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# ENETS updates

## ENETS guidance paper for nonfunctioning pancreatic neuroendocrine tumours

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## ENETS guidance paper for appendiceal neuroendocrine tumours

* DOI: [10.1111/jne.13332](https://doi.org/10.1111/jne.13332)

## ENETS guidance paper for functioning pancreatic NET syndromes

* DOI: [10.1111/jne.13318](https://doi.org/10.1111/jne.13318)

## ENETS guidance paper for colorectal neuroendocrine tumours

* DOI: [10.1111/jne.13309](https://doi.org/10.1111/jne.13309)

## ENETS guidance paper for gastroduodenal NET G1-G3

* DOI: [10.1111/jne.13306](https://doi.org/10.1111/jne.13306)

## ENETS guidance paper for digestive neuroendocrine carcinoma

* DOI: [10.1111/jne.13249](https://doi.org/10.1111/jne.13249)

## ENETS guidance paper for carcinoid syndrome and carcinoid heart disease

* DOI: [10.1111/jne.13146](https://doi.org/10.1111/jne.13146)

## ENETS standardized (synoptic) reporting for radiological imaging in neuroendocrine tumours

This expert consensus document represents an initiative by the European Neuroendocrine Tumor Society (ENETS) to provide guidance for synoptic reporting of radiological examinations critical to the diagnosis, grading, staging and treatment of neuroendocrine neoplasms (NENs). Template drafts for initial tumor staging and follow-up by computed tomography (CT) and magnetic resonance imaging (MRI) were established, based on existing institutional and organisational reporting templates relevant for NEN imaging, and applying the RadLex lexicon of radiological information (Radiological Society of North America), for consistency regarding the radiological terms. During the ENETS Scientific Advisory Board meeting 2018, the template drafts were subject to iterative interdisciplinary discussions among experts in imaging, surgery, gastroenterology, oncology and pathology. Members of the imaging group stated a strong preference for a combination of limited and standardised options by way of drop-down menus. Separate templates were produced for the initial work-up and for follow-up, respectively. To provide a detailed description of the radiological findings of the primary tumor and its local extension and spread, different templates were developed for bronchial, pancreatic and gastrointestinal NENs for CT and MRI, respectively. Each template was structured in 10 sections: clinical details, comparative imaging modality, acquisition technique, primary tumor findings, regional lymph node metastases, distant metastases, TNM classification, reference lesions according to RECIST 1.1, additional findings and conclusion. Two templates were developed for follow-up, for CT and MRI, respectively, and were specifically focused on assessment of therapy response. These included a qualitative response assessment, such as decrease of vascularisation and presence of necrosis, and a quantitative assessment according to RECIST 1.1 and the modified RECIST (mRECIST) for assessing tumor response following transarterial chemoembolisation.

DOI: [10.1111/jne.13044](https://doi.org/10.1111/jne.13044)

## ENETS standardized (synoptic) reporting for endoscopy in neuroendocrine tumors

Despite efforts from various endoscopy societies, reporting in the field of endoscopy remains extremely heterogeneous. Harmonisation of clinical practice in endoscopy has been highlighted by application of many clinical practice guidelines and standards pertaining to the endoscopic procedures and reporting are underlined. The aim of the proposed "standardised reporting" is to (1) facilitate recognition of gastrointestinal neuroendocrine neoplasms (NEN) on initial endoscopy, (2) to enable interdisciplinary decision making for treatment by a multidisciplinary team, (3) to provide a basis for a standardised endoscopic follow-up which allows detection of recurrence or progression reliably, (4) to make endoscopic reports on NEN comparable between different units, and (5) to allow research collaboration between NEN centres in terms of consistency of their endoscopic data. The ultimate goal is to improve disease management, patient outcome and reduce the diagnostic burden on the side of the patient by ensuring the highest possible diagnostic accuracy and validity of endoscopic exams and possibly interventions.

* DOI: [10.1111/jne.13105](https://doi.org/10.1111/jne.13105)

# Reviews and Clinical Updates

## Incidence and survival of neuroendocrine neoplasia in England 1995-2018: A retrospective, population-based study

Neuroendocrine neoplasia (NEN) incidence is rising internationally. We aimed to evaluate the epidemiology of NEN in England and examine changes in survival over time.

A retrospective, population-based study using nationally representative data between 1995 and 2018 from the National Cancer Registry and Analysis Service (NCRAS) in England was conducted on 63,949 tumours. Age-standardized incidence was calculated using Office for National Statistics (ONS) data. Overall survival (OS) was calculated using the Kaplan-Meier estimator. Multivariable analysis was performed using an accelerated failure time model.

Of 63,949 cases, 50.5% (32,309) were female. Age-adjusted incidence increased 3.7-fold between 1995 and 2018 from 2.35 to 8.61 per 100,000. In 2018, highest incidence occurred in lung (1.47 per 100,000), small intestine (1.46 per 100,000), pancreas (1.00 per 100,000) and appendix (0.95 per 100,000). In multivariable analysis, age, sex, morphology, stage, site and deprivation were independent predictors of survival (p < 0.001). Survival of the entire cohort, and by primary site, is improving over time.

NEN incidence continues to rise in England with survival improving over time. Relatively high survival compared to other cancers is an issue for long-term outcomes and funding of care.

* DOI: [10.1016/j.lanepe.2022.100510](https://doi.org/10.1016/j.lanepe.2022.100510)

## Neuroendocrine Tumors: a Relevant Clinical Update

The field of neuroendocrine oncology has changed much since the time of Oberndorfer first described and coined the term carcinoid. The purpose of this review is to summarize recent findings and highlight clinically relevant updates in the management of NENs, particularly those that are practice changing.

Neuroendocrine tumors (NETs) have replaced carcinoid tumor, for the most part. The classification of neuroendocrine neoplasms (NENs) improved, and the epidemiological understanding of this disease group also expanded with global collaborations and maturation of large tumor registries. Clarity in the utility of some NET biomarkers continues to be evolving. Knowledge of molecular drivers of tumorigenesis increases, and scientific/technological advancements lead the way to multiple drug approvals for the treatment of advanced NETs. The incidence and prevalence of NENs continue to increase, and patients are living longer. Better understanding of molecular drivers and further understanding of the role of immunotherapy in NENs will further elevate the level of care and transform care for all patients with NENs.

* DOI: [10.1007/s11912-022-01217-z](https://doi.org/10.1007/s11912-022-01217-z)

## Healthcare cost by primary tumour, functioning status and treatment among patients with metastatic neuroendocrine tumours: The LyREMeNET study

The annual prevalence of metastatic neuroendocrine tumours (mNETs) is rising, leading to significant healthcare costs. The present study aimed to describe healthcare resource use (HRU) and the corresponding costs among patients with mNETs, according to primary tumour location, functioning status and type of treatments. The LyREMeNET study included consecutive mNET patients with a diagnosis performed between January 2010 and December 2017, who were seen at least once in the ENETS center of excellence in Lyon. The median HRU and costs per patient were estimated, up to 3 years before and after the diagnosis. The Cancer database of the center was linked to the French national health data system. HRU and related costs were described per person per month (PPPM). Among 316 patients presenting with a mNET, 48.4% had a small-intestinal mNET, 32.3% had a pancreatic mNET and 39.2% had carcinoid syndrome. The mean overall cost increased from €615 to €2875 PPPM between the years preceding and following the diagnosis, and remained above €2500 in the two subsequent years. The two main cost drivers of total healthcare expenditure were drugs (€1161) and hospital stay (€662). Median costs of mNETs arising from pancreas and small intestine were €2325 and €2540 PPPM, respectively. Costs were higher in patients with a functional mNET (€2807 PPPM for carcinoid syndrome) and during peptide receptor radionuclide therapy (PRRT) (€8835 PPPM). The highest overall cost was found during the first year following the diagnosis. Cost of care was higher for small intestine mNETs, for functional mNETs and during peptide receptor radionuclide therapy.

* DOI: [10.1111/jne.13092](https://doi.org/10.1111/jne.13092)

## Global challenges in access to diagnostics and treatment for neuroendocrine tumor (NET) patients

SCAN, an online survey, measured access to diagnosis, treatments and monitoring of neuroendocrine tumor (NET) patients globally. Between September and November 2019, NET patients and healthcare professionals (HCPs) completed an online, semi-standardized survey with 54 patient questions and 33 HCP questions. A total of 2359 patients with NETs and 436 HCPs responded. Misdiagnosis was common (44% [1043/2359]). Mean time to diagnosis was 4.8 years (standard deviation [SD], 6.2). Compared with global figures (60% [1407/2359]), the availability of 68 Ga-DOTA positron emission tomography (PET)/computed tomography (CT) was significantly lower in Asia (45% [126/280]) and higher in Oceania (86% [171/200]). HCPs reported that 68 Ga-DOTA PET/CT was free/affordable to fewer patients in Emerging and Developing Economies (EDE) than Advanced Economies (AE; 17% [26/150] and 59% [84/142], respectively). Compared with global data (52% [1234/2359]), patient-reported availability of peptide receptor radionuclide therapy (PRRT) was significantly lower in Asia (31% [88/280]) and higher in Oceania (61% [122/200]). Significant differences were observed in average annual NET specialist costs between AE and EDE ($1081 and $2915, respectively). Compared with AE, patients in EDE traveled further for NET specialists (1032 [SD, 1578] and 181 [SD, 496] km, respectively). Patients and HCPs both recommended referral to HCPs that were more knowledgeable in the field of NETs and had better access to NET experts/specialist centers. National care pathways, enhancing HCP NET knowledge and ensuring effective diagnostics and access to appropriate treatments are crucial to improving patient survival and NET care worldwide.

* DOI: [10.1111/jne.13310](https://doi.org/10.1111/jne.13310)

## Health-Related Quality of Life (HRQoL) in Neuroendocrine Tumors: A Systematic Review

Therapeutic advancements in neuroendocrine tumors (NETs) have improved survival outcomes. This study aims to review the impact of the current therapeutics on health-related quality of life (HRQoL) in NET patients. A literature review was performed utilizing PubMed, The Cochrane Library, and EMBASE, using the keywords "Carcinoid", "Neuroendocrine tumor", "NET", "Quality of life", "Chemotherapy", "Chemoembolization", "Radiofrequency ablation", "Peptide receptor radionucleotide therapy", "PRRT", "Surgery", "Everolimus", "Octreotide", "Lanreotide", "Sunitinib", and "Somatostatin analog". Letters, editorials, narrative reviews, case reports, and studies not in English were excluded. Out of 2375 publications, 61 studies met our inclusion criteria. The commonly used instruments were EORTC QLQ-C30, FACT G, and EORTC- QLQ GI.NET-21. HRQoL was assessed in all pivotal trials that led to approvals of systemic therapies. All systemic therapies showed no worsening in HRQoL. The NETTER-1 study was the only study to show a statistically significant improvement in HRQoL in several domains. The trial examining sunitinib versus placebo in pancreatic NETs showed no change in QoL, except for worsening of diarrhea. In addition to clinical outcomes, patient-reported outcomes are a key element in making appropriate treatment decisions. HRQoL data should be readily provided to patients to assist in shared decision-making.

* DOI: [10.3390/cancers14061428](https://doi.org/10.3390/cancers14061428)

## Management of neuroendocrine tumor liver metastases

Neuroendocrine Tumors (NETs) are a group of tumors that arise from neuroendocrine cells, and are increasing in incidence worldwide. These tumors often metastasize to the liver, and management of these neuroendocrine tumor liver metastases (NELMs) requires a multi-disciplinary approach. We aim to provide a comprehensive update for treatment of NELMs.

We completed a comprehensive systemic review of papers involving the diagnosis, treatment, and outcomes of NELMs. We identified 1612 records via Scopus database literature search. Two independent authors reviewed these records, with 318 meeting criteria for inclusion in the final systemic review.

Primary tumor resection with resection of liver metastases is the treatment of choice for patients with NELMs. Liver-directed therapies and liver transplantation can be considered for patients with unresectable liver metastases. Systemic medical therapy is used for managing tumor burden and symptoms caused by NELMs.

 Advancement in liver-directed and targeted systemic therapies provide improved options for patients with unresectable tumors. Given the complexity of NELMs, management of NELMs necessitates multidisciplinary teams at comprehensive health centers.

DOI: [10.1016/j.amjsurg.2023.08.011](https://doi.org/10.1016/j.amjsurg.2023.08.011)

## Clinicopathological and genetic characteristics of gastric neuroendocrine tumour (NET) G3 and comparisons with neuroendocrine carcinoma and NET G2

To characterise the clinicopathological and genetic characteristics of gastric neuroendocrine tumour G3 (gNET G3) and to compare them with those of gastric neuroendocrine carcinoma (gNEC) and gNET G2.

 A total of 115 gastric neuroendocrine neoplasms (NENs) were included, of which gNET G3 was different from gNET G1/G2 in terms of tumour location (P = 0.029), number (P = 0.003), size (P = 0.010), the Ki67 index (P < 0.001), lymph node metastasis (P < 0.001) and TNM stage (P = 0.011), and different from gNEC/gastric mixed neuroendocrine-non-neuroendocrine neoplasm (gMiNEN) in terms of tumour size (P = 0.010) and the Ki67 index (P = 0.001). High-resolution copy number (CN) profiling and validation experiments showed CN gains and high expression of DLL3 in gNET G3. Hierarchical clustering analysis based on CN characteristics showed that gNET G3 was separated from gNEC but mixed with gNET G2. In gene set enrichment analysis, eight pathways were significantly enriched in gNEC when comparing gNET G3 and gNEC (P < 0.05), while no pathways were enriched when comparing gNET G3 and gNET G2. Whole-exome sequencing and validation experiments showed nonsense mutation of TP53 in one gNET G3, with wild-type staining for p53. In gNEC, TP53 mutations were detected in four of eight cases, and abnormal expression of p53 was detected in all cases.

 Gastric NET G3 is a distinct entity with unique genetic characteristics, which are different from those of gNEC than gNET G2. Our results provide insight into some molecular alterations that may contribute to the development and progression of gNET G3 and serve as potential therapeutic targets.

* DOI: [10.1111/his.15002](https://doi.org/10.1111/his.15002)

## Circulating tumour cells and tumour biomarkers in functional midgut neuroendocrine tumours

CALM-NET was a phase IV exploratory study in the UK that aimed to evaluate if the presence of circulating tumour cells (CTCs) at baseline predicted symptomatic response in patients with midgut neuroendocrine tumours (NETs) treated with lanreotide autogel (LAN). Adults with functional, well/moderately differentiated (Ki-67 <20%) midgut NETs received LAN 120 mg/28 days for 1 year. CTCs were present in blood if enumeration was >0. Primary endpoint was the clinical value of baseline CTCs to predict symptomatic response (decrease in diarrhoea or flushing of ≥50% frequency, or ≥1 severity level). Other endpoints included progression-free survival (PFS) and correlations between plasma and urinary biomarkers (including 5-hydroxyindoleacetic acid [5-HIAA]). Fifty patients were enrolled; 40 completed the study. Baseline CTCs were present in 22 (45.8%) patients (missing baseline CTC status n = 2). Overall, 87.5% (95% confidence interval [CI]: 73.9; 94.5) of patients had a symptomatic response; a 5.9-fold higher odds of symptomatic response in patients without CTC versus patients with CTC at baseline was observed, although this was not statistically significant (odds ratio: 0.17 [95% CI: 0.02; 1.65], p = .126). One-year PFS rate was 66.4% (95% CI: 48.8; 79.2). Biomarker concentrations did not correlate to baseline CTC status. However, there was a strong correlation between plasma and urinary 5-HIAA (Spearman correlation coefficients ≥0.87 [p < .001], all time points). In conclusion, patients without CTC at baseline may be more likely to achieve a symptomatic response following LAN treatment than patients with CTC. Plasma 5-HIAA correlated with urinary 5-HIAA during LAN treatment. ClinicalTrials.gov identifier: [NCT02075606](http://clinicaltrials.gov/show/NCT02075606).

* DOI: [10.1111/jne.13096](https://doi.org/10.1111/jne.13096)

## Long-Term Outcomes of Liver Transplantation for the Management of Neuroendocrine Neoplasms: A Systematic Review

Liver transplantation is an uncommonly used, controversially debated therapeutic approach for highly selected individuals with neuroendocrine liver metastases. Synthesising evidence regarding outcomes from this approach is crucial to understand its position within the broad neuroendocrine liver metastases armamentarium. In this narrative systematic review of studies published in PubMed, Scopus and OVID until 1 July 2021, we summarise and critically appraise the existing literature regarding this modality, with a special focus on long-term outcomes data where possible. Fourteen studies were identified that reported outcomes from the use of liver transplantation for metastatic neuroendocrine neoplasms. No randomised trials were identified. Generally, indications and selection criteria were poorly articulated, with the notable exception of studies using the Milan criteria. The median 5-year overall survival was 65% (ranging from 36% to 97.2%, 11 studies), and the median 10-year overall survival was 50% (ranging from 46.1% to 88.8%, 3 studies). One additional study focussed on treatments and outcomes following post-transplant recurrence. No studies reported outcomes past 10 years. Further follow-up of the largest series with explicit selection criteria will deepen our understanding of the role that transplantation has to play in this setting.

* DOI: [10.3390/jpm13101428](https://doi.org/10.3390/jpm13101428)

## Long-term survival of metastatic small intestine neuroendocrine tumors: a meta-analysis

This meta-analysis aims to evaluate the long-term survival and prognostic factors in patients with metastatic small intestine neuroendocrine tumors (siNETs). Patients with siNETs usually present with advanced disease, limiting curative treatment options. The overall survival seems favorable compared to other cancers, but differences in terminology, lack of consistent coding, conflicting results from smaller cohorts, and recent developments of new treatment options make (reliable) survival data difficult to achieve. Nevertheless, accurate survival data are essential for many facets of health care. A systematic literature search was performed using MEDLINE®(PubMed), EMBASE®, Web of Science, and Cochrane Library up to June 30, 2021. Studies were included if the overall survival data in patients with metastatic siNETs were reported. The results were pooled in a random-effects meta-analysis and are reported as hazard ratios and 95% CIs. Subgroup analyses and meta-regression were performed to assess the observed heterogeneity and the impact of important prognostic factors. After screening 9065 abstracts, there were 23 studies, published between 1995 and 2021, that met the inclusion criteria, with a total of 8636 patients. The weighted 5- and 10-year overall survival was 67 and 37%, respectively. Meta-regression identified younger age and primary tumor resection to be associated with better prognosis. Subgroup analyses showed similar results. This study confirms that in an advanced, metastatic setting, the weighted 5- and 10-year overall survival reveal a favorable prognosis, improving over the last few decades. Meta-regression showed that age at diagnosis is an important prognostic factor.

* DOI: [10.1530/ERC-21-0354](https://doi.org/10.1530/erc-21-0354)

## Prognostic Factors across Poorly Differentiated Neuroendocrine Neoplasms: A Pooled Analysis

Poorly differentiated neuroendocrine carcinomas (NECs) are characterized by aggressive clinical course and poor prognosis. No reliable prognostic markers have been validated to date; thus, the definition of a specific NEC prognostic algorithm represents a clinical need. This study aimed to analyze a large NEC case series to validate the specific prognostic factors identified in previous studies on gastro-entero-pancreatic and lung NECs and to assess if further prognostic parameters can be isolated.

A pooled analysis of four NEC retrospective studies was performed to evaluate the prognostic role of Ki-67 cut-off, the overall survival (OS) according to primary cancer site, and further prognostic parameters using multivariable Cox proportional hazards model and machine learning random survival forest (RSF).

422 NECs were analyzed. The most represented tumor site was the colorectum (n = 156, 37%), followed by the lungs (n = 111, 26%), gastroesophageal site (n = 83, 20%; 66 gastric, 79%) and pancreas (n = 42, 10%). The Ki-67 index was the most relevant predictor, followed by morphology (pure or mixed/combined NECs), stage, and site. The predicted RSF response for survival at 1, 2, or 3 years showed decreasing survival with increasing Ki-67, pure NEC morphology, stage III-IV, and colorectal NEC disease. Patients with Ki-67 <55% and mixed/combined morphology had better survival than those with pure morphology. Morphology pure or mixed/combined became irrelevant in NEC survival when Ki-67 was ≥55%. The prognosis of metastatic patients who did not receive any treatment tended to be worse compared to that of the treated group. The prognostic impact of Rb1 immunolabeling appears to be limited when multiple risk factors are simultaneously assessed.

The most effective parameters to predict OS for NEC patients could be Ki-67, pure or mixed/combined morphology, stage, and site.

* DOI: [10.1159/000528186](https://doi.org/10.1159/000528186)

## Feasibility of Home Parenteral Nutrition in Patients with Intestinal Failure Due to Neuroendocrine Tumours: A Systematic Review

Maintaining adequate nutritional status can be a challenge for patients with small bowel neuroendocrine tumours (NETs). Surgical resection could result in short bowel syndrome (SBS), whilst without surgical resection there is a considerable risk of ischemia or developing an inoperable malignant bowel obstruction (IMBO). SBS or IMBO are forms of intestinal failure (IF) which might require treatment with home parenteral nutrition (HPN). Limited data exist regarding the use of HPN in patients with small bowel neuroendocrine tumours, and it is not frequently considered as a possible treatment.

A systematic review was performed regarding patients with small bowel NETs and IF to report on overall survival and HPN-related complications and create awareness for this treatment.

Five articles regarding patients with small bowel NETs or a subgroup of patients with NETs could be identified, mainly case series with major concerns regarding bias. The studies included 60 patients (range 1-41). The overall survival time varied between 0.5 and 154 months on HPN. However, 58% of patients were alive 1 year after commencing HPN. The reported catheter-related bloodstream infection rate was 0.64-2 per 1000 catheter days.

This systematic review demonstrates the feasibility of the use of HPN in patients with NETs and IF in expert centres with a reasonable 1-year survival rate and low complication rate. Further research is necessary to compare patients with NETs and IF with and without HPN and the effect of HPN on their quality of life.

* DOI: [10.3390/nu15173787](https://doi.org/10.3390/nu15173787)