Perspectives on the current status and recent advances in GEP-NETs

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Agenda

- Treatment options for patients with GEP-NETs: Where are we now?
- Innovation and integration: Do we need to adapt existing guidelines?
- Progression and treatment response: Towards an individualized approach

GEP, gastroenteropancreatic; NET, neuroendocrine tumour.

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Treatment options for patients with GEP-NETs: Where are we now?

Prof. Jonathan R Strosberg

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GEP-NETs: Increasing incidence and prolonged survival

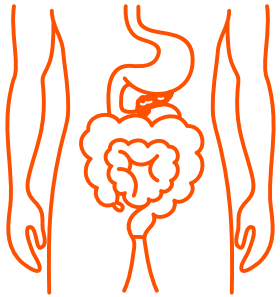
Overall 5-year survival rate in GEP-NETs ≈70%[1]

Incidence has changed variably by anatomical site[†1–3]

Gastric and rectal NETs showed greatest increase in incidence[3]

Gastric
9.3%

Small intestine
30.8–75.8%



Pancreas
10.5–14.1%

Rectum
33.1%

Age-adjusted incidence increased steadily
(3.65-fold in the USA and 3.8–4.8-fold in Europe)
in the last four decades[3]

Predictors of increased risk of death:[4]

- Pancreatic NET vs SI-NET for patients with distant metastases (not regional metastases)
- Liver metastases vs other distant metastases

Predictors of increased OS:[4]

- Radical resection
- Age at diagnosis
- Low histological grade
- Type of treatment
- Isolated liver involvement
- Early CgA decrease after treatment

[†] Incidence rates by anatomical site taken from data published from the Swedish National Cohort study (N=811)[1] and US SEER database (N=28,056).[2]

CgA, chromogranin A; GEP, gastroenteropancreatic; NET, neuroendocrine tumour; OS, overall survival; SI, small intestine.

1. Lesen E, et al. *J Cancer.* 2019;10:6876–87; 2. Zhong Q, et al. *Cancer Med.* 2018;7:3521–33; 3. Fraenkel M, et al. *Endocrine-Related Cancer.* 2014;21:R153–63; 4. Massironi S, et al. *J Pancreas (Online).* 2018; S(3):371–9.

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Well-differentiated GEP-NETs: Current therapy options[1–4]

SSAs (octreotide, lanreotide) **+ symptomatic control**

Progressive disease

Midgut NETs

Hepatic arterial embolization
liver-dominant

PRRT (^{177}Lu-DOTATATE)
Extrahepatic, strong SSTR expression

mTOR inhibitor (everolimus)
Extrahepatic, weak SSTR expression

Pancreatic NETs

CT (capecitabine/temozolomide)

Multi-receptor TKIs
(sunitinib: VEGFR, PDGFR, KIT)

mTOR inhibitor (everolimus)
Extrahepatic, weak SSTR expression

Liver-directed therapies
Liver metastases

PRRT (^{177}Lu-DOTATATE)

Non-midgut GI/lung NETs

mTOR inhibitor (everolimus)
Extrahepatic, weak SSTR expression

PRRT (^{177}Lu-DOTATATE)
Strong SSTR expression

Liver-directed therapies
Liver metastases

CT (capecitabine/temozolomide)
Relatively aggressive, foregut (lung/stomach/thymus)

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; CT, chemotherapy; GEP-NET, gastroenteropancreatic neuroendocrine tumour; GI, gastrointestinal; KIT, proto-oncogene c-Kit; mTOR, mechanistic target of rapamycin; NET, neuroendocrine tumour; PDFGR, platelet-derived growth factor receptor; PRRT, peptide receptor radionuclide therapy; SSAs, somatostatin analogues; SSTR, somatostatin receptor; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Uri I, Grozinsky-Glasberg S. *Clin Diabetes Endocrinol.* 2018;4:16; 2. Pavel M, et al. *Ann Oncol.* 2020;31:844–60; 3. Herrera-Martínez AD, et al. *Drugs* 2019;79:21–42; 4. Starr JS, et al. *OncoTargets Ther*. 2020;13:3545–55.

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AXINET (GETNE 1107): Axitinib plus SSA (octreotide LAR)

N=256

- G1–2 extra-pancreatic NET
- ECOG PS 0–2
- <2 prior systemic treatments
- PD within ≤1 year

Primary tumour sites

- SI — 47%
- Lung — 28%
- Rectum — 6%
- Gastric — 3%
- Colon — 2%
- Unknown — 8%

Patients randomized

SSA-AXITINIB
Octreotide LAR 30 mg IM Q4W + axitinib 5 mg BID
n=126

SSA-PLACEBO
Octreotide LAR 30 mg IM Q4W + placebo BID
n=130

Safety profile consistent with data at ASCO GI 2021[2]

Data presented ESMO 2021[1]

Tumour shrinkage	ORR	PFS
80% of patients	13.2%	16.6 months
	p=0.0045	HR 0.71 p=0.017
61% of patients	3.2%	9.9 months

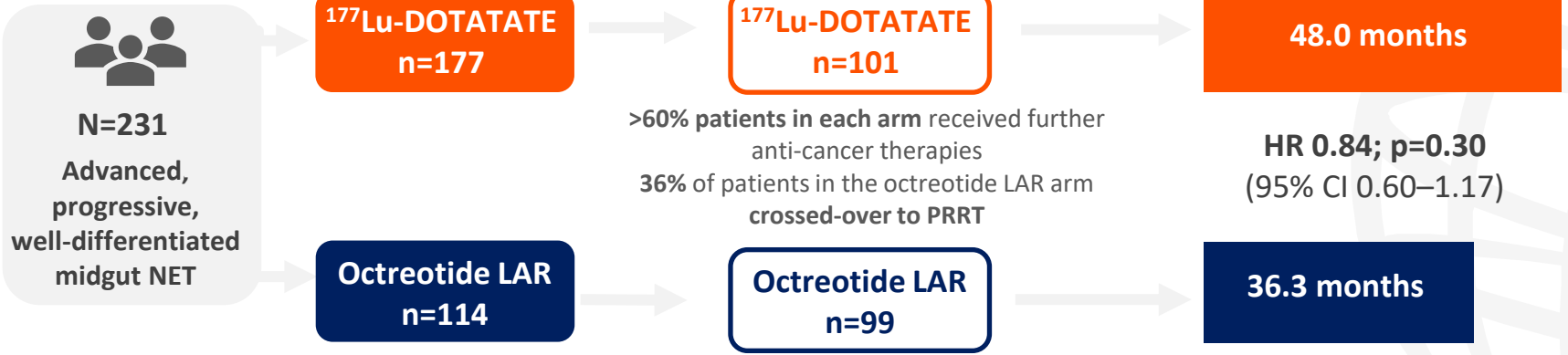
Axitinib plus SSA (octreotide LAR) significantly improved PFS and ORR in G1–G2 extra-pancreatic NET (treatment-blinded independent radiological assessment)

ASCO, American Society of Clinical Oncology; BID, twice daily; ChT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society of Medical Oncology; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; IM, intramuscular; LAR, long-acting release; NET, neuroendocrine tumour; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; Q4W, every 4 weeks; SI, small intestine; SSA, somatostatin analogue.

Garcia-Carbonero R, et al. *Ann Oncol.* 2021;32(Suppl. 5):S907–8; 2. Garcia-Carbonero R, et al. *J Clin Oncol.* 2021;39(Suppl. 3): Abstr 360.
AXINET trial (NCT01744249) available at https://www.clinicaltrials.gov/ct2/show/NCT01744249 (accessed October 2021).

NETTER-1: Final analysis of OS

^{177}Lu-DOTATATE prolonged median OS by 11.7 months compared with high-dose octreotide



OS consistent across prespecified subgroups

- Age
- Karnofsky score
- Baseline tumour burden

^{177}Lu-DOTATATE, ^{177}Lu-DOTA0-Tyr3-Octreotate; CI, confidence interval; HR, hazard ratio; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; OS, overall survival.

Ruszniewski PB, et al. *Ann Oncol.* 2021;32(Suppl. 5):S911–12.
NETTER-1 trial (NCT01578239) available at https://clinicaltrials.gov/ct2/show/NCT01578239 (accessed October 2021).

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Innovation and integration: Do we need to adapt existing guidelines?

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Novel agents and emerging approaches to therapy: PRRT

PRRT
^{177}Lu-DOTATOC
(NCT03049189; NCT04919226)

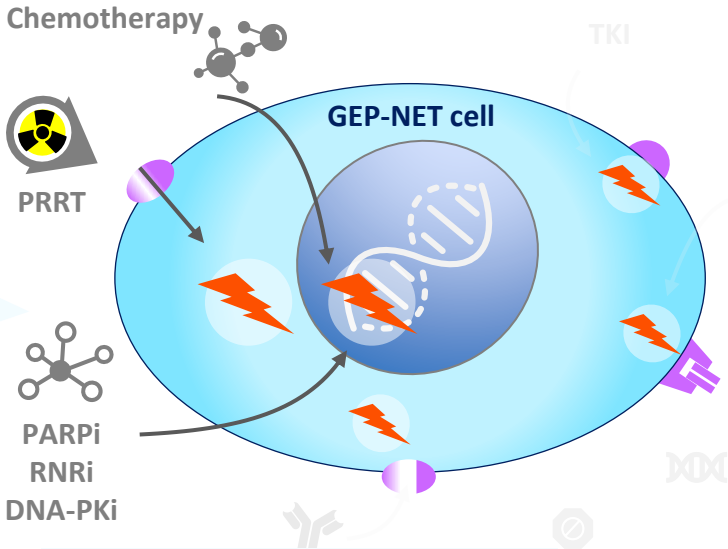
Combination therapy with PRRT
^{177}Lu-DOTATATE + CAPTEM
(NCT04194125; NCT02358356)

^{177}Lu-DOTATATE + iobenguane I^{131}
(NCT04614766)

^{177}Lu-DOTATATE + olaparib
(NCT04086485)

^{177}Lu-DOTATATE + triapine
(NCT04234568)

^{177}Lu-DOTATATE + peposertib
(NCT04750954)



Novel radioligand theranostics
e.g. ^{177}Lu-OPS201 (NCT02592707)
^{212}Pb-DOTAMTATE (NCT03466216)
^{225}Ac-DOTATATE TAT

Treatment options for GEP-NETs are expanding, notably in the field of PRRT

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; ^{177}Lu-DOTATOC, ^{177}Lu-edotreotide; CAPTEM, capecitabine + temozolomide; DNA-PKi, DNA-dependent protein kinase inhibitor; GEP, gastroenteropancreatic; NET, neuroendocrine tumour; PARPi, poly (adenosine diphosphate-ribose) polymerase inhibitor; PRRT, peptide receptor radionuclide therapy; RNRi, ribonucleotide reductase inhibitor; TAT, targeted alpha therapy; TKI, tyrosine kinase inhibitor.
Clinical trials listed by their ClinicalTrials.gov identifiers. Trial information available at https://clinicaltrials.gov/ (accessed September 2021).
Das S, Dasari A. *Ther Adv Med Oncol.* 2021;13:1–15.

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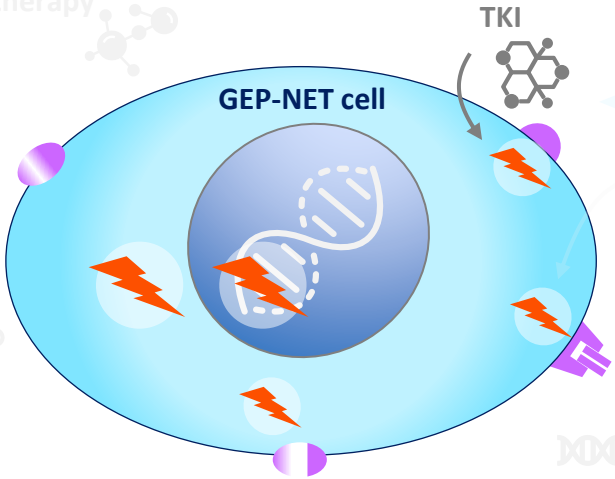
Novel agents and emerging approaches to therapy: TKIs

Multiple TKIs with antiangiogenic properties under clinical investigation in patients with advanced GEP-NETs



Novel TKIs (antiangiogenics)

Anlotinib (NCT03457844)
Axitinib (NCT01435122)
Cabozantinib (NCT01466036)
Famitinib (NCT01994213)
Foslinanib (NCT03600233)
Lenvatinib (NCT02678780)
Nintedanib (NCT02399215)
Pazopanib (NCT01841736)
Regorafenib (NCT02259725)
Surufatinib* (NCT02589821; NCT02588170)

*US Food and Drug Administration approval under consideration.
GEP, gastroenteropancreatic; ICI, immune checkpoint inhibitors; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; TKI, tyrosine kinase inhibitor.
Clinical trials listed by their ClinicalTrials.gov identifiers. Trial information available at https://clinicaltrials.gov/ (accessed September 2021).
Das S, Dasari A. *Ther Adv Med Oncol.* 2021;13:1–15.

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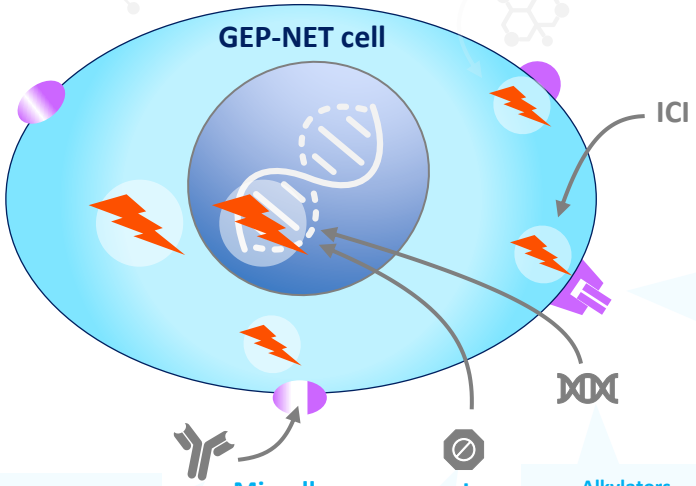
Novel agents and emerging approaches to therapy: ICIs

Other novel immunotherapy options involve SSTR-directed CAR-T cells and vaccines



SSTR bispecific antibodies
(NCT03411915;
NCT02936323)

Miscellaneous agents

CDK4/6i
Abemaciclib
(NCT03891784)

Alkylators
Lurbinectedin
+ irinotecan
(NCT02611024)

ICI (PD-1/PD-L1 axis)
Durvalumab + tremelimumab
(NCT03095274)
Nivolumab + temozolomide
(NCT03728361)
Spartalizumab (NCT02955069)
Nivolumab + ipilimumab
(NCT03420521)

ICI/VEGFRi
Atezolizumab + bevacizumab
(NCT03074513)
Avelumab + regorafenib
(NCT03475953)

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; ^{177}Lu-DOTATOC, ^{177}Lu-edotreotide; CAR, chimeric antigen receptor; CDK4/6i, cyclin dependent kinase 4/6 inhibitor; GEP, gastroenteropancreatic; ICI, immune checkpoint inhibitors; NET, neuroendocrine tumour; PD-1, programmed death-1; PD-L1, programmed cell death ligand-1; SSTR, somatostatin receptor; TKI, tyrosine kinase inhibitor; VEGFRi, vascular endothelial growth receptor inhibitor.

Clinical trials listed by their ClinicalTrials.gov identifiers. Trial information available at https://clinicaltrials.gov/ (accessed September 2021).

Das S, Dasari A. *Ther Adv Med Oncol.* 2021;13:1–15.

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IO in GEP-NECs and NENs: NIPINEC and NICE-NEC phase II trials

NIPINEC[1] (≥2L NIVO±IPI)

N=185

- Advanced refractory GEP-NECs
- Progression after ≥1 prior line including at least 1 line ChT
- GEP n=93; lung n=92

NIVO Q2W (n=91) **VS** **NIVO Q2W + IPI Q6W** (n=94)

Serious TRAEs
NIVO: 7.7%
NIVO + IPI: 10%

ORR–8-week

All patients

NIVO	NIVO+IPI
7.2% (n=83)	14.9% (n=87)

GEP-NEC cohort

NIVO	NIVO+IPI
7.1% (n=42)	11.6% (n=43)

Combination NIVO + IPI, but not NIVO alone, achieved the primary endpoint (ORR–8-week) >10% as 2L or 3L treatment

NICE-NEC[2] (1L NIVO ± ChT)

N=38

- Treatment-naive metastatic or unresectable G3 NENs
- GEP or unknown origin
- Poorly differentiated NEC: 53%
- GEP: 81.6%; pancreas: 37%; stomach: 16%; colorectum: 16%

NIVO + Platinum-based ChT Q3W (up to 6 cycles)

NIVO Q4W (maintenance up to 2 years)

8.2 mo median follow-up

DCR 84.2%

ORR 52.6%

6 mo-PFS 39%

mPFS 5.7 mo
(95% CI 5.1–7.9)

Grade ≥3 AEs in 60.5% patients
Neutropenia 52.6%
Febrile neutropenia 10.5%

Addition of NIVO to standard ChT safe and well-tolerated, with promising preliminary efficacy data

1L, first-line; 2L, second-line; 3L, third-line; AE, adverse event; ChT, chemotherapy; CI, confidence interval; DCR, disease control rate; G, grade; GEP, gastroenteropancreatic; IPI, ipilimumab; IO, immunotherapy; m, median; mo, months; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; TRAE, treatment-related AE.

1. Girard N, et al. *Ann Oncol.* 2021;32:(Suppl. 5)S1318; 2. Riesco-Martinez MC, et al. *Ann Oncol.* 2021;32(Suppl. 5):S908–9. NIPI-NEC (EudraCT 2017-003863-37) and NICE-NEC (EudraCT 2019-001546-18) available at https://www.clinicaltrialsregister.eu/ (accessed October 2021).

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FOLFIRINOX in advanced GEP-NECs

N=37
2014–2020

Tumour sites

- Colon (30%)
- Pancreas (27%)
- Oesophagus (10%)
- Rectum (10%)

- 86% WHO PS 0 or 1
- Median Ki67 80% (range 22—100%)

FOLFIRINOX received as:

- 1st-line: n=8
- 2nd-line: n=21
- ≥3rd-line: n=8

Response rates: ORR (all lines) 46%

Response	1L	2L	≥3L	Ki67 21–55%	Ki67 >55%	Total
PR	6 (75)	8 (38)	3 (37)	6 (75)	11 (38)	17 (46)
SD	2 (25)	5 (24)	1 (12)	1 (12)	7 (24)	8 (22)
PD	0	8 (38)	4 (50)	1 (12)	11 (38)	12 (32)
Total	8	21	8	8	29	37

Survival

mOS 17.8 months
(95% CI 11.4–23.3)

mPFS* 5.4 months
(95% CI 3.5–6.9) **from 1st course of FOLFIRINOX*

- **FOLFIRINOX is an active regimen for the treatment of GEP-NEC and may be considered in the treatment of advanced disease**
- **Prospective RCTs are needed**

1L, first-line; 2L, second-line; 3L, third-line; CI, confidence interval; FOLFIRINOX, fluorouracil/leucovorin/irinotecan/oxaliplatin; GEP, gastroenteropancreatic; m, median; NEC, neuroendocrine carcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; SD, stable disease; WHO PS, World Health Organization performance status.

Butt BP, et al. *Ann Oncol.* 2021;32(Suppl. 5):S915. Poster presentation at ESMO 2021 (1108P).

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Progression and treatment response: Towards an individualized approach

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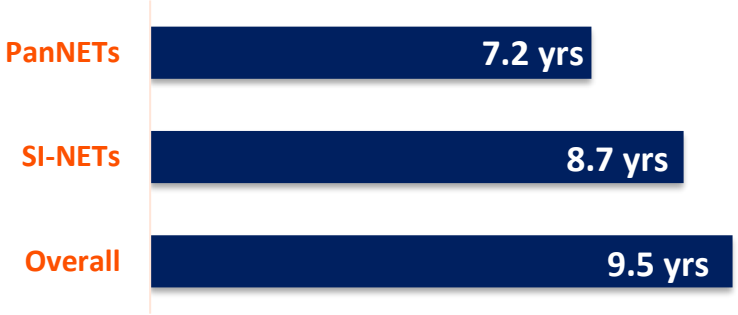
GEP-NETs: Best monitoring practice

No consensus on optimal follow-up for fully resected GEP-NETs; tailor follow-up to individual patient and disease status[1–3]

Recurrence patterns from two large patient series (N=936)[1]



	R0/R1-resected NET G1–G2	NEC G3
ESMO[2]	CT or MRI every 3–6 months + life-long follow-up	CT or MRI every 2–3 months
NCCN[3]	CT or MRI every 12 weeks to 12 months up to 1 year post-resection then every 6–12 months up to 10 yrs	CT or MRI every 3–6 months for 2 years and every 6–12 months up to 10 yrs

What is the optimal frequency of follow-up?

Small localized NETs G1 (<1 cm in size) with origin in the appendix or rectum do not need follow-up if R0-resected and no adverse histological features reported[2]

CT, computerized tomography; ESMO, European Society of Medical Oncology; G, grade; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PanNET, pancreatic NET; R0, microscopic tumour clearance; R1, cancer cells present microscopically at the primary tumour site; SI-NET, small intestine NET; yrs, years.

1. Singh S, et al. *JAMA Oncol.* 2018;4:1597–604; 2. Pavel M, et al. *Ann Oncol.* 2020;31:844; 2. NCCN. 2021. NCCN Guidelines Version 3.2021: Neuroendocrine and Adrenal Tumors [Discussion update in progress]. Available at www.nccn.org/guidelines/category_1 (accessed September 2021).

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Recommended imaging modalities for evaluating progression of GEP-NETs

In well-differentiated GEP-NETs, the choice of molecular imaging technique depends on the proliferation rate and grade of the disease

CT	Extrahepatic disease (e.g. thorax, abdomen and pelvis)
MRI	Liver metastases (detection + follow-up) Preferable to avoid radiation exposure, especially in younger patients requiring long-term serial imaging
SR-PET	Appearance and/or progression of GEP-NET lesions Follow-up well-differentiated GEP-NETs and metastases, including SSTR-positive **^{68}Ga-DOTA peptides and WB-MRI can be considered for bone metastases in patients with spine symptoms**
F-FDG-PET	Limited to patients with SSTR-negative NETs

^{68}Ga-DOTA, Gallium 68 DOTATE; CT, computerized tomography; F-FDG, ^{18}F-fluoro-D-glucose; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; PET, positron emission tomography; SR, super resolution; SSTR, somatostatin receptor; WB-MRI, whole-body MRI.

Merino-Casabiel X, et al. *Clin Transl Oncol.* 2018;20:1522–8.

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Medical oncologist-monitored care for patients with NETs

Survey of challenges in access to diagnostics and treatment for patients with NETs: EU vs NA

2,795 respondents
Sept–Nov 2019
(68 countries)

Most visited HCP:
medical oncologist
43%

80% of patients
EU and NA

GEP-NETs
most frequent primary NET:
76% EU
72% NA

Challenges

Delayed diagnosis

Stage IV NET at diagnosis:
55% EU
61% NA
46% Global

MDTs rarely used

35% EU
32% NA

Variations in practice

Treatment

- **SSA:** EU 58%; NA 57%
- **Surgery:** EU 12%; NA 21%
- **Oral ChT:** EU 15%; NA 11%
- **PRRT:** EU 12%; NA 14%

Ongoing monitoring

- **Conventional imaging:** EU 79%; NA 83%
- **CgA:** EU 64%; NA 60%

Global standard for NET monitoring and higher expertise amongst HCPs involved in NET care are needed

CgA, chromogranin A; ChT, chemotherapy; EU, Europe (including 22 countries); GEP, gastroenteropancreatic; HCP, healthcare professional; MDT, multidisciplinary team; NA, North America (USA and Canada); NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue.

Kolaraova T, et al. *Ann Oncol.* 2021;32(Suppl. 5):S917. Poster presentation at ESMO 2021 (1113P).

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