ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

REVIEW

Clinical practice guidelines for the management of non-functioning advanced GEP-NENs: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology (AIOM) in collaboration with the Italian Association for Neuroendocrine Tumors (ITANET)

F. Spada[1], F. Gelsomino[2], M. Rinzivillo[3], M. Cinquini[4], V. A. Fittipaldo[4], A. Tralongo[4], I. Moschetti[4], M. Albertelli[5,6], V. Ambrosini[7,8], V. Amoroso[9], L. Antonuzzo[10,11,12], G. Badalamenti[13], E. Bajetta[14], S. Baldari[15], M. Barberis[16], A. Berruti[9], E. Bertani[17], G. Bonomo[18], L. Bodei[19], R. Buzzoni[20], M. P. Brizzi[21], D. Campana[22,23], G. Capurso[3], R. Casadei[24], M. Castellano[25], S. Cingarlini[26], M. Cives[27,28], A. M. Colao[29,30], J. Coppa[31], N. Cremonini[32], M. V. Davì[33], C. G. De Angelis[34], F. de Braud[20,35], R. De Robertis[36], A. Faggiano[29], M. Falconi[37], M. Fassan[38,39], P. Ferolla[40], D. Ferone[5,6], A. Filice[41], F. Fiore[42], L. Funicelli[43], V. Granata[44], D. Giuffrida[45], C. M. Grana[46], F. Grimaldi[47], T. Ibrahim[48], A. La Salvia[49], A. Laghi[50], G. Luppi[2], M. Maccauro[51], R. Marconcini[52], S. Massironi[53], V. Mazzaferro[31,54], E. Merola[55], M. Milione[56], R. Modica[29], S. Ortolani[57], M. G. Papotti[58,59], S. Partelli[37], G. Pelosi[54], S. Pusceddu[20], V. Ramundo[60], D. Ravizza[61], P. Razzore[62], G. Reimondo[63], C. Ricci[64], G. Rindi[65,66], F. M. Rizzo[67], R. E. Rossi[68], S. Tafuto[69], G. A. M. Tiberio[70], A. Versari[41], R. Vigorito[43], M. C. Zatelli[71], M. Di Maio[72], F. Perrone[73], S. Cinieri[67], F. Panzuto[3]* & N. Fazio[1]*

[1]Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IEO, IRCCS, ENETS and EURACAN NEN Center of Excellence, Milan; [2]Department of Oncology and Hematology, University Hospital of Modena, Modena; [3]Digestive Disease Unit, Department of Medical-Surgical Sciences and Translational Medicine, ENETS Center of Excellence, Sant'Andrea University Hospital, Sapienza University of Rome, Rome; [4]Department of Clinical Oncology, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan; [5]Endocrine Unit, Department of Internal Medicine & Medical Specialties, University of Genova, Genova; [6]Endocrine Unit, IRCCS Ospedale Policlinico San Martino, Genova; [7]Nuclear Medicine, Alma Mater Studiorum University of Bologna, Bologna; [8]Nuclear Medicine, IRCCS Azienda Ospedaliero-Universitaria, Bologna; [9]Medical Oncology Unit, Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, ASST Spedali Civili, Brescia; [10]Clinical Oncology Unit, Careggi University Hospital, Florence; [11]Department of Experimental and Clinical Medicine, University of Florence, Florence; [12]Medical Oncology Unit, Careggi University Hospital, Florence; [13]Department of Precision Medicine in Medical, Surgical and Critical Care (Me.Pre.C.C.), University of Palermo, Palermo; [14]Istituto di Oncologia, Policlinico di Monza, Monza; [15]Department of Biomedical and Dental Sciences and Morphofunctional Imaging, Nuclear Medicine Unit, University of Messina, Messina; [16]Division of Experimental Oncology, European Institute of Oncology, IEO, IRCCS, Milan; [17]Division of Digestive Surgery IEO, European Institute of Oncology, IEO, IRCCS, ENETS and Center of Excellence, Milan; [18]Department of Interventional Radiology, European Institute of Oncology, IEO, IRCCS, ENETS and EURACAN NEN Center of Excellence, Milan, Italy; [19]Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, USA; [20]Department of Medical Oncology, Foundation National Cancer Institute, ENETS Center of Excellence, Milan; [21]Department of Oncology, 'San Luigi Gonzaga' University Hospital, University of Turin, Orbassano; [22]Department of Experimental Diagnostic and Specialized Medicine, Alma Mater Studiorum, University of Bologna, Bologna; [23]Division of Medical Oncology, IRCCS Azienda Ospedaliera-Universitaria, Neuroendocrine Tumor Team Bologna, Bologna; [24]Department of Internal Medicine and Surgery (DIMEC), Alma Mater Studiorum, University of Bologna, S.Orsola-Malpighi Hospital, Bologna; [25]Department of Internal Medicine and Endocrinology, University of Brescia, ASST Spedali Civili, Brescia; [26]Department of Medicine, Oncology, University and Hospital Trust of Verona, ENETS Center of Excellence, Verona; [27]Interdisciplinary Department of Medicine, University 'Aldo Moro', Bari; [28]Medical Oncology, AOU Consorziale Policlinico di Bari, Bari; [29]Endocrinology Unit, Department of Clinical Medicine and Surgery, Federico II University, ENETS Center of Excellence, Naples; [30]UNESCO Chair on Health Education and Sustainable Development, Federico II University, Naples; [31]Gastro-entero-pancreatic Surgical and Liver Transplantation Unit, Foundation National Cancer Institute, ENETS Center of Excellence, Milan; [32]Endocrinology Clinics, Clinica Villalba, Bologna; [33]Department of Medicine, Section of Endocrinology, University and Hospital Trust of Verona, ENETS Center of Excellence, Verona; [34]Gastroenterology and Digestive Endoscopy Unit, AOU Città della Salute e della Scienza, University of Turin, Turin; [35]Department of Oncology and Hemato-Oncology, Università deli Studi di Milano, Milan; [36]Department of Radiology, G.B. Rossi Hospital, University of Verona, Verona; [37]Pancreatic Surgery, Pancreas Translational and Clinical Research Center, San Raffaele Hospital IRCCS, Università Vita-Salute San Raffaele, ENETS Center of Excellence, Milan; [38]Department of Medicine (DIMED), University of Padova, Padova; [39]Veneto Institute of Oncology IOV-IRCCS, Padova; [40]NET Multidisciplinary Group, Umbria Regional Cancer Network, Perugia; [41]Nuclear Medicine Unit, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia; [42]Onco Interventional Radiology, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples; [43]Division of Radiology, European Institute of Oncology, IEO, IRCCS, ENETS and EURACAN NEN Center of Excellence, Milan; [44]Division of Radiology, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples; [45]Oncologia Medica, Istituto Oncologico del Mediterraneo, Viagrande, Catania; [46]Division of Nuclear Medicine, European Institute of Oncology, IEO, IRCCS, ENETS and EURACAN NEN Center of Excellence, Milan; [47]AME Past

*_Correspondence to:_ Dr Nicola Fazio, Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, ENETS GEP NEN and Lung NET Center of Excellence, EURACAN Domain G4 NET Center of Excellence, ITANET-affiliated NET Center, European Institute of Oncology, IEO, IRCCS, Via G. Ripamonti 435, 20141, Milan, Italy. Tel: +39-0257489258

E-mail: nicola.fazio@ieo.it (N. Fazio).

Dr Francesco Panzuto, Digestive Disease Unit, Department of Medical-Surgical Sciences and Translational Medicine, ENETS GEP NEN and Lung NET Center of Excellence, Sant'Andrea University Hospital, Sapienza University of Rome, Via di Grottarossa 1035, 00189, Rome, Italy. Tel: +39-0633775605

E-mail: francesco.panzuto@uniroma1.it (F. Panzuto).

2059-7029/© 2025 The Authors. Published by Elsevier Ltd on behalf of European Society for Medical Oncology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

President, Udine; [48]Osteoncology and Rare Tumor Center (CDO-TR), IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) 'Dino Amadori', Meldola; [49]National Center for Drug Research and Evaluation, National Institute of Health (Istituto Superiore di Sanità, ISS), Rome; [50]Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome—Radiology Unit—Sant'Andrea University Hospital, Rome; [51]Department of Nuclear Medicine, IRCCS Foundation National Cancer Institute, ENETS Center of Excellence, Milan; [52]Department of Medical Oncology Unit, Azienda Ospedaliero Universitaria Pisana, Pisa; [53]Fondazione IRCCS Policlinico, Divisione Gastroenterologia ed Endoscopia Digestiva, Milan; [54]Department of Oncology and Hemato-Oncology, University of Milan, Milan; [55]Gastroenterology and Digestive Endoscopy Unit, Santa Chiara Hospital, Trento; [56]First Division of Pathology, Department of Pathology and Laboratory Medicine, IRCCS Foundation National Cancer Institute, ENETS Center of Excellence, Milan; [57]Department of Oncology, Ospedale P. Pederzoli, Peschiera del Garda; [58]Unit of Pathology, Città della Salute e della Scienza, Turin; [59]Department of Oncology, University of Turin, Turin; [60]Departments of Clinical Medicine and Surgery, Federico II University, ENETS Center of Excellence, Naples; [61]Division of Endoscopy, European Institute of Oncology, IEO, IRCCS, ENETS and EURACAN NEN Center of Excellence, Milan; [62]SC Endocrinologia, Diabetologia e Malattie del Metabolismo, AO Ordine Mauriziano, Turin; [63]Internal Medicine, Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano; [64]Division of Pancreatic Surgery, IRCCS, Azienda Ospedaliero-Universitaria di Bologna, Bologna; [65]Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, Rome; [66]Anatomic Pathology Unit, Department of Woman and Child Health Sciences and Public Health, Fondazione Policlinico Universitario A. Gemelli-IRCCS, ENETS Center of Excellence, Rome; [67]Oncology and Breast Unit, Ospedale 'A. Perrino', Brindisi; [68]Gastroenterology and Endoscopy Unit, IRCCS Humanitas Research Hospital, ENETS Center of Excellence, Milan; [69]Oncologia Clinica e Sperimentale Sarcomi e Tumori Rari, Istituto Nazionale Tumori IRCCS Fondazione Pascale, ENETS Center of Excellence, Naples; [70]General Surgery, Department of Clinical and Experimental Sciences, University of Brescia, ASST Spedali Civili, Brescia; [71]Department of Medical Sciences, Section of Endocrinology, Geriatrics and Internal Medicine, University of Ferrara, Ferrara; [72]Department of Oncology, University of Turin, A.O. Ordine Mauriziano, Turin; [73]Clinical Trial Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy

Available online 12 November 2025

Neuroendocrine neoplasms (NENs) of the gastroenteropancreatic (GEP) tract represent a rare and heterogeneous group of malignancies. They are distinguished into well-differentiated and poorly differentiated neoplasms, with clinical behavior ranging from relatively indolent to fast-growing, respectively. Surgery is the curative option for localized disease, especially in well-differentiated neoplasms, while various systemic therapies are approved and clinically available for advanced disease. However, considering the complexity of these malignancies, the choice of therapeutic strategy must take into account multiple factors, such as histological diagnosis, primary site, extent of disease, evolution features, functional status, patients and treatment characteristics, treatment availability, and safety profile. A multidisciplinary approach dedicated to NENs and conducted by experienced teams is therefore strongly recommended. Since 2013, the Italian Association of Medical Oncology (AIOM), in collaboration with the Italian Association for Neuroendocrine Tumors (ITANET), has produced guidelines using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach for assessing the certainty of evidence. This updated version (2024) summarized the main diagnostic and therapeutic decision-making processes on specific topics selected by a panel of experts from the AIOM, ITANET, and other national scientific societies with the aim of guiding clinicians in the diagnosis, treatment, and monitoring of patients with GEP-NENs. The integration of these guidelines into daily clinical practice is expected to improve patient care and drive the evolving landscape of GEP-NEN management.

Key words: clinical practice guidelines, gastroenteropancreatic neuroendocrine neoplasms, GEP-NENs, AIOM, ITANET

INTRODUCTION

Neuroendocrine neoplasms (NENs) encompass a broad spectrum of rare tumors, characterized by significant biological and clinical heterogeneity. Low-grade tumors follow an indolent course, whereas high-grade tumors are associated with a poor prognosis. NENs can arise throughout the body, but most frequently originate in the gastroenteropancreatic (GEP) tract and thorax.[1] Given their ability to synthesize and secrete a large number of peptides and biogenic amines, which can lead to the development of distinct clinical syndromes, they are broadly subdivided into 'functioning' and 'non-functioning' tumors, with the latter representing the most prevalent subgroup.[2] Although historically considered rare tumors, the incidence of NENs has greatly increased over recent decades, at least in part due to improved disease knowledge, the wider use of large-scale screening programs, and advances in diagnostic tools.[3] Although their incidence is rare, owing to their indolent nature, NENs are more prevalent than gastric and pancreatic adenocarcinomas combined, thus representing a greater public health concern than previously recognized.[1,4] In recent years, significant advances have been made in the understanding of NEN epidemiology, classification, biology, diagnostics, and treatment. In particular, the therapeutic armamentarium for advanced disease has expanded, creating the new challenge of navigating an increasingly complex treatment landscape. Treatment selection must take into account multiple factors, including disease extent, growth rate, primary site, grade, functional status, and treatment characteristics, including potential side-effects. Therefore, the management of such a complex and heterogeneous disease requires a coordinated multidisciplinary approach by experienced teams. In this evolving scenario, the Italian Association of Medical Oncology (AIOM) in collaboration with the Italian Association for Neuroendocrine Tumors (ITANET) and with contributions from several other Italian scientific societies has developed evidence-based guidelines to support

professionals involved in the management of NENs in their daily clinical practice. These guidelines aim to provide a comprehensive overview of the disease picture and facilitate the adoption of updated and integrated treatment strategies. In this article, we present a summary of the main clinical recommendations for the diagnosis and therapeutic management of advanced non-functioning GEP-NENs.

METHODS

The NEN Guidelines working group (WG) has been selected by an AIOM representative, appointed as the Guideline Coordinator, and by the Chairs of the other scientific societies collaborating in this project, many of whom are also affiliated with ITANET. Multidisciplinarity was identified as one of the core criteria for establishing the WG. Accordingly, the team included oncologists, gastroenterologists, pathologists, radiologists, radiotherapists, surgeons, endocrinologists, nuclear medicine physicians, methodologists, and also patients affected by cancer. The WG selected, prioritized, and voted the population, intervention, comparison, and outcomes (PICO) questions and outcomes based on the clinical needs, ranking them by relative importance. The results of the evidence review and synthesis activities were critically assessed, and finally the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach was applied in order to formulate the recommendations ([5]; www.aiom.it).

Before the final publication on the AIOM website (www.aiom.it) and approval by the National Health Institute (ISS), the guideline was reviewed by leading external reviewers from the main Italian scientific societies (Italian Society of Gastroenterology and Endoscopy, Italian Society of Radiotherapy and Clinical Oncology, Italian Society of Nuclear Medicine, Italian Society of Endocrinology, Italian Society of Oncological Surgery, Italian Society of Medical Radiology and Interventional Radiology, Italian Society of Dermatology and Venereology, Italian Society of Endocrinology, Italian Society of Pathology, and the Italian Society for the Study of the Pancreas). The guideline is also published on the ITANET website (www.ita-net.org).

Development of clinical questions

The following clinical questions are structured according to the PICO framework.

For the purpose of this publication we selected 15 of the 56 questions included in the main NEN guideline, which are summarized in Table 1.

The outcomes were identified by the panel members as either 'critical' or 'important', based on their degree of priority.

Search strategy and selection of evidence

For each question, a systematic literature search was conducted in PubMed, Embase, and the Cochrane Library without language or date restrictions. The full search strategy is available in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105878. Key articles were cross-referenced to ensure that all relevant literature was identified. The PRISMA flowchart for each question is as also provided in the Supplementary Material, available at https://doi.org/10.1016/j.esmoop.2025.105878.

To address the proposed questions, systematic reviews or randomized controlled trials were sought. If these were not available, non-randomized studies were considered. Narrative reviews and case reports were excluded.

Certainty of evidence

Following the GRADE approach[5], the certainty of evidence was assessed for each selected outcome. The GRADE evaluation encompasses five main domains: study limitations, imprecision, indirectness, inconsistency, and publication bias. Based on the study design, the certainty level begins at a pre-specified level (high certainty for randomized controlled trials). The detection of limitations in one or more of the five domains may lead to downgrading the certainty of evidence. The final judgment is expressed as one of the following: high, moderate, low, and very low.

According to the GRADE approach, a recommendation is formulated when it receives a simple majority—defined as 50% plus one of all eligible voting panel members, i.e. those with no conflicts of interest.

The overall certainty of evidence was defined as follows:

- High (high grade of confidence in the study results): high probability that the estimated effect is similar to the true effect.
- Moderate (moderate grade of confidence in the study results): moderate probability that the estimated effect is similar to the true effect, but limited possibility that it is substantially different.
- Low (low grade of confidence in the study results): limited probability that the estimated effect is similar to the true effect, with high possibility that it is substantially different.
- Very low (very low grade of confidence in the study results): very limited probability that the estimated effect is similar to the true effect, with very high possibility that it is substantially different.

Benefit/harm balance and clinical recommendation

- For the decision making, the panel voted on one of the following options regarding the balance between benefits and harms of the intervention versus the comparison: in favor of the comparison, probably in favor of the comparison, probably in favor of the intervention, in favor of the intervention. The panel also voted on the strength of the recommendation according to the following options: strong in favor, conditional in favor, conditional against, strong against the intervention.

Table 1. Summary of clinical questions and recommendations

Question	Recommendation	Strength of recommendation	Overall certainty of evidence
1. In GEP-NET staging should [68Ga]Ga-DOTA-peptides PET—CT be preferred to [111In]In-pentetreotide scintigraphy?	In GEP-NETs staging, [68Ga]Ga-DOTA-peptides PET—CT should be considered as primary option compared with [111In]In-pentetreotide scintigraphy.	Strong in favor	Moderate
2. In patients with G2-G3 GEP-NET, should a functional characterization with the dual [68Ga]Ga-DOTA-peptides PET—CT and [18F]F-FDG —PET—CT be preferred to [68Ga]Ga-DOTA-peptide PET—CT alone?	In patients with G2-G3 GEP-NET dual [68Ga]Ga-DOTA-peptide PET—CT and [18F]F-FDG—PET—CT could be taken into account in selected cases.	Conditional in favor	Low
3. In patients with non-functioning GEP-NET who underwent radical surgery of the primary tumor, should adjuvant treatment with SSA be preferred compared with follow-up?	In patients with non-functioning GEP-NET who underwent radical surgery of the primary tumor, adjuvant treatment with SSA should not be recommended.	Conditional against	Expert opinion
4. In patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, not rapidly progressive, low Ki-67, SSTR-2-positive, should SSA be preferred to follow-up without therapy?	In patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, not rapidly progressive, low Ki-67, SSTR-2-positive, SSA should be considered as the primary option as compared with follow-up without any therapy.	Strong in favor	Moderate
5. In patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, progressive on SSA, SSTR-2-positive, should [177Lu]Lu-oxodotreotide be proposed?	In patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, progressive on SSA, SSTR-2-positive, [177Lu]Lu-oxodotreotide should be recommended.	Strong in favor	Low
6. In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, should cis/carboplatinum + etoposide be proposed as first-line systemic chemotherapy?	In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, cis/carboplatinum + etoposide should be proposed as first-line systemic chemotherapy.	Conditional in favor	Very low
7. In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC and Ki-67 > 20% e < 55%, should temozolomide-based chemotherapy be preferred to cis/carboplatinum + etoposide as first-line systemic chemotherapy?	In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC and Ki-67 > 20% e < 55%, temozolomide-based chemotherapy could be preferred to cis/carboplatinum + etoposide as first-line systemic chemotherapy.	Conditional in favor	Very low
8. In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, progressive on cis/carboplatin + etoposide first-line, should a second-line with temozolomide or irinotecan or oxaliplatin or fluoropyrimidine be preferred to best supportive care?	In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, progressive on cis/carboplatin + etoposide first-line, a second-line with temozolomide or irinotecan or oxaliplatin or fluoropyrimidine could be preferred to best supportive care.	Conditional in favor	Very low
9. In patients with advanced (locally advanced not resectable or metastatic), progressive G1-G2 Pan-NET, should a TMZ-based chemotherapy be preferred to other chemotherapies (e.g. oxaliplatin or irinotecan)?	In patients with advanced (locally advanced not resectable or metastatic), progressive G1-G2 Pan-NET, a TMZ-based chemotherapy could be preferred to other chemotherapies (e.g. oxaliplatin or irinotecan)?	Conditional in favor	Very low
10. In patients with non-functioning GEP-NEN, borderline resectable on the primary site, with concomitant liver metastases in which >90% of the liver disease is expected to be resected, should a surgical approach be preferred to a non-surgical approach?	In patients with non-functioning GEP-NEN, borderline resectable on the primary site, with concomitant liver metastases in which >90% of the liver disease is expected to be resected, a surgical approach could be preferred.	Conditional in favor	Very low
11. In patients with non-functioning GEP-NEN, should vascular interventional locoregional treatments be preferred to other therapies?	In patients with non-functioning GEP-NEN, vascular interventional locoregional treatments could be preferred to other therapies	Conditional in favor	Low
12. In patients with GEP-NETs with concomitant liver metastases, should abdominal MRI with biliary excretion be preferred to MRI or CT scan with contrast?	In patients with GEP-NETs with concomitant liver metastases, abdominal MRI with biliary excretion could be preferred to MRI or CT scan with contrast.	Conditional in favor	Low
13. In patients with GEP-NETs with concomitant liver metastases, should liver transplantation be preferred to systemic therapy?	In patients with GEP-NETs with concomitant liver metastases, liver transplantation could be preferred to systemic therapy.	Conditional in favor	Low
14. In patients with Pan-NETs well/moderately differentiated, advanced, progressive, should everolimus/sunitinib be recommended?	In patients with Pan-NETs well/moderately differentiated, advanced, progressive, everolimus/sunitinib should be recommended.	Strong in favor	Moderate

[18F]FDG, [18F]2-fluoro-2-deoxy-D-glucose; [68Ga], [68]-gallium; [111In], [111]indium; CT, computed tomography; G, grade; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasms; NET, neuroendocrine tumor; Pan-NET, pancreatic NET; PET, positron emission tomography; SSA, somatostatin analogs; SSTR, somatostatin receptor; TMZ, temozolomide.

Strength of recommendation is defined as follows:

- Strong for: the intervention should be considered as the treatment of choice (benefits are higher than risks).
- Conditional for: the intervention may be considered as the treatment of choice (not sure that benefits are higher than risks).
- Conditional against: the intervention should not be considered as the treatment of choice, except for selected cases after discussion with the patient (not sure that benefits are higher than risks).
- Strong against: the intervention must never be considered as a treatment option (risks are higher than benefits).

The AGREE-reporting checklist[6] was followed to guide the reporting of the present recommendation.

GENERAL PART

Diagnosis and characterization

Pathology. GEP-NENs are classified according to the World Health Organization (WHO) classification of digestive tumors, updated in 2022. This classification integrates both morphological (histological differentiation) and proliferative (grade) features and identifies three main groups: well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine/non-neuroendocrine neoplasms (MiNENs).[7] NETs are graded based on the proliferation index (mitotic count and/or Ki-67) and are divided into three categories [NET grade (G)1 with Ki-67 $<$ 3%, NET G2 Ki-67 3%-20%, and NET G3 Ki-67 $>$ 20%-55%]. NECs, which are by definition high-grade neoplasms, are further subdivided, according to their morphology, into small-cell and large-cell NECs. Traditional general neuroendocrine markers include synaptophysin and chromogranin A, with the former generally considered more sensitive and the latter more specific.[8] The demonstration of positivity for general neuroendocrine markers is mandatory. However, NECs may occasionally show reduced chromogranin A (CgA) expression. In NETs of unknown origin, markers such as TTF-1 (lung), CDX-2 (GEP), and Islet-1 can be useful in identifying the site of origin in the appropriate clinical context. None the less, especially in poorly differentiated neoplasms, aberrant expression of these markers may occur.[9] Staging of radically resected NENs should be reported according to the American Joint Committee on Cancer/Union for International Cancer Control (eighth edition) or ENETS staging classification.

The minimal requirements for a pathology report of a NEN are as follows:

- Tumor morphology (differentiation)
- Grading (Ki-67 and/or mitotic index)
- Immunohistochemistry for CgA and synaptophysin

For surgical specimens, the pathology report should also include the following:

- Presence of angioinvasion
- Presence of perineural invasion
- Local invasion
- TNM staging

Biochemical markers. Laboratory diagnostics play a key role in the management of NENs, especially in the following conditions:

- Carcinoid syndrome, in which measurement of the serotonin breakdown metabolite, urinary 5-hydroxyindoleacetic acid (U-5-HIAA) is particularly useful, with an overall sensitivity of 70% and specificity of 90%.[10] However, the test is subject to dietary restrictions and drug interference problems associated with the measurement of U-5-HIAA. Patients should therefore be instructed to avoid inappropriate foods and medications for 3 days before and during urine collection.[11]
- Zollinger—Ellison syndrome (ZES) diagnosis requires the demonstration of elevated fasting serum gastrin (FSG) ($>$10-fold normal) in the presence of low gastric pH.[12,13] However, elevated FSG can also be observed in other clinical conditions; therefore, the gold standard for the diagnosis of ZES is the secretin test.[14]
- Insulinoma is strongly suggested by the combination of elevated serum insulin levels ($\geq$3.0 μU/ml or 18 pmol/l), hypoglycemia ($<$55 mg/dl), and elevated C-peptide ($\geq$0.6 ng/ml) and proinsulin ($\geq$5.0 pmol/l) levels. The 72-h fast is the gold standard for diagnosing insulinoma, with a diagnostic accuracy of 100%.[15]
- Glucagonoma is strongly suggested by elevated serum glucagon levels ($>$500-1000 pg/ml) after exclusion of other clinical conditions.[15]
- CgA is considered the main general serum marker in patients with NENs.[16] Depending on tumor type, disease burden, and the assay used, its sensitivity ranges between 70% and 90%, while its specificity is extremely variable and influenced by a number of potential false positives, such as *Helicobacter pylori* infection, chronic use of proton pump inhibitors, inflammatory bowel disease, and uncontrolled hypertension.[17] For these reasons, measurement of CgA should not be used for screening in patients without a documented diagnosis of NEN, but should be reserved for the follow-up of patients with NENs.[18,19]

Morphological imaging. Imaging plays a pivotal role in diagnosis and management of NENs (Figure 1).[20] Taking into account the clinical presentation, morphological imaging aims to detect the primary tumor, define the disease stage, and monitor treatment response. Multidetector computed tomography (CT) of the thorax and abdomen, a widely available technique with a high spatial resolution, represents the most common initial imaging modality in the diagnostic work-up of a suspected NEN. Magnetic resonance imaging (MRI) is another valuable technique, offering superior intrinsic soft-tissue contrast combined with multiplanar acquisitions for improved lesion detection and characterization.[21] Furthermore, owing to its good spatial resolution and ability to scan in multiple phases of contrast enhancement, CT enteroclysis is considered the gold standard for detecting small intestine NENs, with a sensitivity of 100% and a specificity of 96%.[22]

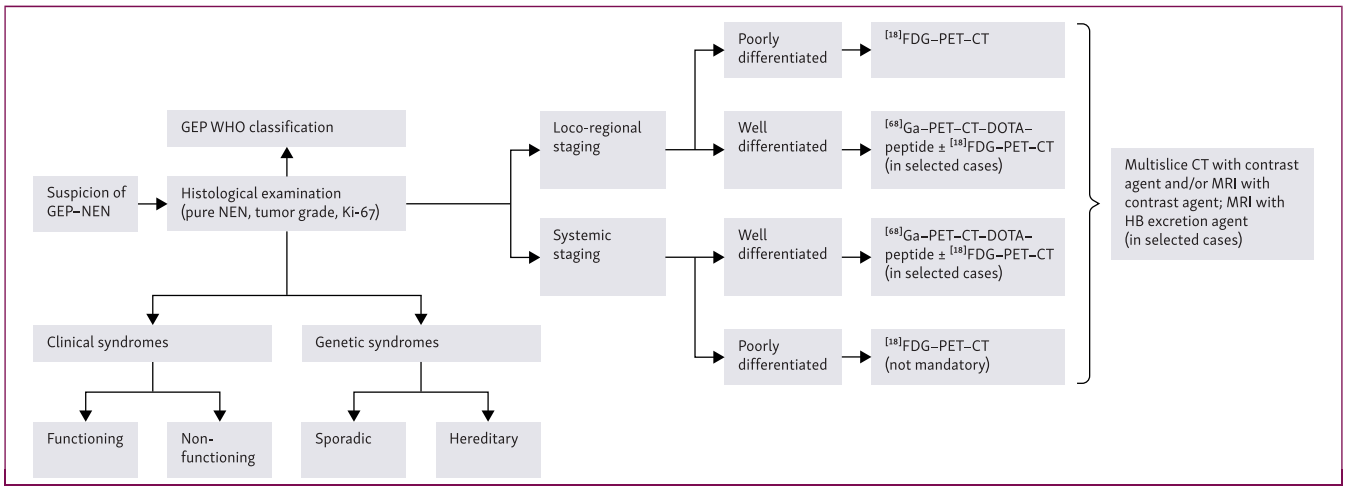

Figure 1. Diagnostic and therapeutic approach criteria in GEP-NENs.
[18]FDG, [18F]2-fluoro-2-deoxy-D-glucose; [68]Ga, [68]-gallium; CT, computed tomography; GEP, gastroenteropancreatic; HB, hepatobiliary; MRI, magnetic resonance imaging; NEN, neuroendocrine neoplasms; PET, positron emission tomography; WHO, World Health Organization.

Nuclear imaging. Nuclear imaging techniques play a pivotal role in the diagnosis and staging of NENs (Figure 1). Many NENs, especially NETs, express somatostatin receptors (SSTRs), in particular SSTR-2, on the cell surface. Over the past decades, radiolabeled somatostatin analogs (SSAs) have been developed to allow the *in vivo* demonstration of their expression. The indications for SSTR imaging in NENs include staging, localization of an occult primary tumor in patients with documented metastatic disease, identification of SSTR-2 expression in patients who may be candidates for peptide receptor radionuclide therapy (PRRT) (theranostic role), and restaging of disease.[23,24] ^{111}Indium-pentetreotide (Octreoscan®) was the first commercially approved technique for the diagnosis and staging of SSTR-2-expressing tumors and remained the gold standard technique for many years.[23] However, owing to its greater spatial resolution, lower radiation dose, and improved diagnostic accuracy, $^{[68Ga]}$Ga-DOTA-peptides positron emission tomography (PET)—CT has replaced scintigraphy as the standard imaging technique for NEN staging.[25] There are three commercially available tracers ($^{[68Ga]}$Ga-DOTA-TATE, $^{[68Ga]}$Ga-DOTA-TOC, $^{[68Ga]}$Ga-DOTA-NOC) which, despite some differences in affinity for the SSTR-2 receptors, may be considered substantially equivalent from a clinical point of view.[25] Furthermore, while [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]F-FDG)—PET—CT has an established role in NECs and in patients with negative lesions on $^{[68Ga]}$Ga-DOTA-peptides PET—CT, there is no international consensus about its use in G1-2 NETs.[26] However, in selected cases discussed within a multidisciplinary board, [^{18}F]F-FDG—PET—CT may be used, in addition to $^{[68Ga]}$Ga-DOTA-peptides PET—CT, especially in patients with G2 NETs with a high Ki-67 and in G3 NETs.

Systemic therapies approved in Italy in GEP-NENs

Somatostatin analogs. SSAs represent the mainstay of treatment for NETs and are indicated for the treatment of non-functioning advanced NETs or for controlling clinical syndromes in functioning tumors. Randomized clinical trials demonstrated the superiority of octreotide long-acting repeatable (LAR) and lanreotide LAR, respectively, over placebo in terms of time-to-progression (TTP) and progression-free survival (PFS). These are therefore indicated in patients with advanced, non-rapidly progressive, SSTR-2-positive, GEP-NETs, with a low Ki-67 index.[27-30]

Everolimus. Everolimus has been extensively studied in various types of NETs at a dose of 10 mg/day, showing efficacy, activity, and relatively good tolerability in advanced, progressive pancreatic, gastrointestinal, and pulmonary non-functioning NETs in the phase III trials RADIANT-3 and RADIANT-4.[31,32] Everolimus also demonstrated efficacy in advanced, progressive NETs of various origins with carcinoid syndrome, although these results were not statistically significant in the phase III RADIANT-2 trial.[33] Median PFS ranged from 11 months in pretreated patients (RADIANT-3) to 16.4 months in patients with few prior therapies (RADIANT-2). The most frequent G3-G4 toxicities associated with everolimus were stomatitis, hyperglycemia, pneumonitis, anemia, thrombocytopenia, diarrhea, fatigue, infections, and nausea.

Sunitinib. Sunitinib is the only tyrosine kinase inhibitor (TKI) approved for the treatment of advanced progressive pancreatic NETs (Pan-NETs) at the dose of 37.5 mg/day, based on the results of a phase III, multicenter, randomized, international trial comparing sunitinib with placebo, which demonstrated a significantly longer PFS (11.4 versus 5.5 months) in favor of sunitinib.[34] The overall response rate (ORR) was <10%; there was also a trend toward an overall survival (OS) benefit with sunitinib. The most frequent side-effects included diarrhea, nausea, asthenia, vomiting, and fatigue. Other side-effects included hypertension, lymphopenia, and changes in hair color. The results

of a phase IV trial confirmed the efficacy and safety of sunitinib in patients with advanced, well-differentiated treatment-naive or previously treated Pan-NETs.[35]

Peptide receptor radionuclide therapy. PRRT involves the systemic administration of a specific radiopharmaceutical composed of a β-emitting radionuclide chelated to a peptide designed to target receptors overexpressed on neoplastic cells, thereby delivering cytotoxic radiation to the tumor.[36] Historically, PRRT with the radiolabeled SSTR agonists $^{[90Y]}$Y-DOTA-TOC ([^{90}Y-DOTA^{0},Tyr^{3}]-octreotide) or $^{[177Lu]}$Lu-DOTA-TATE ([^{177}Lu-DOTA^{0}, Tyr^{3}, Thr^{8}]-octreotide or [^{177}Lu-DOTA^{0},Tyr^{3}]-octreotate) demonstrated clinical benefit in patients with advanced NETs overexpressing SSTR-2.[37-39] However, these results were skewed by substantial heterogeneity in dosing, regimens, number, and interval of treatment cycles, and patient inclusion criteria.[38-42] Currently, $^{[177Lu]}$Lu-oxodotreotide is the only approved radioligand therapy and is indicated for unresectable, metastatic or locally advanced, G1 or G2, SSTR-positive GEP-NETs that have progressed after SSA therapy. The recommended treatment regimen of $^{[177Lu]}$Lu-oxodotreotide consists of four infusions of 7400 MBq each. The recommended interval between each administration is 8 weeks ($\pm$1 week).[43]

Systemic chemotherapy. Chemotherapy plays a pivotal role in the treatment of high-grade NENs, especially in NECs, which, despite relative chemosensitivity, are associated with a dismal prognosis.[44] The use of a cis-carboplatin/etoposide combination in patients with distant metastases from high-grade small- or large-cell NEC, regardless of the primary tumor origin, is widely accepted, with ORRs ranging from 30% to 67% and limited median OS (11-19 months).[45,46] By contrast, the role of systemic chemotherapy in advanced NETs remains a matter of debate, and is more frequently used in Pan-NETs, depending on patient and disease characteristics. In NETs, the most common regimens are (i) temozolomide (TMZ)/capecitabine supported by various retrospective studies exploring the role of this combination in NET patients and a phase II trial in patients with advanced Pan-NETs treated with TMZ/capecitabine versus TMZ alone, which showed a PFS of 22.7 months, statistically significant for the capecitabine—TMZ arm, and an ORR of almost 40% in both arms[47]; (ii) streptozotocin—5-fluorouracil (STZ—5-FU) mostly used in Pan-NETs, as highlighted in a recently published systematic review reporting a 33% ORR, 79% disease control rate, a median PFS of 14.5 months, and a median OS of 10.9-69 months.[48] The safety profile was manageable with both combinations.

Management of liver metastases. Approximately 60%-80% of GEP-NETs are diagnosed at stage IV, with the liver being the most frequently involved organ. Therapeutic options for the treatment of liver metastases include surgery, locoregional treatments, and, in highly selected cases, liver transplantation.[49]

CLINICAL QUESTIONS

Question 1: In GEP-NET staging, should $^{[68Ga]}$Ga-DOTA-peptides PET—CT be preferred to $^{[111In]}$In-pentetreotide scintigraphy?

Recommendation: in GEP-NETs staging, $^{[68Ga]}$Ga-DOTA-peptides PET—CT should be considered as the primary option compared with $^{[111In]}$In-pentetreotide scintigraphy.

Strength of recommendation: strong in favor.

Overall certainty of evidence: moderate (due to detection bias).

Motivation/comments on the benefit/risk balance: the $^{[68Ga]}$Ga-DOTA-peptides PET—CT is the method of choice for the study of GEP-NEN lesions that express SSTR-2. Its numerous advantages (superior spatial resolution of the radiopharmaceuticals used in PET, better biodistribution, reduced costs, and ease of synthesis) over somatostatin receptors scintigraphy are the basis for the growing use of PET—CT imaging. Furthermore, the use of $^{[68Ga]}$Ga-DOTA-peptides PET—CT shows greater accuracy in lesion detection when favorable dosimetry is present. Possible false negatives are $^{[18F]}$FDG-positive and small lesions (<5 mm).

Question 2: In patients with G2-G3 GEP-NET, should a functional characterization with the dual $^{[68Ga]}$Ga-DOTA-peptides PET—CT and $^{[18F]}$F-FDG—PET—CT be preferred to $^{[68]}$Ga-DOTA-peptide PET—CT alone?

Recommendation: in patients with G2-G3 GEP-NET, dual $^{[68]}$Ga-DOTA-peptide PET—CT and $^{[18F]}$F-FDG—PET—CT could be taken into account in selected cases.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: low (due to indirectness bias).

Motivation/comments on the benefit/risk balance: no consensus exists regarding the use of $^{[18F]}$F-FDG—PET—CT in the staging and characterization of NENs, although international guidelines, mainly based on expert opinion, recommend its use in NECs, G3 NETs, and G2 NETs, especially those with a high Ki-67 and $^{[68Ga]}$Ga-DOTA-peptide-negative lesions.[23,26] Indeed, while $^{[18F]}$FDG—PET—CT enables the identification of dedifferentiated clones that may suggest a more aggressive disease course, no standardized therapeutic approach has yet been validated or recommended by international guidelines.

Question 3: In patients with localized non-functioning GEP-NET who underwent radical surgery of the primary tumor, should adjuvant treatment with SSA be preferred compared with follow-up?

Recommendation: in patients with localized non-functioning GEP-NET who underwent radical surgery of the primary tumor, adjuvant treatment with SSA should not be recommended.

Strength of recommendation: conditional against.

Overall certainty of evidence: expert opinion.

Motivation/comments on the benefit/risk balance: to date, adjuvant therapy with SSA in radically resected localized NETs has not been studied in *ad hoc* clinical trials. International guidelines, therefore, do not recommend its use in this setting.[50-52] Future clinical trials aiming to answer this clinical question are eagerly awaited.

Question 4: In patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, not rapidly progressive, low Ki-67, SSTR-2-positive, should SSA be preferred to follow-up without active therapy? (Figures 2 and 3)

Recommendation: in patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, not rapidly progressive, low Ki-67, SSTR-2-positive, SSA should be considered as the primary option as compared with follow-up without any therapy.

Strength of recommendation: strong in favor.

Overall certainty of evidence: moderate (due to indirectness bias).

Motivation/comments on the benefit/risk balance: two randomized clinical trials demonstrated a significant clinical benefit in terms of prolongation of TTP or PFS with SSAs as compared with placebo in the first-line treatment of locally advanced or metastatic NETs, irrespective of grading (G1 or G2), state of disease (stable or progressive), or hepatic tumor load (<10% or >25%), with an acceptable safety profile.[27-30]

Question 5: In patients with non-functioning, advanced (locally advanced non-resectable or metastatic) GEP-NET, progressive on SSA, SSTR-2-positive, should $^{[177Lu]}$Lu-oxodotreotide be proposed? (Figures 2 and 3)

Recommendation: in patients with non-functioning, advanced (locally advanced not resectable or metastatic) GEP-NET, progressive on SSA, SSTR-2 positive, [$_{177}$Lu] Lu-oxodotreotide should be recommended.

Motivation/comments on the benefit/risk balance: the NETTER-1 trial, a phase III study evaluating the efficacy and safety of $^{[177Lu]}$Lu-DOTA-TATE compared with high-dose octreotide LAR in patients with advanced midgut NETs, demonstrated the superiority in terms of PFS and response rate of PRRT, with a manageable safety profile. This trial led to the approval of the first radiolabeled compound in patients with advanced, progressive, SSTR-2-positive, G1-G2 GEP-NET.[53] Recently, results from the NETTER-2 trial were published. This randomized phase III trial compared $^{[177Lu]}$Lu-DOTA-TATE with high-dose octreotide LAR in patients with newly diagnosed, advanced G2 and G3 GEP-NETs (Ki-67 ≥10% and ≤55%). Median PFS was 8.5 months [95% confidence interval (CI) 7.7-13.8 months] in the control group and 22.8 months (19.4 months-not estimated) in the $^{[177Lu]}$Lu-DOTA-TATE group [stratified hazard ratio (HR) 0.276 (0.182-0.418), $P < 0.0001$]. The safety profile of PRRT was consistent with other clinical trials.[54] Since this therapy has not yet been approved in this setting, these guidelines do not provide any specific recommendations.

In 2017, a retrospective single-center analysis was published on 1214 patients with NETs of various origins treated with $^{[177Lu]}$Lu-DOTA-TATE at the Erasmus Center in Rotterdam from 2000 to 2015.[55] Of these patients, 203 had a GE-NET, 133 a pancreatic NET, and 82 a NET of unknown primary origin. The primary outcomes were PFS, TTP, and OS. After careful patient selection, efficacy data referred to 443 patients who had completed the therapy cycle, (i.e. received >600 mCi of radiopharmaceutical). Safety data were available for 610 patients (those who had received an activity of at least 100 mCi). The median follow-up time was 64 months (95% CI 58-70 months). The primary endpoint of median PFS was 29 months, median TTP 35 months, and median OS 58 months. Based on the primary tumor site, the median OS was 71 months for pancreatic NETs (PFS 31 months, TTP 31 months, partial response rate 50%), 60 months for patients with midgut NETs (PFS 30 months, TTP 42 months), 53 months for unknown primaries (PFS 29 months, TTP 37 months), and 52 months for bronchial primaries (PFS 20 months, TTP 25 months). Regarding safety, G3-G4 hematological adverse events (reduction in platelets, white blood cells, or hemoglobin) were observed in 10% of cases. Myelodysplastic syndrome was reported in 1.5% of cases and acute leukemia in 0.7% of cases.

The study has the strength of reporting real-world data from a very large patient population, including pancreatic NETs, observed over a long follow-up period in a reference center.

Question 6: In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, should cis/carboplatin + etoposide be proposed as first-line systemic chemotherapy?

Recommendation: in patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, cis/carboplatinum + etoposide should be proposed as first-line systemic chemotherapy (Figures 2 and 3).

Strength of recommendation: conditional in favor.

Overall certainty of evidence: very low (due to precision bias).

Motivation/comments on the benefit/risk balance: although the evidence is mainly based on outdated, retrospective studies, with a low number of patients enrolled and considerable heterogeneity in terms of disease characteristics, doses, and schedules administered, a combination of a platinum derivatives (cisplatin or carboplatin) and etoposide represents the conventional first-line regimen in the treatment of NECs.[44,45]

Question 7: In patients with advanced (locally advanced not resectable or metastatic) GEP-NET and Ki-67 > 20% e < 55%, should TMZ-based chemotherapy be preferred to cis/carboplatinum + etoposide as first-line systemic chemotherapy? (Figures 2 and 3).

Recommendation: in patients with advanced (locally advanced not resectable or metastatic) GEP-NET and Ki-67 > 20% e < 55%, TMZ-based chemotherapy could be preferred to cis/carboplatinum + etoposide as first-line systemic chemotherapy.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: very low (due to precision and indirectness bias).

Motivation/comments on the benefit/risk balance: over the past years, several studies have investigated large series of high-grade NENs, demonstrating that the G3 category is highly heterogeneous and encompasses a broad spectrum of different diseases.[56] The first clinical report indicating that GEP-NECs, according to the 2010 WHO classification, represent a heterogeneous category was from the Nordic group.[57] A retrospective analysis of

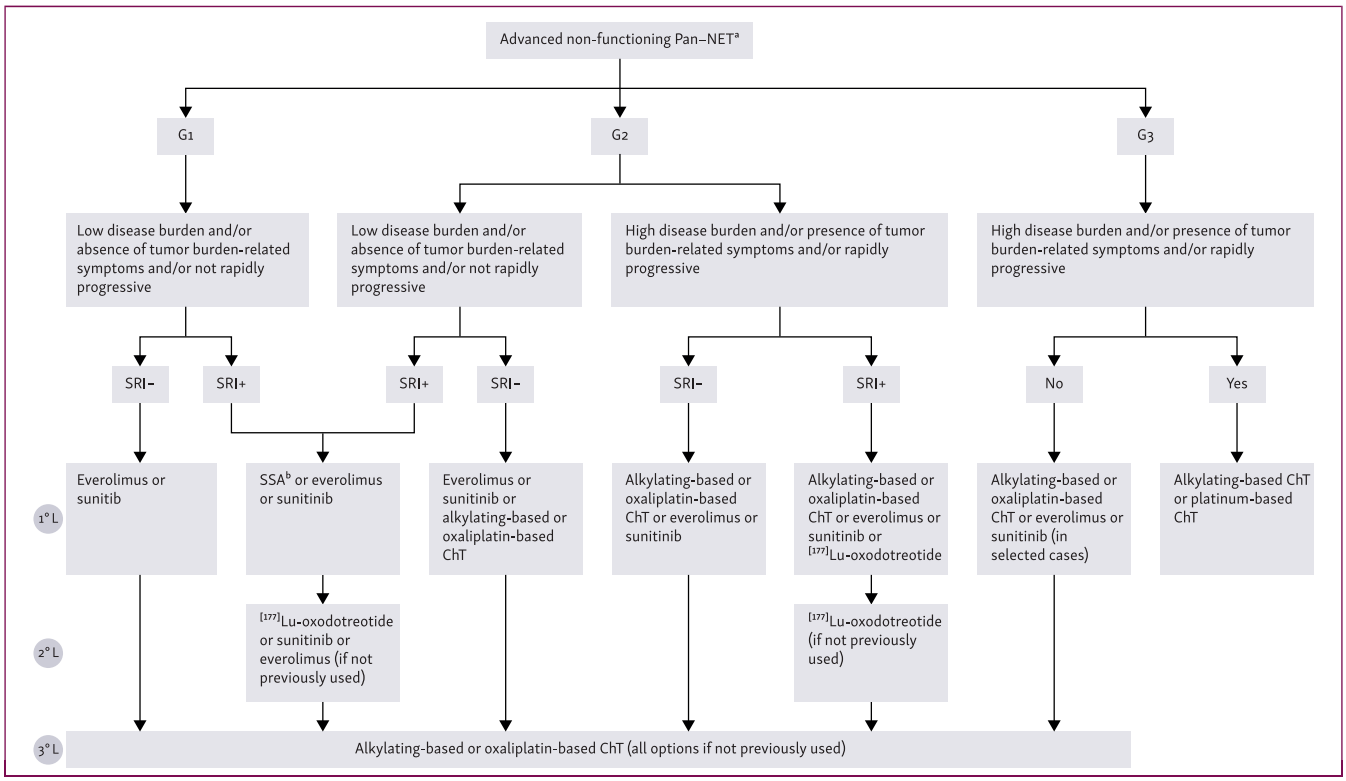

Figure 2. Therapeutic approach in advanced non-functioning Pan-NET. Cabozantinib, just EMA approved, will be a treatment option in progressive disease after at least one line of therapy beyond the SSA, as soon as it becomes available in Italy.
ChT, chemotherapy; EMA, European Medicines Agency; G, grade; NET, neuroendocrine tumor; Pan-NET, pancreatic NET; SRI, somatostatin receptors imaging; 1°L, first line; 2°L, second line; 3°L, third line; SSA, somatostatin analogs.
[a]Considering the lack of a validated sequence of therapies, enrollment in clinical trials is desirable, where available;
[b]Preferably with Ki-67 <10%.

305 patients revealed that a 55% Ki-67 threshold separated two prognostically different subgroups of GEP-NECs. Notably, OS and response rate were 14 months and 15% versus 10 months ($P < 0.05$) and 42% for <55% versus >55% Ki-67, respectively. Furthermore, this threshold identified two subgroups with different response rates and OS in association with platinum-based chemotherapy. These data were confirmed in other series, which included a review of the slides from expert pathologists.[58-60] Therefore, in patients with NEN and Ki-67 between 20% and 55%, given the lower efficacy of platinum-based combinations, alternative schedules such as TMZ-based regimens, can be clinically justified, taking into account the rarity of this subcategory and the relative difficulty in conducting well-designed, prospective clinical trials.

Question 8: In patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, progressive on cis/carboplatin + etoposide first-line, should a second-line with TMZ or irinotecan or oxaliplatin or fluoropyrimidine be preferred to best supportive care?

Recommendation: in patients with advanced (locally advanced not resectable or metastatic) GEP-NEC, progressive on cis/carboplatin + etoposide first-line, a second-line with TMZ or irinotecan or oxaliplatin or fluoropyrimidine could be preferred to best supportive care.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: very low (due to precision and indirectness bias).

Motivation/comments on the benefit/risk balance: given the rarity of this clinical context, the low level of evidence, the difficulty of conducting well-designed, prospective clinical trials, treatment with TMZ or TMZ-based schedules, fluoropyrimidines, irinotecan or oxaliplatin may be justified in patients with good performance status and preserved organ function. Enrollment in clinical trials is strongly recommended in this setting.[61-63]

Question 9: In patients with non-functioning, advanced (locally advanced not resectable or metastatic), progressive G1-G2 Pan-NET, could a TMZ-based chemotherapy be preferred to other chemotherapies (e.g. oxaliplatin or irinotecan)? (Figure 2).

Recommendation: in patients with advanced (locally advanced not resectable or metastatic), progressive G1-G2 Pan-NET, a TMZ-based chemotherapy could be preferred to other chemotherapies (e.g. oxaliplatin or irinotecan) (Figures 2 and 3).

Strength of recommendation: conditional in favor.

Overall certainty of evidence: very low (due to precision bias).

Motivation/comments on the benefit/risk balance: despite the low number of patients enrolled, given the high response rate and the manageable safety profile, TMZ-based chemotherapy (especially combined with

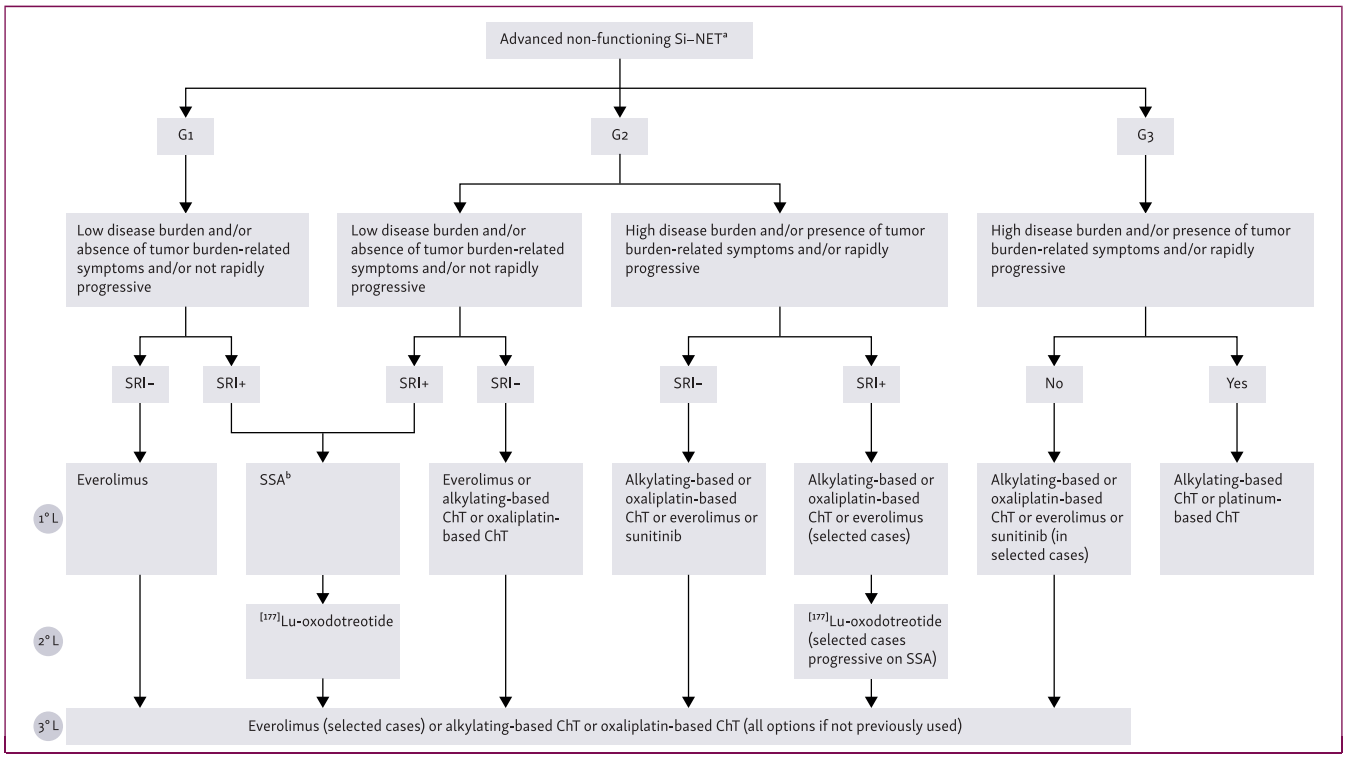

Figure 3. Therapeutic approach in advanced non-functioning Si-NET. Cabozantinib, just EMA approved, will be a treatment option in progressive disease after at least one line of therapy beyond the SSA, as soon as it becomes available in Italy. ChT, chemotherapy; EMA, European Medicines Agency; G, grade; NET, neuroendocrine tumor; Si-NET, small intestine NET; SRI, somatostatin receptors imaging; SSA, somatostatin analogs.
[a]Considering the lack of a validated sequence of therapies, enrollment in clinical trials is desirable, where available;
[b]Preferably with Ki-67 <10%.

capecitabine) could be a reasonable option in patients with progressive Pan-NETs.[47,64]

The retrospective analysis published by Strosberg et al. in 2011 in chemotherapy-naive patients with Pan-NET showed that 70% of patients (21/30) achieved an objective radiological response, with a median PFS of 18 months and a 2-year survival rate of 92%.[64] Preliminary results from a prospective phase II[47] two-arm study conducted on 145 patients with Pan-NET were also presented at the American Society of Clinical Oncology 2018, confirming the efficacy of TMZ chemotherapy and suggesting greater effectiveness of the TMZ—capecitabine combination in terms of PFS (22.7 versus 14.4 months; HR 0.58, $P = 0.023$). No difference in ORR was observed between TMZ (27.8%) and CAP—TMZ (33.3%).

The role of O(6)-methylguanine-DNA methyltransferase expression or its methylation for patient selection remains controversial and is under investigation.[47]

Preliminary data from the SEQTOR study (EudraCT: 2013-000726-66/Clinical Trial identifier: NCT02246127), a phase III, multicenter, international trial coordinated by the Spanish Neuroendocrine Tumor Group (GETNE), aimed to evaluate the efficacy and safety of the sequence of therapies, (i) everolimus and STZ—5-FU or (ii) vice versa, in patients with progressive advanced Pan-NET, were presented at the main European International Congresses in recent years, with the final data reported at the European Society of Medical Oncology Congress in 2024. The study shows that STZ—5-FU is more effective in achieving treatment responses, regardless of sequentiality, especially in patients with G2 tumors.

In clinical practice, STZ can be considered in patients with advanced G1 and G2 Pan-NETs progressing after previous therapies (GU Serie Generale n° 145 del 23-06-203) or even as upfront therapy in cases of clinical progression due to rapid disease evolution.

Question 10: In patients with non-functioning GEP-NEN, borderline resectable on the primary site, with concomitant liver metastases in which >90% of the liver disease is expected to be resected, should a surgical approach be preferred to a non-surgical approach?

Recommendation: in patients with non-functioning GEP-NEN, borderline resectable on the primary site, with concomitant liver metastases in which >90% of the liver disease is expected to be resected, a surgical approach could be preferred.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: very low (due to precision and indirectness bias).

Motivation/comments on the benefit/risk balance: despite the absence of prospective data and universally accepted criteria defining the ideal candidates to liver metastases resection in patients with GEP-NEN, liver surgery plays a crucial role in this setting. Several retrospective series have demonstrated a survival advantage of liver

resection, reporting 5-year OS rates of up to 80%. However, most patients ultimately relapse, with 5-year relapse-free survival rates below 40%.[65-68]

Question 11: In patients with liver metastases by non-functioning GEP-NEN, should vascular interventional locoregional treatments be preferred to other liver-directed therapies?

Recommendation: in patients with non-functioning GEP-NEN, vascular interventional locoregional treatments could be preferred to other liver-directed therapies.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: low (due to precision bias).

Motivation/comments on the benefit/risk balance: given the clinical and biological heterogeneity of NENs, vascular interventional treatments may be an option, with the aim of controlling disease and symptoms due to excessive hormonal production, particularly in patients with poor performance status and/or extensive liver involvement who are not eligible for liver surgery and are carefully selected after multidisciplinary discussion. To date, very few studies have compared the different techniques, including transarterial embolization, conventional transarterial chemoembolization, drug-eluting bead transarterial chemoembolization, and transarterial radioembolization with ^{90}Yttrium.[69-71]

Question 12: In patients with GEP-NETs with concomitant liver metastases should abdominal MRI with biliary excretion be preferred to MRI or CT scan with contrast?

Recommendation: in patients with GEP-NETs with concomitant liver metastases, abdominal MRI with biliary excretion could be preferred to MRI or CT scan with contrast.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: low (due to precision and indirectness bias).

Motivation/comments on the benefit/risk balance: gadoxetic acid-enhanced MRI should be recommended in routine clinical practice to improve the detection of neuroendocrine liver metastases. In particular, the combined set of diffusion-weighted and hepatobiliary phase images yields the highest sensitivity and specificity for detecting neuroendocrine liver metastasis.[72-74]

Question 13: In selected patients with GEP-NETs and concomitant liver metastases not amenable of directed liver therapies, could liver transplantation be considered compared with systemic therapy?

Recommendation: in well-selected GEP-NET patients, aged <60 years, with liver metastases and liver involvement <50%, from NET to primary site drained by the portal system radically removed, with radiologically stable disease for at least 6 months, and the absolute absence of extrahepatic disease, liver transplantation may be considered, after multidisciplinary discussion.

Strength of recommendation: conditional in favor.

Overall certainty of evidence: low (due to indirectness bias).

Motivation/comments on the benefit/risk balance: liver transplantation is an option in the management of neuroendocrine liver metastases, although no rigorous and validated selection criteria have been identified, since only retrospective or prospective non-randomized studies have been published.[75-77] Liver transplantation may be considered after multidisciplinary discussion, in young patients (<60 years of age), with a primary low-grade tumor (already removed) drained by the portal system, a liver involvement <50%, and stable disease for at least 6 months, and in the absence of extrahepatic disease.

Question 14: In patients with non-functioning Pan-NETs, well/moderately differentiated, advanced, progressive, should everolimus/sunitinib be recommended?

Recommendation: in patients with non-functioning Pan-NETs, well/moderately differentiated, advanced, progressive, everolimus/sunitinib should be recommended.

Strength of recommendation: strong in favor.

Overall certainty of evidence: moderate (due to crossover).

Motivation/comments on the benefit/risk balance: in the absence of direct comparisons among studies evaluating various therapeutic options, the main limitations of the published meta-analyses are linked to the heterogeneity of study design, response evaluation criteria, and concomitant use of SSAs. Furthermore, in some studies with PRRT, short follow-up may have led to underreporting of certain long-term adverse events. The available data on the efficacy and manageability profile of everolimus support a favorable benefit/harm ratio. However, its optimal placement within the treatment sequence for patients with Pan-NET remains to be defined.

Moreover, the data relating to the effectiveness and manageability profile of sunitinib make the benefit/harm ratio favorable. As with everolimus, their optimal placement within a treatment sequence for patients with Pan-NET remains to be defined.

FINAL CONSIDERATIONS

This work aims to summarize the main recommendations for the treatment of advanced non-functioning GEP-NENs, which are more extensively addressed in the full Italian Guidelines manuscript of the AIOM Neuroendocrine Neoplasms Guidelines, developed in collaboration with ITANET (www.aiom.it; www.ita-net.org) and other Italian scientific societies. The management of patients with GEP-NENs represents a clinical challenge; therefore, given the complexity and rarity of these neoplasms, it is strongly recommended that therapeutic strategies be discussed within a dedicated multidisciplinary team, involving experienced centers as early as possible in the patients' clinical history.

It is noteworthy that over the past 15 years, research in NENs has achieved substantial progress, reaching levels of evidence that had long been lacking due to the rarity and complexity of these diseases. Remarkable advances have been made, particularly in well-differentiated NENs, with the refinement of nuclear medicine techniques and the emergence of molecular targeted therapies. In July 2025,

the European Medicines Agency approved cabozantinib for the treatment of adult patients with unresectable or metastatic, well-differentiated pancreatic and extra-pancreatic NETs who had progressed following at least one prior systemic therapy other than SSAs. This approval was based on the results of the pivotal phase III international multicenter CABINET trial which demonstrated a 77% and 62% reduction in the risk of disease progression or death compared with placebo in advanced pancreatic and extra-pancreatic NETs, respectively. Cabozantinib, therefore, is the second TKI approved for the treatment of NETs after sunitinib, with the important distinction that cabozantinib covers a broader spectrum of tumors compared with sunitinib, including extra-pancreatic, pulmonary, and high-grade NETs of unknown primary origin (Figures 2 and 3).

However, in the absence of definite predictive markers and the paucity of comparative randomized trials, therapeutic selection in advanced disease continues to rely on the clinical features of the patients and the disease.

Several unsolved issues not addressed in these guidelines remain, including the optimal systemic therapies for advanced pure high-grade NENs; the management of MiNENs; the potential role of adjuvant therapy after radical surgery, and if so, which regimen; the use of approved drugs in contexts other than those formally indicated or in frail patients; the timing of surgery for potentially resectable liver metastases; the role of immune checkpoint inhibitors; and the role of certain prognostic markers such as plasmatic CgA and the NETest.

In this field, scientific societies play a vital role. Their task is to educate, share knowledge, foster research, and bridge the gulf that all too often separates the laboratory bench from the patient's bedside.

ACKNOWLEDGEMENTS

The authors of this guidelines are grateful to the Societies listed below which contributed to revise the main manuscripts of AIOM/ITANET guidelines over the past years: ITANET, SIGE, AIRO, AIMN, AIOT, AME, SICO, SIRM, SIDEMAST, SIE, SIAPEC, and AISP.

The authors are also grateful to Mrs Giovanna Niero[†] for her contribution as member of this working group as appointed by AIOM. The authors are also grateful to Mrs Elena Moro and AIOM secretary for the continuous assistance over the years. The authors thank Dr William Russell-Edu for English language revision.

FUNDING

None declared.

DISCLOSURES

FS has served as advisory board member and she has received speaker honoraria from Advanced Accelerator Applications, Hutchmed, Ipsen, Novartis, MSD/Merck, and Pfizer; she has served as principal investigator in Clinical Trials for GETNE, Hutchmed, Incyte, and MSD/Merck; she has received support for travel grant from Novartis and Esteve; she served as speaker honoraria for ESMO; she has non-financial interest for AIOM as she is Coordinator of Neuroendocrine Neoplasms Guidelines, Coordinator of NEN Guidelines for ITANET, member of NETs and Endocrine Tumours Faculty of ESMO, member of the ENETS advisory board, and a member of the Scientific Board of ITANET. **FG** has received honoraria for speaker/advisory roles from Servier, Eli Lilly, Iqvia, Merck Serono, Amgen, and Bristol-Myers Squibb; he has non-financial interest for AIOM as Secretary of NEN Guidelines. **MR** has non-financial interest for AIOM as past Secretary of NEN Guidelines for AIOM. **MC, VAF, AT, IM** serve as methodologist consultants for AIOM Guidelines. **MA** has non-financial interest as member of the ENETS Advisor Board. **VAmb** has served as speaker honoraria for Advanced Accelator Applications, ESMO/EANM/ESMIT, ELMIT Academy; she received travel grant from THEMA Sinergie; she has non-financial interest for ESMO as faculty member, ENETS as member of the advisory board, EANM as Oncology and Theranostic Committee, and ITANET as member of the scientific board. **Gba** has non-financial interest as he serves as member of the Director Board of ITANET. **LA** has received honoraria from AstraZeneca, Roche, Astellas, Novartis, MSD, BMS, Ipsen, Merck Serono, Amgen, and Bayer for lectures and presentation; he received support for travel grant from AstraZeneca, Novartis, Ipsen, and Merck Serono; he received institutional founding from Novartis and AstraZeneca. **LB** has served as non-remunerated consultant for Novartis, Ipsen, IBA, Great Point Partners, Point Biopharma, Rayzebio, Abdera, Fusion, Solve TX, and Wren Labs; she also has received institutional research grant from Novartis. **GC** received honoraria from Boston Scientific, Amgen, Pangenix, Viatris, and Dr. Falk. **MC** has served as advisor for Advanz, Esteve, Harbour Biomed, and Harpoon Therapeutics; he also received speaker honoraria from Novartis, Ipsen, and Istituto Gentili; he is co-inventor in patent applications filed by Moffitt Cancer Center (Tampa, FL, USA) involving adoptive immunotherapy products; he has non-financial interest as member of the ENETS Advisor Board. **AFi** has received honoraria from Novartis; she has non-financial interest as she serve as member of the Director Board of ITANET; has received honoraria and research and travel support from Ipsen, Novartis; Advanced Accelerator Applications, Recordati Rare Disease, and Istituto Gentili; he has non-financial interest for ENETS as past member of the advisory board. **MFal** has non-financial interest for AIOM as member of working group of NEN Guidelines, ITANET as Past President, and ENETS as past member of the advisory board, and President of ENETS (2016-2018); **MFas** has received honoraria from Amgen, Astellas, AstraZeneca, BMS, Diapath, Eli Lilly, GSK, Incyte, IQVIA, Jansen Pharma, MSD, Novartis, Pierre Fabre, Roche, Pfizer, and Sanofi. **CMG** has received honoraria from ITM and Novartis. **RMa** has served as advisor for Ipsen, Novartis, Sanofi, MSD, BMS, and Pierre Fabre; has

[†]Deceased

non-financial interest as he served as member of the Director Board of ITANET. **MGP** received honoraria from Eli Lilly, AbbVie, and AstraZeneca. **SP** has non-financial interest for AIOM as member of the working group of NEN Guidelines, ITANET as Secretary, and ENETS as past member of the advisory board; has received honoraria from Ipsen, Advanced Accelerator Applications, Novartis, Pfizer, Merck, and MSD. **GP** received honoraria from Roche and Sakura. **CR** has non-financial interest as he serves as member of the Director Board of ITANET. **GR** has received honoraria from Ipsen. **RER** has non-financial interest as she serves as member of the Director Board of ITANET. **ST** has served as advisor for Advanced Accelerator Applications-Novartis, Esteve, Camurus, Deciphera, Boehringer, Gentili, Ipsen, and Springworks. **SC** is past president of AIOM. **MDM** is Elect President of AIOM. **FPe** is President of AIOM; **FPa** has served as advisory board member for Mylan (Viatris) and Advanz pharma; he has served as local Principal Investigator Novartis, Camurus, and Ipsen; he has non-financial interest for AIOM as member of working group of NEN Guidelines, ITANET as Current President, and ENETS as past chair of the advisory board. **NF** has served as advisory board member for Ipsen, Personal Merck, Personal MSD, and Personal Novartis; and has served as an Invited Speaker for Steering Committee Novartis; he has served as Local Principal Investigator for Astellas, Beigene, Fibrogen, Ipsen, MSD, and Nucana; he has received research grants from Ipsen, Merck, and Novartis; he is also an internal reviewer of NET guidelines for AIOM, a member of the Board of Directors for ENETS, Elect President of ENETS, a member of the NET Faculty of ESMO, and a part of the Steering Committee of SPARC Europe. **MR, MA, VA, VA, LA, EB, SB, MB, AB, EB, GB, LB, RB, MPB, DC, GC, RC, MC, SC, MC, AMC, JC, NC, MVD, CGDA, FdB, RDR, PF, DF, FF, LF, VG, DG, FG, TI, ALS, AL, GL, MM, SM, VM, EM, MM, RM, SO, MGP, GP, SP, VR, GR, ST, AV,** and **MCZ** serve as member of the Scientific Board of ITANET. All the listed authors served as member of the working group of AIOM Guidelines. All other authors have declared no conflicts of interest.

REFERENCES

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol*. 2008;26(18):3063-3072.
2. Díez M, Teulé A, Salazar R. Gastroenteropancreatic neuroendocrine tumors: diagnosis and treatment. *Ann Gastroenterol*. 2013;26(1):29-36.
3. Rossi RE, Massironi S. The increasing incidence of neuroendocrine neoplasms worldwide: current knowledge and open issues. *J Clin Med*. 2022;11(13):3794.
4. Kunz PL. Carcinoid and neuroendocrine tumors: building on success. *J Clin Oncol*. 2015;33(16):1855-1863.
5. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406.
6. Brouwers MC, Kerkvliet K, Spithoff K, AGREE Next Steps Consortium. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. *BMJ*. 2016;352:i1152.
7. Rindi G, Mete O, Uccella S, et al. Overview of the 2022 WHO classification of neuroendocrine neoplasms. *Endocr Pathol*. 2022;33(1):115-154.
8. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? *Hum Pathol*. 2020;96:8-33.
9. Agaimy A, Erlenbach-Wünsch K, et al. ISL1 expression is not restricted to pancreatic well-differentiated neuroendocrine neoplasms, but is also commonly found in well and poorly differentiated neuroendocrine neoplasms of extrapancreatic origin. *Mod Pathol*. 2013;26(7):995-1003.
10. Meijer WG, Kema IP, Volmer M, Willemse PH, de Vries EG. Discriminating capacity of indole markers in the diagnosis of carcinoid tumors. *Clin Chem*. 2000;46(10):1588-1596.
11. Ramage JK, Ahmed A, Ardill J, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). *Gut*. 2012;61(1):6-32.
12. Oberg K, Couvelard A, Delle Fave G, et al. ENETS Consensus Guidelines for standard of care in neuroendocrine tumours: biochemical markers. *Neuroendocrinology*. 2017;105(3):201-211.
13. Berna MJ, Hoffmann KM, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. *Medicine (Baltimore)*. 2006;85(6):295-330.
14. Berna MJ, Hoffmann KM, Long SH, Serrano J, Gibril F, Jensen RT. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. *Medicine (Baltimore)*. 2006;85(6):331-364.
15. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728.
16. Deftos LJ. Chromogranin A: its role in endocrine function and as an endocrine and neuroendocrine tumor marker. *Endocr Rev*. 1991;12(2):181-187.
17. Campana D, Nori F, Piscitelli L, et al. Chromogranin A: is it a useful marker of neuroendocrine tumors? *J Clin Oncol*. 2007;25(15):1967-1973.
18. Welin S, Stridsberg M, Cunningham J, et al. Elevated plasma chromogranin A is the first indication of recurrence in radically operated midgut carcinoid tumors. *Neuroendocrinology*. 2009;89(3):302-307.
19. Oberg K. Circulating biomarkers in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer*. 2011;18(suppl 1):S17-S25.
20. Sahani DV, Bonaffini PA, Fernández-Del Castillo C, Blake MA. Gastroenteropancreatic neuroendocrine tumors: role of imaging in diagnosis and management. *Radiology*. 2013;266(1):38-61.
21. Tan EH, Tan CH. Imaging of gastroenteropancreatic neuroendocrine tumors. *World J Clin Oncol*. 2011;2(1):28-43.
22. Kamaoui I, De-Luca V, Ficarelli S, Mennesson N, Lombard-Bohas C, Pilleul F. Value of CT enteroclysis in suspected small-bowel carcinoid tumors. *AJR Am J Roentgenol*. 2010;194(3):629-633.
23. Kwekkeboom DJ, Krenning EP, Scheidhauer K, et al. ENETS Consensus Guidelines for the standards of care in neuroendocrine tumors: somatostatin receptor imaging with ^{111}In-pentetreotide. *Neuroendocrinology*. 2009;90(2):184-189.
24. Bozkurt MF, Virgolini I, Balogova S, et al. Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and 18F-DOPA. *Eur J Nucl Med Mol Imaging*. 2017;44(9):1588-1601.
25. Poeppel TD, Binse I, Petersenn S, et al. ^{68}Ga-DOTATOC versus ^{68}Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med*. 2011;52(12):1864-1870.
26. Oberg K, Krenning E, Sundin A, et al. A Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management. *Endocr Connect*. 2016;5(5):174-187.
27. Caplin ME, Pavel M, Ćwikła JB, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.

28. Caplin ME, Pavel M, Ćwikła JB, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer.* 2016;23(3):191-199.
29. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
30. Rinke A, Wittenberg M, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors (PROMID): results of long-term survival. *Neuroendocrinology*. 2017;104(1):26-32.
31. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):514-523.
32. Yao JC, Fazio N, Singh S, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016;387(10022):968-977.
33. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2011;378(9808):2005-2012.
34. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513. Erratum in: *N Engl J Med*. 2011;364(11):1082.
35. Raymond E, Kulke MH, Qin S, et al. Efficacy and safety of sunitinib in patients with well-differentiated pancreatic neuroendocrine tumours. *Neuroendocrinology*. 2018;107(3):237-245.
36. Zaknun JJ, Bodei L, Mueller-Brand J, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours. *Eur J Nucl Med Mol Imaging*. 2013;40(5):800-816.
37. Kwekkeboom DJ, Krenning EP. Peptide receptor radionuclide therapy in the treatment of neuroendocrine tumors. *Hematol Oncol Clin North Am*. 2016;30(1):179-191.
38. Yordanova A, Mayer K, Brossart P, et al. Safety of multiple repeated cycles of 177Lu-octreotate in patients with recurrent neuroendocrine tumour. *Eur J Nucl Med Mol Imaging*. 2017;44(7):1207-1214.
39. Kwekkeboom DJ, Teunissen JJ, Bakker WH, et al. Radiolabeled somatostatin analog [^{177}LuDOTA^{0},Tyr^{3}]octreotate in patients with endocrine gastroenteropancreatic tumors. *J Clin Oncol*. 2005;23(12):2754-2762.
40. Menda Y, Madsen MT, O'Dorisio TM, et al. ^{90}Y-DOTATOC dosimetry-based personalized peptide receptor radionuclide therapy. *J Nucl Med*. 2018;59(11):1692-1698.
41. Hindorf C, Chittenden S, Causer L, Lewington VJ, Mäcke HR, Flux GD. Dosimetry for ^{90}Y-DOTATOC therapies in patients with neuroendocrine tumors. *Cancer Biother Radiopharm*. 2007;22(1):130-135.
42. Bergsma H, van Lom K, Raaijmakers MHGP, et al. Persistent hematologic dysfunction after peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE: incidence, course, and predicting factors in patients with gastroenteropancreatic neuroendocrine tumors. *J Nucl Med*. 2018;59(3):452-458.
43. Panzuto F, Albertelli M, De Rimini ML, et al. Radioligand therapy in the therapeutic strategy for patients with gastro-entero-pancreatic neuroendocrine tumors: a consensus statement from the Italian Association for Neuroendocrine Tumors (Itanet), Italian Association of Nuclear Medicine (AIMN), Italian Society of Endocrinology (SIE), Italian Association of Medical Oncology (AIOM). *J Endocrinol Invest*. 2025;48(1):23-36.
44. Sorbye H, Strosberg J, Baudin E, Klimstra DS, Yao JC. Gastroenteropancreatic high-grade neuroendocrine carcinoma. *Cancer*. 2014;120(18):2814-2823.
45. Mitry E, Baudin E, Ducreux M, et al. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer*. 1999;81(8):1351-1355.
46. Fjällskog ML, Granberg DP, Welin SL, et al. Treatment with cisplatin and etoposide in patients with neuroendocrine tumors. *Cancer*. 2001;92(5):1101-1107.
47. Kunz PL, Graham NT, Catalano PJ, et al. Randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors (ECOG-ACRIN E2211). *J Clin Oncol*. 2023;41(7):1359-1369.
48. Arrivi G, Fazio N, Tafuto S, et al. The efficacy of streptozotocin in managing pancreatic neuroendocrine neoplasms - a systematic review. *Cancer Treat Rev*. 2025;134:102899.
49. Pavel M, O'Toole D, Costa F, et al. ENETS Consensus Guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology*. 2016;103(2):172-185.
50. Lamarca A, Bartsch DK, Caplin M, et al. European Neuroendocrine Tumor Society (ENETS) 2024 guidance paper for the management of well-differentiated small intestine neuroendocrine tumours. *J Neuroendocrinology*. 2024;36(9):e13423.
51. Pavel M, Öberg K, Falconi M, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(7):844-860.
52. NCCN Clinical Practice Guidelines in Oncology. Neuroendocrine and adrenal tumors. Version 1.2020. Available at www.nccn.org.
53. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med*. 2017;376(2):125-135.
54. Singh S, Halperin D, Myrehaug S, et al. [^{177}Lu]Lu-DOTA-TATE plus long-acting octreotide versus high-dose long-acting octreotide for the treatment of newly diagnosed, advanced grade 2-3, well-differentiated, gastroenteropancreatic neuroendocrine tumours (NETTER-2): an open-label, randomised, phase 3 study. *Lancet*. 2024;403(10446):2807-2817.
55. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res*. 2017;23(16):4617-4624.
56. Fazio N, Milione M. Heterogeneity of grade 3 gastroenteropancreatic neuroendocrine carcinomas: new insights and treatment implications. *Cancer Treat Rev*. 2016;50:61-67.
57. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24(1):152-160.
58. Vélayoudom-Céphise FL, Duvillard P, Foucan L, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? *Endocr Relat Cancer*. 2013;20(5):649-657.
59. Milione M, Maisonneuve P, Spada F, et al. The clinicopathologic heterogeneity of grade 3 gastroenteropancreatic neuroendocrine neoplasms: morphological differentiation and proliferation identify different prognostic categories. *Neuroendocrinology*. 2017;104(1):85-93.
60. Basturk O, Yang Z, Tang LH, et al. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. *Am J Surg Pathol*. 2015;39(5):683-690.
61. Hentic O, Hammel P, Couvelard A, et al. FOLFIRI regimen: an effective second-line chemotherapy after failure of etoposide-platinum combination in patients with neuroendocrine carcinomas grade 3. *Endocr Relat Cancer*. 2012;19(6):751-757.
62. Hadoux J, Malka D, Planchard D, et al. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer*. 2015;22(3):289-298.
63. Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C, Oberg K. Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. *Cancer*. 2011;117(20):4617-4622.
64. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer*. 2011;117:268-275.

65. Maxwell JE, Sherman SK, O'Dorisio TM, Bellizzi AM, Howe JR. Liver-directed surgery of neuroendocrine metastases: what is the optimal strategy? *Surgery*. 2016;159(1):320-333.
66. Saxena A, Chua TC, Perera M, Chu F, Morris DL. Surgical resection of hepatic metastases from neuroendocrine neoplasms: a systematic review. *Surg Oncol*. 2012;21(3):e131-e141.
67. Fairweather M, Swanson R, Wang J, et al. Management of neuroendocrine tumor liver metastases: long-term outcomes and prognostic factors from a large prospective database. *Ann Surg Oncol*. 2017;24(8):2319-2325.
68. Mayo SC, de Jong MC, Pulitano C, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol*. 2010;17(12):3129-3136.
69. Egger ME, Armstrong E, Martin RC 2nd, et al. Transarterial chemoembolization vs radioembolization for neuroendocrine liver metastases: a multi-institutional analysis. *J Am Coll Surg*. 2020;230(4):363-370.
70. Do Minh D, Chapiro J, Gorodetski B, et al. Intra-arterial therapy of neuroendocrine tumour liver metastases: comparing conventional TACE, drug-eluting beads TACE and yttrium-90 radioembolisation as treatment options using a propensity score analysis model. *Eur Radiol*. 2017;27(12):4995-5005.
71. Chen JX, Wileyto EP, Soulen MC. Randomized Embolization Trial for NeuroEndocrine Tumor Metastases to the Liver (RETNET): study protocol for a randomized controlled trial. *Trials*. 2018;19(1):390.
72. Armbruster M, Zech CJ, Sourbron S, et al. Diagnostic accuracy of dynamic gadoxetic-acid-enhanced MRI and PET/CT compared in patients with liver metastases from neuroendocrine neoplasms. *J Magn Reson Imaging*. 2014;40(2):457-466.
73. Hayoz R, Vietti-Violi N, Duran R, Knebel JF, Ledoux JB, Dromain C. The combination of hepatobiliary phase with Gd-EOB-DTPA and DWI is highly accurate for the detection and characterization of liver metastases from neuroendocrine tumor. *Eur Radiol*. 2020;30(12):6593-6602.
74. Luersen GF, Wei W, Tamm EP, Bhosale PR, Szklaruk J. Evaluation of magnetic resonance (MR) biomarkers for assessment of response with response evaluation criteria in solid tumors: comparison of the measurements of neuroendocrine tumor liver metastases (NETLM) with various MR sequences and at multiple phases of contrast administration. *J Comput Assist Tomogr*. 2016;40(5):717-722.
75. Sposito C, Droz Dit Busset M, Citterio D, Bongini M, Mazzaferro V. The place of liver transplantation in the treatment of hepatic metastases from neuroendocrine tumors: pros and cons. *Rev Endocr Metab Disord*. 2017;18(4):473-483.
76. Gedaly R, Daily MF, Davenport D, et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. *Arch Surg*. 2011;146(8):953-958.
77. Mazzaferro V, Sposito C, Coppa J, et al. The long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. *Am J Transplant*. 2016;16(10):2892-2902.