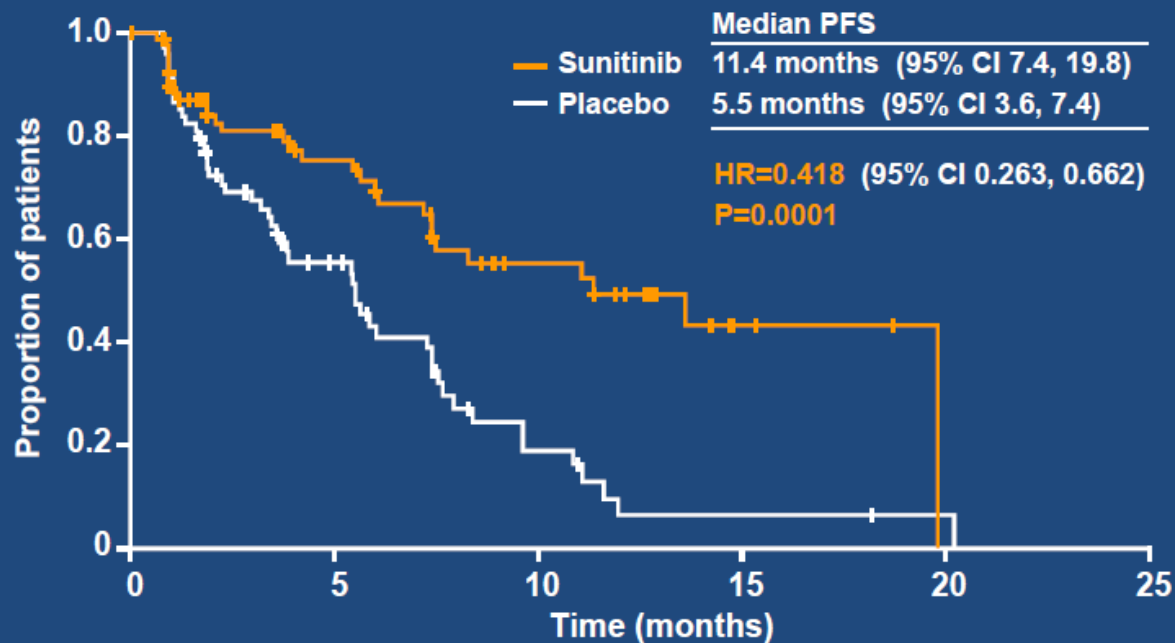
-Pankreas NET tanılı hastada pankreas kuyruk düzeyinde yerleşimli mide büyük kurvatür ve pankreas hilusu ile yakın komşuluk halinde kitle lezyonda kısmen regresyon saptanmakla birlikte halen yoğun somatostatin tip II reseptör ekspresyonu gösterdiği dikkati çekmiştir. Dalak parankimi içerisinde yerleşimli yoğun aktivite tutulumunun gözlendiği diğer bir kitle lezyonda ise boyutlarında ve nekrotik komponentinde artış izlenirken aktivite tutulumunda belirgin regresyon mevcut olup periferik minimal aktivite tutulumu göstermektedir.

-Karaciğer her iki lobunda izlenen yoğun somatostatin reseptör tip II ekspresyonu içeren metastatik nodüler - kitlesel lezyonlarda boyut ve aktivite tutulumunda artış mevcuttur.

-Lomber 4. vertebra korpusunda metastaz ile uyumlu sklerotik görünümlü lezyonda ise aktivite tutulumunda kısmen regresyon saptanmakla birlikte tanımlanan lezyonda halen periferik yoğun somatostatin tip II reseptör ekspresyonu mevcuttur.

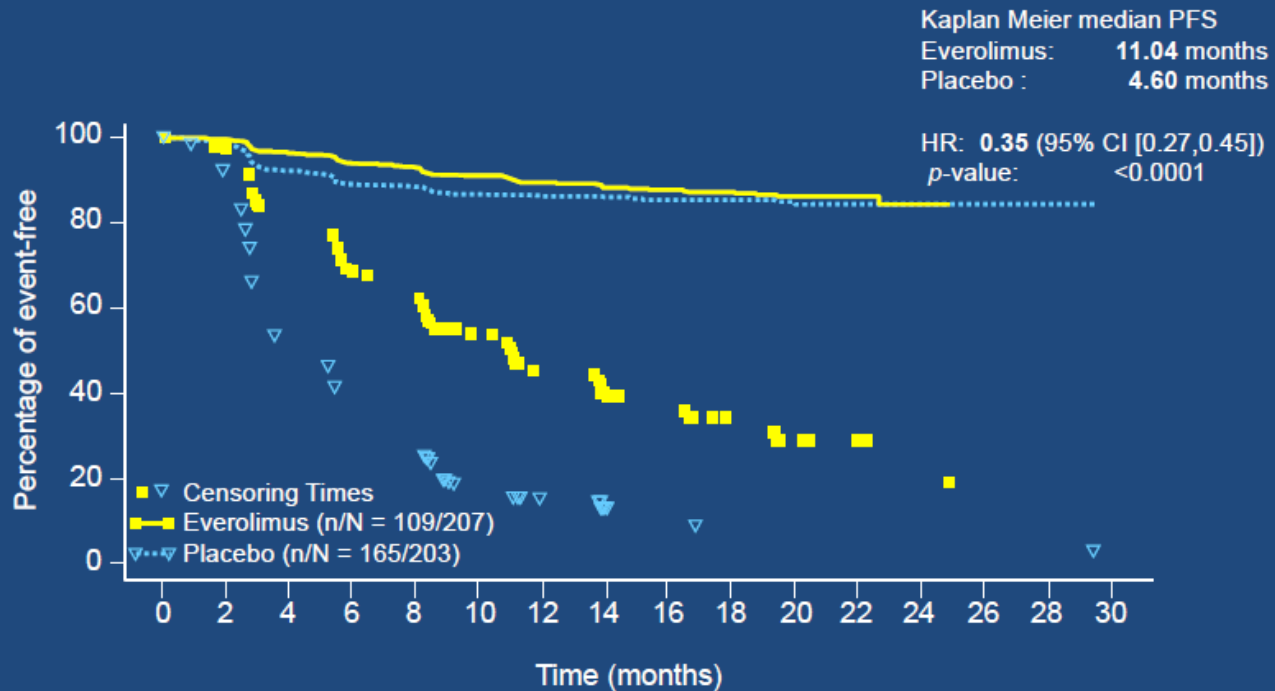
NET Tedavi Seçenekleri

Sunitinib in Pancreatic NET: Investigator-Assessed Progression-Free Survival



NET Tedavi Seçenekleri

Everolimus in Pancreatic NET (RADIANT 3): Investigator-Assessed Progression-Free Survival



NET Tedavi Seçenekleri

RADIANT-4 Study Design

* Yao et al, presented at ECCO/ESMO, 2015

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Radiologic disease progression in ≤ 6 months

R
A
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E

2:1

Everolimus 10 mg/day
N=205

Placebo
N=97

Treated until PD,
intolerable AE, or
consent withdrawal

Endpoints:

Primary: PFS (central)
Key Secondary: OS
Secondary: ORR, DCR, safety, HRQoL (FACT-G),
WHO PS, NSE/CgA, PK

Stratified by:

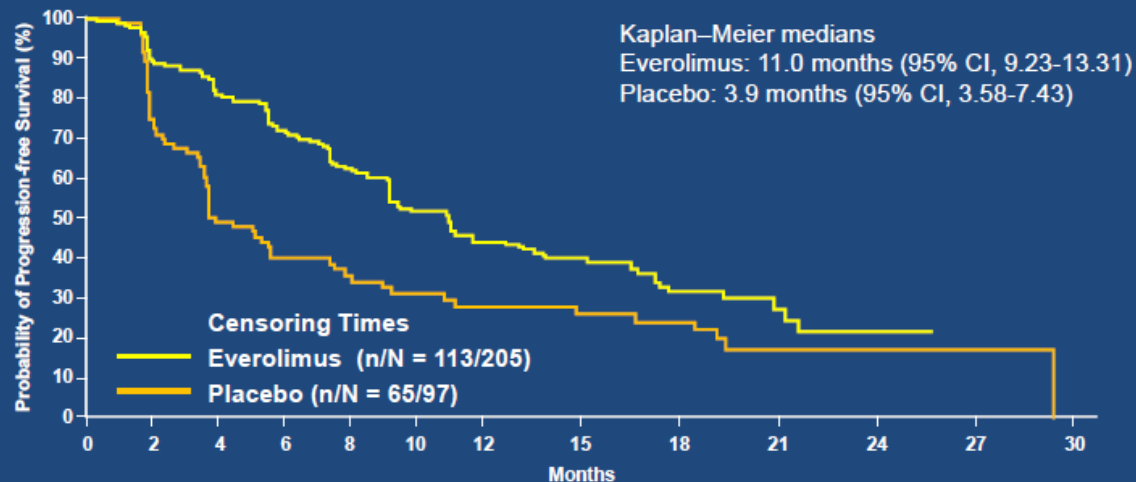
Prior SSA treatment (yes vs. no)
Tumor origin (stratum A vs. B)*
WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: Stratum A (better prognosis) – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. Stratum B (worst prognosis) – lung, stomach, rectum, and colon except caecum.

Crossover to open-label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

NET Tedavi Seçenekleri

RADIANT 4: PFS by Central Review



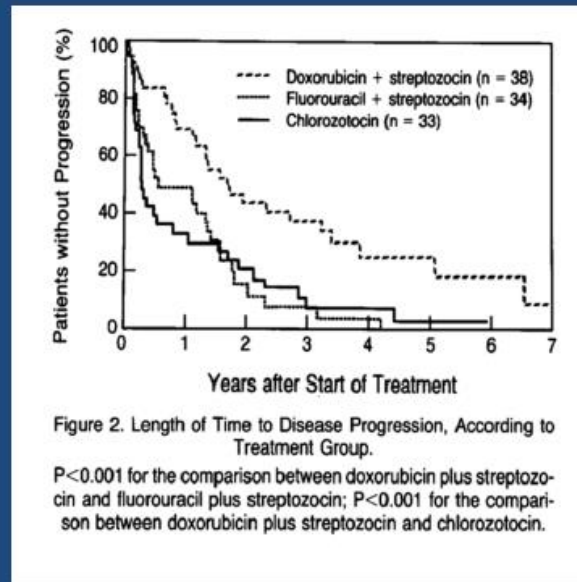
	0	2	4	6	8	10	12	15	18	21	24	27	30
Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
CI, confidence interval; HR, hazard ratio

NET Tedavi Seçenekleri

Streptozocin-based Therapy for Pancreatic NET

- Streptozocin approved for pancreatic NET in 1982
- Streptozocin/doxorubicin associated with survival benefit compared to streptozocin/5-FU (2.2 vs. 1.5 years)
- Response rates 30-40% in retrospective series



NET Tedavi Seçenekleri

Temozolomide-Based Therapy in Pancreatic NET

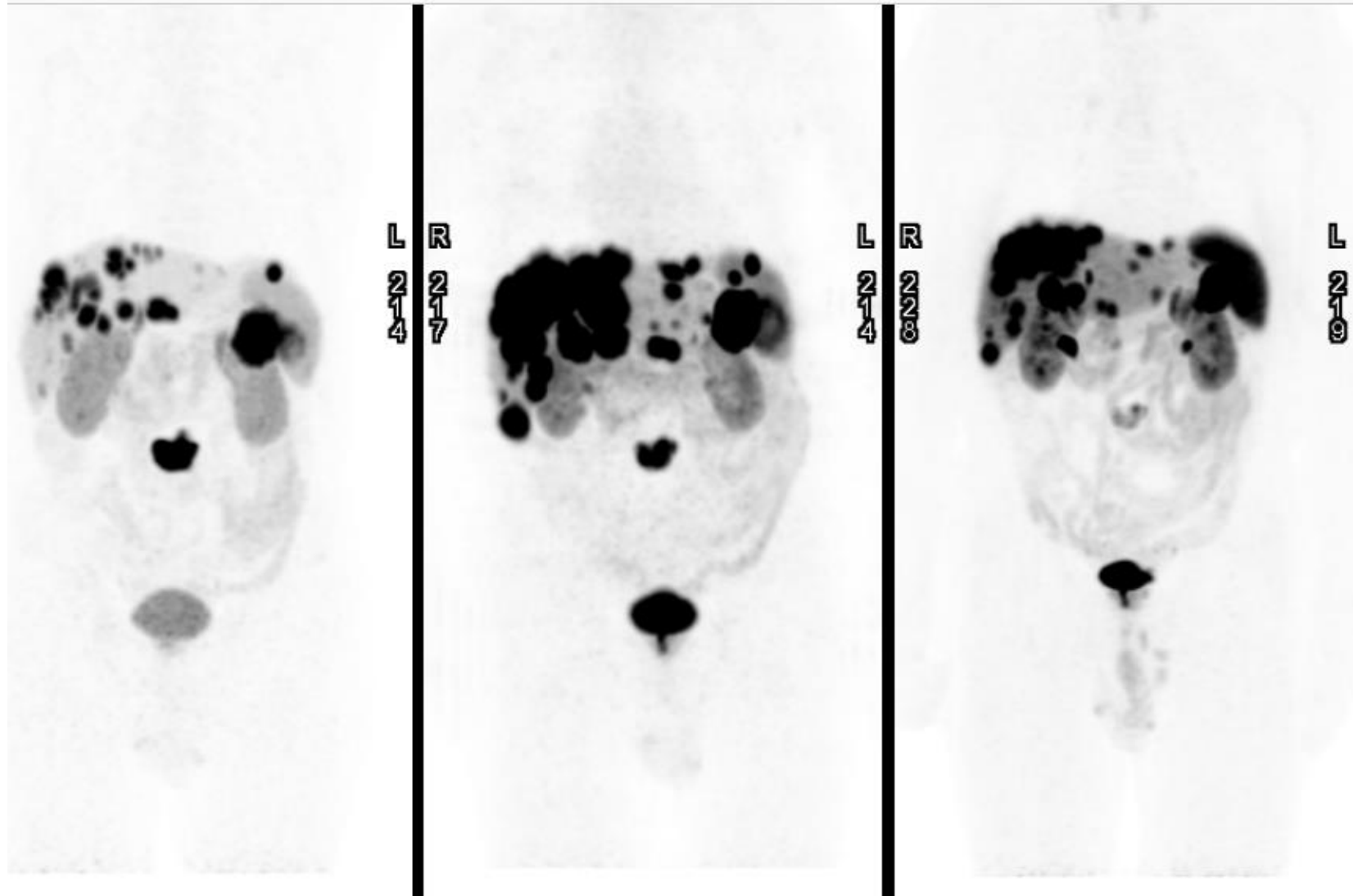
	Regimen	N	Response Rate
Retrospective Series			
	Tem (single agent)	12	8%
	Tem/capecitabine	30	70%
	Tem (various)	53	34%
Prospective Trials			
	Tem/Thalidomide	11	45%
	Tem/Everolimus	40	40%
	Tem/Bevacizumab	15	33%
	Tem/Bevacizumab	15	64%

1. Ekeblad et al, Clin Cancer Res 2007; 2986-91 2. Strosberg et al Cancer 2011; 117: 268-75 3. Kulke et al, Clin Cancer Res 2009; 15: 338-45 4. Kulke et al, J Clin Onco 2006; 24: 401-6 5. Kulke et al J Clin Oncol 2006; 24(18S) A4044; 6. Chan et al, Cancer 2013; 119: 3212-18. 7. Koumarianou et al, Endoc Rel Cancer 2012; 19: L1-4.

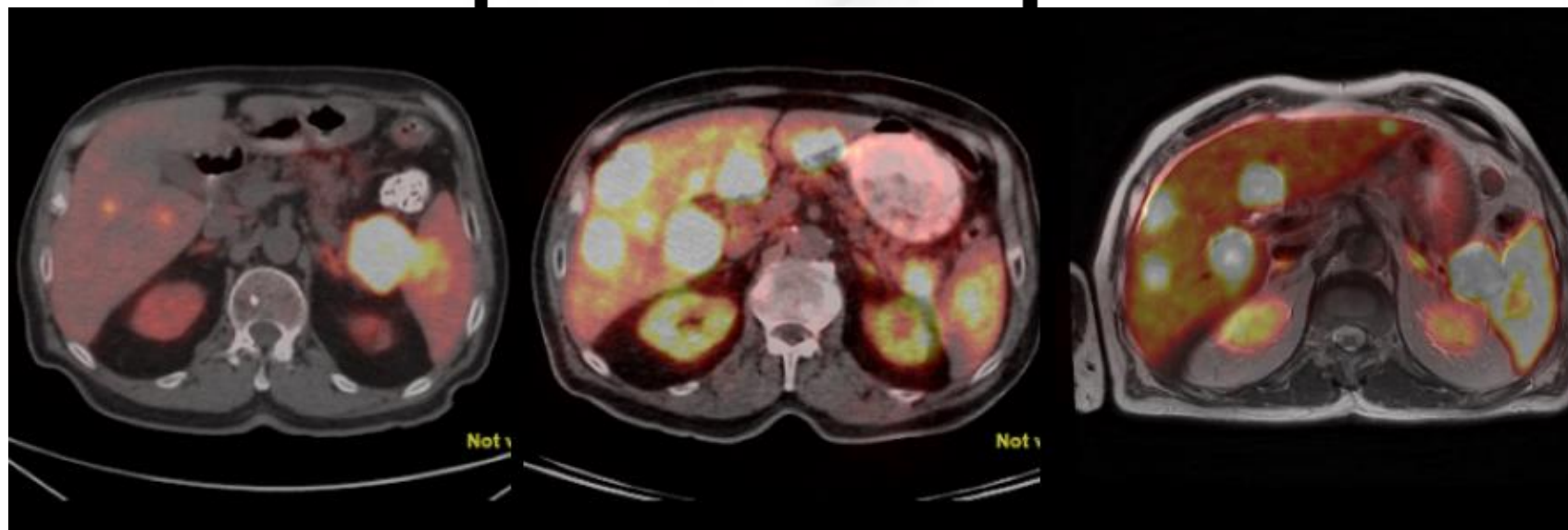
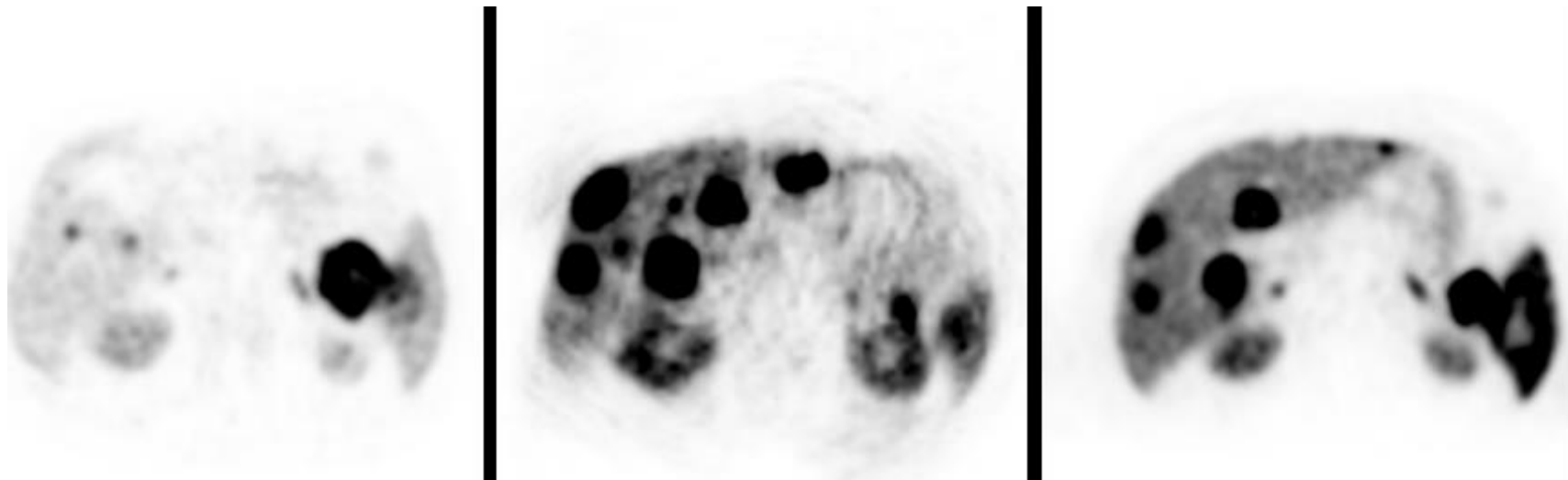
03/2017 Tedavi Uygulaması

- ❑ Somatuline 120 mg(Lanreotide) 28 günde bir
- ❑ Zolendronik asid 4 mg İV 28 günde bir
- ❑ Lu-177, 4 kez iv uygulandı

01/2016, 03/2017, 12/2017; Ga-68 PET-CT



01/2016, 03/2017, 12/2017 Ga-68 PET-CT



12/2017 Ga-68 PET-CT

Tetkik : Onkolojik PET (Ga-68 ile işaretli bileşikler)

Sonuç:

Pankreas kuyruk düzeyinde yerleşimli primer tümöral lezyonda önceki çalışmaya kıyasla kısmen regresyon saptanmakla birlikte halen yoğun somatostatin reseptör tip II ekspresyonu devam etmektedir. Dalak parankimi içerisinde önceki çalışmaya kıyasla kısmen regrese görünümde santrali nekrotik inaktif periferik hafifçe aktivite tutulumunun devam ettiği metastatik lezyon mevcuttur. Karaciğer her iki lobunda yoğun somatostatin reseptör tip II ekspresyonu içeren metastatik nodüler-kitlesel lezyonlarda kısmen regresyon saptanmıştır. Ayrıca hepatogastrik alanda kısmen regrese görünümde artmış aktivite tutulumunun devam ettiği metastatik lenf nodu mevcuttur. Lomber 4.vertebra korpusunda metastaz ile uyumlu santrali sklerotik inaktif periferik yoğun somatostatin reseptör tip II ekspresyonu içeren kemik lezyonunda kısmen regresyon saptanmıştır.

Saygılarımızla
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