Real-world presentation and outcomes of gastroenteropancreatic neuroendocrine neoplasms in Italy: findings from the nationwide Itanet prospective database

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Summary

Background The incidence of gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) is increasing, but population registries seldom capture detailed clinical data. The Italian Association for Neuroendocrine Tumours (Itanet) established a nationwide prospective database to describe presentation, diagnostic pathways, management, and outcomes of newly diagnosed GEP-NENs in Italy.

Methods This multicentre prospective observational study enrolled 2138 consecutive patients with newly diagnosed GEP-NENs across 38 Italian centres (2019–2024). Clinical, pathological, imaging, and treatment data were prospectively collected and centrally validated. Descriptive and survival analyses were performed; Ki-67 was modelled as a continuous variable.

Findings Median age was 60.6 years, and 55.9% (1195/2138) were male. Tumours were well-differentiated NETs in 90.8% of patients (1942/2138), mainly of pancreatic (41.4%, 886/2138) or ileal (19.7%, 422/2138) origin. Median Ki-67 was 2%. An incidental diagnosis occurred in 58.6% (1254/2138) of cases. Among symptomatic patients, the mean diagnostic delay was 197 days (224 for pancreatic vs 184 for small bowel; p = 0.039). ^{68}Ga-DOTA-peptide PET showed higher diagnostic yield than CT or MRI in small-bowel primaries (93.7% vs 83.1% vs 67.4%), whereas performance was similar in pancreatic tumours. Data on first-line treatment were available for 2050 patients. Initial management

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included surgery in 36.4% (746/2050), watchful waiting in 19.7% (404/2050), endoscopic resection in 7.7% (158/2050). Overall, 30.6% (627/2050) of patients received systemic therapy, most commonly somatostatin analogues in 23.7% (487/2050). Over a median follow-up of 271 days (IQR 121–530), 62 deaths were observed (event rate 4.9%). Overall survival differed markedly according to metastatic status and tumour grade. Ki-67 was prognostic when modelled continuously ($p < 0.001$), and a 15% cutoff identified poorer outcomes.

Interpretation This nationwide prospective study delineates real-world diagnostic and therapeutic patterns of GEP-NENs in Italy, confirms Ki-67 as a continuous prognostic biomarker, and identifies a 15% threshold associated with worse survival, providing a benchmark for outcome assessment and future clinical research.

Funding None.

Keywords: Neuroendocrine neoplasms; Real-world; Tumour registry; Epidemiology; Management

Research in context

Evidence before this study

Epidemiological data on gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) primarily derive from population-based registries, such as national cancer databases, which often lack detailed clinical, pathological, and management information. Available reports are largely retrospective and heterogeneous, with limited detail on tumour grading, imaging performance, and therapeutic pathways, and few provided prospective nationwide data.

Added value of this study

This study represents the largest prospective nationwide database capturing detailed, real-world data on newly diagnosed GEP-NENs across Italy. The systematic enrolment of more than 2000 patients provides valuable insight into diagnostic pathways, imaging performance, treatment allocation, and early outcomes. The database also enables comparisons between pancreatic and non-pancreatic primaries, as well as across tumour grades, in a contemporary, unselected population. These findings expand the evidence base beyond retrospective or population-level registries by offering prospective, high-quality data that reflect routine clinical practice.

Implications of all the available evidence

The Itanet database demonstrates that prospective, standardised data collection at the national level is feasible for rare tumours such as GEP-NENs. When combined with existing evidence, these data highlight significant heterogeneity in diagnostic approaches and treatment allocation, support the use of Ki-67 as a continuous prognostic biomarker, and provide a benchmark for harmonising real-world management and informing future international collaborative registries.

Introduction

Neuroendocrine neoplasms (NENs) are rare diseases, yet their incidence has significantly increased over the past decades across all primary tumour sites, including gastroenteropancreatic (GEP) origins.[1] The progression of these neoplasms is influenced by numerous factors, with grading being the most significant.[2] According to the World Health Organisation (WHO) classification, NENs are categorised based on tumour cell morphology and the Ki-67 proliferation index.[3] Well-differentiated neuroendocrine tumours (NETs) are classified as G1, G2, and G3, depending on the proliferation rate. Specifically, G1 NETs have a Ki-67 index of less than 3%, G2 NETs have a Ki-67 index between 3% and 20%, while G3 NETs exhibit a Ki-67 index greater than 20%. In contrast, neuroendocrine carcinomas (NECs), which are poorly differentiated and inherently high-grade, typically show a Ki-67 index exceeding 20%.

Beyond grading, prognosis and treatment selection are influenced by tumour site, disease extent, somatostatin receptor expression, and functional status. Management ranges from surgery or endoscopic resection of localised disease to systemic options for advanced cases, including somatostatin analogues (SSA), targeted therapies, radioligand therapy (RLT), and chemotherapy[4,5]

Epidemiological data on GEP-NENs largely derive from retrospective registries,[6–9] which, although informative, often lack grading and detailed clinical variables, leading to misclassification and limiting their applicability to real-world settings.[10] In Italy, the 2015 national registry reported an incidence of 2 per 100,000,[11] but an unexpectedly high proportion of NECs. A subsequent review reclassified 33% of these cases as NET G1 and 25% as NET G2,[12] underscoring the limitations of ICD-based coding in such a heterogeneous disease. These discrepancies highlight the

need for prospective, clinically oriented data collection. To address this, the Italian Association for Neuroendocrine Tumours (ITANET) launched a national, multicentre, prospective database in 2019[13] to capture the presentation, clinicopathological features, management, and long-term outcomes of newly diagnosed GEP-NENs.

This study presents data from the first five years of the ITANET database, aiming to describe the clinical presentation, pathological features, and diagnostic–therapeutic approaches, including real-world management and follow-up, of newly diagnosed GEP-NEN patients across Italy.

Methods

Study design

This prospective, multicentre observational study involved 38 Italian centres within the ITANET network, including all eight national ENETS Centres of Excellence and four EURACAN-certified centres for NENs. Patient management was multidisciplinary across centres, which were led by medical oncology (n = 22), endocrinology (n = 7), surgical (n = 5), gastroenterology (n = 2), or nuclear medicine (n = 2) units. Recruitment began in May 2019, with the first patient enrolled in October 2019. The study was registered at ClinicalTrials.gov (NCT04282083); the list of participating centres is provided in Supplemental Figure S1.

As part of the initial framework, a subset of data from approximately 200 patients had previously been entered into the international ENETS Registry. Following a suspension of data acquisition within the ENETS platform, an amendment to the original protocol enabled ITANET to migrate these cases into a dedicated national database, allowing for continued prospective data collection and updates without interruption.

Based on protocol projections, the estimated target enrolment was 3600 patients over three years. This target was defined a priori in the registered protocol based on feasibility considerations and expected case volume at participating centres. For the present report, data were locked on 1 August 2024, a time point proposed by ITANET and agreed upon by all participating centres to allow analysis over a sufficiently mature and methodologically coherent observation period, while ensuring high completeness and validation of key clinical variables across the network.

The current analysis, therefore, includes all consecutively enrolled patients with fully validated data available at the time of database lock, representing the complete national cohort accrued within the study period defined for this report.

Participants

The study enrolled all patients with GEP-NENs whose histological diagnosis was confirmed within 12 months prior to enrolment. Inclusion criteria were: age ≥18 years; histologically or cytologically confirmed NEN diagnosis, or a diagnosis supported by positive somatostatin receptor imaging together with at least one second-level contrast-enhanced imaging modality (CT scan or MRI); grading G1, G2, or G3 according to the 2019 WHO classification (including both well-differentiated and poorly differentiated neoplasms); and signed informed consent.

Patients with metastatic disease of unknown primary origin were also included, provided that comprehensive radiological and nuclear medicine staging, together with immunohistochemical profiling, was consistent with a digestive origin. An incidental diagnosis was defined as the identification of a GEP-NEN in asymptomatic patients undergoing imaging or endoscopic procedures for reasons unrelated to the tumour.

Procedures

Data were collected using a standardised national web-based case report form with pseudo-anonymised identifiers and centrally validated according to predefined quality control procedures.[13] Completeness and accuracy were ensured through technical and medical manual validation; each case was definitively recorded only after any queries raised with the participating centre were resolved. The database was updated after each follow-up visit, in accordance with routine clinical practice.

Outcome

The primary outcome of this study was to describe the real-world clinical presentation, pathological features, and management of patients with newly diagnosed GEP-NENs across Italian centres participating in the ITANET database. This included characterisation of tumour site, grade, functional status, diagnostic imaging performance, and initial therapeutic approaches.

Secondary outcomes were overall survival (OS), defined as the time from histological diagnosis to death from any cause or last follow-up; progression-free survival (PFS), defined as the time from diagnosis or radical surgery to radiological or clinical progression or death; and recurrence-free survival (RFS), defined as the time from curative-intent surgery to radiological or clinical recurrence or death from any cause. Only patients with a valid date of diagnosis and at least one recorded follow-up at the time of database lock were included in overall survival analyses. For PFS and RFS analyses, patients were classified into two predefined cohorts: Cohort A included patients with metastatic disease at diagnosis, whereas Cohort B included patients with non-metastatic disease undergoing curative-intent surgery.

Exploratory analyses evaluated the association between the Ki-67 index and survival outcomes, as well as treatment sequencing in patients who progressed after first-line therapy.

Statistical analysis

Categorical variables were summarised as counts and percentages (using available-case denominators), and continuous variables as medians with 95% CIs. Diagnostic intervals were defined as the time from diagnosis to subsequent key clinical milestones and were summarised as means with standard errors (SE) and 95% confidence intervals (CI). Differences between pancreatic and small bowel neuroendocrine neoplasms were assessed using a two-sided Mann–Whitney U test ($\alpha = 0.05$). Imaging outcomes were tabulated as percentages of the total number of examinations. Diagnostic yield was defined as the probability of obtaining a pathological (positive) imaging result.

Comparative diagnostic yield across imaging techniques and primary tumour sites was analysed using a logistic mixed-effects model, with imaging result (positive vs negative or uncertain) as the dependent variable. Imaging technique (CT, MRI, ^{68}Ga-DOTA-peptide PET), primary tumour site (pancreas vs small bowel), and their interaction were included a priori as fixed effects, with random intercepts for patient ID and recruiting centre to account for repeated measures and centre-level clustering. Fixed-effect inferences were based on Wald χ^2 tests; in the presence of a significant interaction, post-hoc pairwise comparisons were performed within each tumour site with Holm-adjusted p-values.

Treatment strategies were described in terms of counts and percentages.

Overall survival was estimated using the Kaplan–Meier method, with censoring at last follow-up; survival probabilities at 3 years were reported with 95% CIs. Restricted mean survival time (RMST) and corresponding 95% CIs were calculated up to a prespecified horizon ($\tau = 3$ years) using a Kaplan–Meier–based approach, to provide an absolute and clinically interpretable summary of survival, particularly when median survival was not reached, or follow-up was limited. Associations with OS were explored using Cox proportional hazards regression.

Univariable analyses included metastatic status (M0 vs M1), ENETS stage (I–III vs IV), tumour site (pancreatic vs non-pancreatic), tumour grade, and Ki-67. Ki-67 was modelled both as a continuous variable (hazard ratio per 1% increase) and, exploratorily, as a dichotomous variable using a cutoff derived from maximally selected rank statistics, which was applied in Kaplan–Meier, log-rank, and Cox analyses. Survival differences by tumour grade (NET G1, NET G2, NET G3, NEC) were assessed using Kaplan–Meier curves, log-rank tests, and univariable Cox regression with NET G1 as the reference category. Statistical significance in Cox models was assessed using Wald tests.

A multivariable Cox model including ENETS stage and Ki-67 as a continuous covariate was fitted to jointly account for disease extent and biological aggressiveness, with a shared frailty term for centre to account for clustering. Proportional hazards assumptions were assessed using Schoenfeld residuals and graphical diagnostics.

PFS was analysed using Kaplan–Meier estimates and compared between pancreatic and non-pancreatic primaries using Cox regression, reporting hazard ratios and 95% CIs. All analyses were conducted using a complete-case approach. Statistical analyses were performed using R (version 4.3.3).

Ethics approval

The ethics committee of each of the 38 participating centres approved the study. Every included patient provided written informed consent, which was retained at the centre where the patient was enrolled. This study adheres to the STROBE guidelines[14] to ensure comprehensive and transparent reporting of this observational research.

Role of the funding source

The present study received no external funding.

Results

A total of 2138 subjects were included, of whom 1195 (55.9%) were males and 943 (44.1%) were females, with a median age of 60.6 years (95% CI 60.0–61.2). Regarding functional status, 1948 (91.1%) tumours were non-functioning (NF), while the remaining 190 (8.9%) were associated with a specific hormonal syndrome and were thus considered functioning (F). Of these, 88 (4.1% of total patients, 46% among the F tumours) had carcinoid syndrome, which was accompanied by carcinoid heart disease in 6 cases (6.8% of those with carcinoid syndrome). Among patients with NF tumours, 694 (35.6%) presented with non-specific symptoms such as pain, weight loss, jaundice, or nausea. The ECOG performance status score at diagnosis was available for 1984 patients, detailed as follows: ECOG 0 (1,780, 89.7%), ECOG 1 (172, 8.7%), ECOG 2 (24, 1.2%), and ECOG 3 (8, 0.4%).

Regarding the primary tumour site, the most common sites were the pancreas (886, 41.4%), the ileum (422, 19.7%), the stomach (171, 8%), and the rectum (109, 5.0%). The primary site was unknown in 264 cases (12.3%). As far as tumour grading is concerned, data were available in 2030 patients. Ki-67 was assessed on surgical specimens in 823 patients (40.5%) and on biopsies in 1207 (59.5%) and derived from the primary tumour in 1348 cases (66.4%) or from metastases in 682 (33.6%); the highest value was recorded when multiple assessments were available. Overall, 1942 patients (90.8% of the whole cohort) had a well-differentiated NET. Among those with available grading, G1, G2 and G3 tumours accounted for 59.9% (1217), 31.1% (632), and 4.6% (93), respectively. Overall,

the mean Ki-67 value was 7.9% (SE = 0.386; 95% CI 7.19–8.70), whereas the median Ki-67 value was 2%.

Of the 2053 patients for whom tumour stage information (referred to radiological or pathological staging according to the ENETS staging system) was available, 645 (31.4%) were classified as stage 1 (pancreatic 373 pts vs non-pancreatic 272 pts), 258 (12.6%) as stage 2A (pancreatic 171 pts vs non-pancreatic 87 pts), 90 (4.4%) as stage 2B (pancreatic 45 pts vs non-pancreatic 45 pts), 17 (0.8%) as stage 3A (pancreatic 5 pts vs non-pancreatic 12 pts), 292 (14.2%) as stage 3B (pancreatic 62 pts vs non-pancreatic 230 pts), and 751 (36.6%) as stage 4 (pancreatic 282 pts vs non-pancreatic 469 pts). The patients' clinicopathologic characteristics are summarised in Table 1.

The total number of patients with incidental diagnoses was 1254 (58.6% of the total population). Among them, 599 (47.8%) had pancreatic tumours, 189 (15.1%) had small bowel tumours, and 466 (37.1%) had tumours from other locations.

In patients who were symptomatic at presentation, including those with F NENs and those with NF NENs presenting with non-specific symptoms, the mean time from symptom onset to diagnosis was 197 days (SE = 17.6; 95% CI 163–232). Specifically, for pancreatic NENs, the mean interval was 224 days (SE = 29.6; 95% CI 165–282), while for small bowel NENs, it was 184 days (SE = 26.9; 95% CI 131–237). A statistically significant difference was observed in the time interval between symptom onset and diagnosis between the two sites (U = 20,487, p = 0.039).

Second primary malignancies were observed in 317 patients (14.8%), including 111 synchronous (35.0%) and 206 metachronous (65.0%) cancers. The most frequent sites were breast (n = 57, 18.0%), colorectal (n = 42, 13.2%), prostate (n = 40, 12.6%), haematological (n = 28, 8.8%), genitourinary (n = 23, 7.3%), melanoma (n = 22, 6.9%), renal (n = 16, 5.0%), thyroid (n = 14, 4.4%), lung (n = 13, 4.1%), and pancreatic (n = 9, 2.8%) cancers.

Regarding radiological examinations performed at diagnosis, 761 patients (86.3%) with pancreatic NENs and 344 (81.5%) with small bowel NENs underwent contrast-enhanced (CE) CT. Overall, 734 patients (96.5%) in the pancreas group had a pathological finding on imaging, 19 (2.5%) a negative result, and 8 (1.0%) an uncertain finding. In the small bowel group, 286 patients (83.1%) had a pathological finding, 48 (14.0%) a negative result, and 10 (2.9%) an uncertain finding.

CE-MRI was performed in 428 patients (48.5%) with pancreatic NENs and 95 (22.5%) with small bowel NENs. In the pancreas group, 401 patients (93.7%) had a positive result, 21 (4.9%) a negative result, and 6 (1.4%) an uncertain finding. In the small bowel group, 64 patients (67.4%) had a positive result, 28 (29.5%) a negative result, and 3 (3.1%) an uncertain finding.

N.of patients	Total (n = 2138)	%
Gender		
Male	1195	55.9
Female	943	44.1
Age	60.6 (60.0–61.2)	
Primary tumour localisation		
Pancreas	886	41.4
Small Bowel	422	19.7
Stomach	171	8
Rectum	109	5.0
Appendix	104	4.8
Colon	50	2.3
Unknown origin	264	12.3
Other	132	6.1
Grading according to WHO[a]		
NET G1	1217	59.9
NET G2	632	31.1
NET G3	93	4.6
NEC	77	3.8
MiNEN	11	0.5
Median Ki-67	2%	
Staging[b]		
Stage I	645	31.4
Stage II	348	16.9
Stage III	309	15.1
Stage IV	751	36.6
Site of metastases		
Liver	556	26.0
Lymph nodes	520	24.3
Bone	77	3.6
Peritoneum	87	4.1
Other	30	1.4
Patient with functional syndrome associated	190	8.9
Carcinoid Syndrome	88	4.1
Insulinoma	71	3.3
Gastrinoma/ZES	17	0.8
Other	14	0.6

Data are n and %, median (IQR). [a]Data available in 2030 patients. [b]Data available in 2053 patients.

Table 1: **Patients' general features.**

As far as ^{68}Ga-DOTA-peptide PET is concerned, 606 patients (68.7%) with pancreatic NENs and 255 (60.4%) with small bowel NENs underwent the procedure. Among these, 584 patients (96.4%) in the pancreas group had a positive result, 19 (3.1%) a negative result, and 3 (0.5%) an uncertain finding. In the small bowel group, 239 patients (93.7%) had a positive result, 14 (5.5%) a negative result, and 2 (0.8%) an uncertain finding.

The diagnostic yield of CT, MRI, and ^{68}Ga-DOTA-peptide PET varied by primary tumour location (Fig. 1), with a significant interaction between imaging technique and tumour site ($\chi^2(2) = 52.25$, $p < 0.001$). Among patients with pancreatic NENs, no statistically significant differences in diagnostic yield were observed between imaging techniques. MRI showed higher odds of

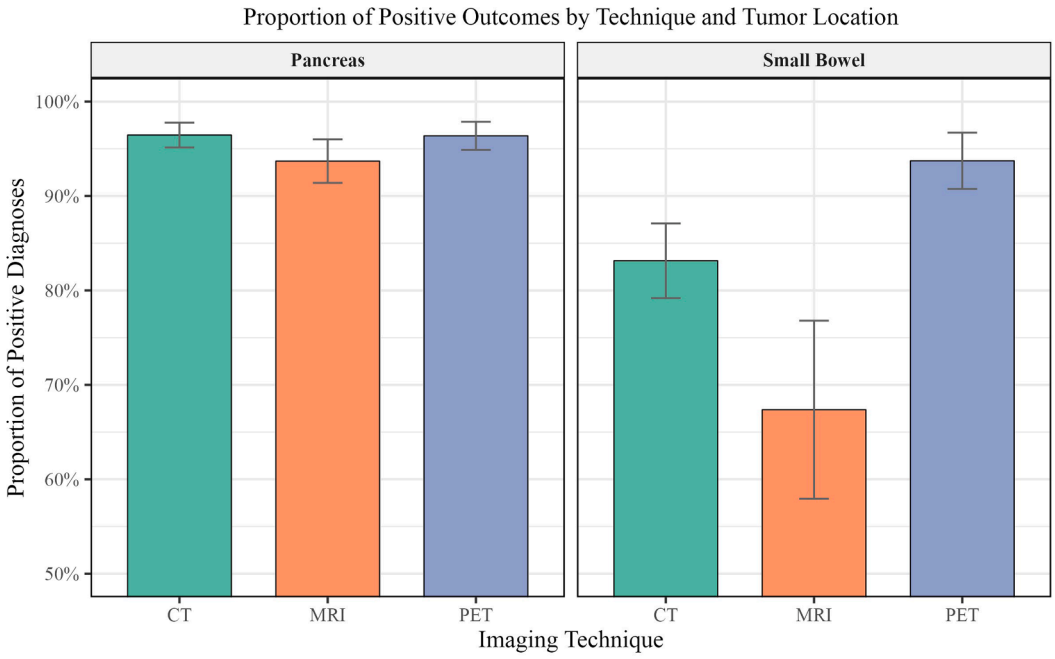

***Fig. 1:* Proportion of positive imaging results by primary tumour site.** Bar charts show the proportion of positive diagnostic findings obtained with CT, MRI, and PET (^{68}Ga-DOTA-peptide PET) according to the primary tumour location (pancreas vs small bowel). Error bars indicate 95% confidence intervals.

a positive finding compared with CT (OR = 3.44, 95% CI 0.95–12.46; p = 0.065), while ^{68}Ga-DOTA-peptide PET performed similarly to CT (OR = 1.64, 95% CI 0.46–5.83; p = 0.353) and MRI (OR = 0.48, 95% CI 0.13–1.76; p = 0.350). In small bowel NENs, ^{68}Ga-DOTA-peptide PET showed a clear diagnostic advantage. ^{68}Ga-DOTA-peptide PET was associated with significantly higher odds of a positive finding compared with CT (OR = 0.003, 95% CI 0.0005–0.016; p < 0.001) and MRI (OR = 0.001, 95% CI 0.0002–0.009; p < 0.001), whereas no significant difference was observed between CT and MRI (OR = 2.09, 95% CI 0.53–8.26; p = 0.20).

Data on first-line treatment were available for 2050 patients. The most common initial therapeutic approach was surgery, performed in 746 cases (36.4%). A total of 404 patients (19.7%) were managed with a watchful waiting strategy. Most of these patients had pancreatic primary tumours (300, 74.3%), followed by gastric (63, 15.6%), duodenal (21, 5.2%), and rectal NENs (20, 5.0%); the majority had non-metastatic disease at diagnosis, with only 4% presenting with metastatic disease. Endoscopic resection was adopted in 158 cases (7.7%). Among the 746 patients who underwent surgery, 307 (41.1%) had pancreatic NEN, 214 (28.7%) had ileal, 86 (11.5%) had appendiceal, 25 (3.4%) had colonic, 24 (3.2%) had duodenal, 21 (2.8%) had gastric, and 17 (2.3%) had rectal NENs. An additional 52 (7%) patients had tumours located in other sites, including the peritoneum, gallbladder, and oesophagus. Of the patients who underwent surgery with curative intent (n = 697), 632 (90.7%) achieved an R0 resection, 303 of whom had pancreatic NENs, while the remaining cases involved other sites. Conversely, 59 patients (8.5%), including 36 with pancreatic NENs, underwent an R1 or R2 resection; data were unavailable for 6 patients (0.9%).

Overall, 627 patients (30.6%) received systemic first-line therapy after NEN diagnosis, including 238 with pancreatic primaries (37.9%) and 389 with non-pancreatic NENs (62.1%). Specifically, SSA was administered to 487 patients (23.7%), chemotherapy to 141 (6.9%), and RLT to 39 (1.9%). Among those who received chemotherapy, 79 patients (56.0%) were treated with alkylating or antimetabolite-based regimens, 56 (39.7%) with platinum-based regimens, and 6 (4.3%) with other agents. Among those who received SSA as first-line therapy (n = 487), 56.3% had G2 NET, and 34.7% had G1 NET. Overall, SSA was used as first-line therapy in combination with other treatments in 43 patients (6.8%).

Among the 487 patients who received SSA as first-line therapy, 188 (38.6%) required a second-line treatment during a median follow-up of 48 months (95% CI 0–65) due to tumour progression (Fig. 2). Of these, 86 patients (45.7%) received chemotherapy, 42 (48.8%) with pancreatic and 44 (51.2%) with gastrointestinal primaries, including 5 (5.8%) G1, 44 (51.2%) G2, and 37 (43.0%) G3 tumours. Chemotherapy regimens were

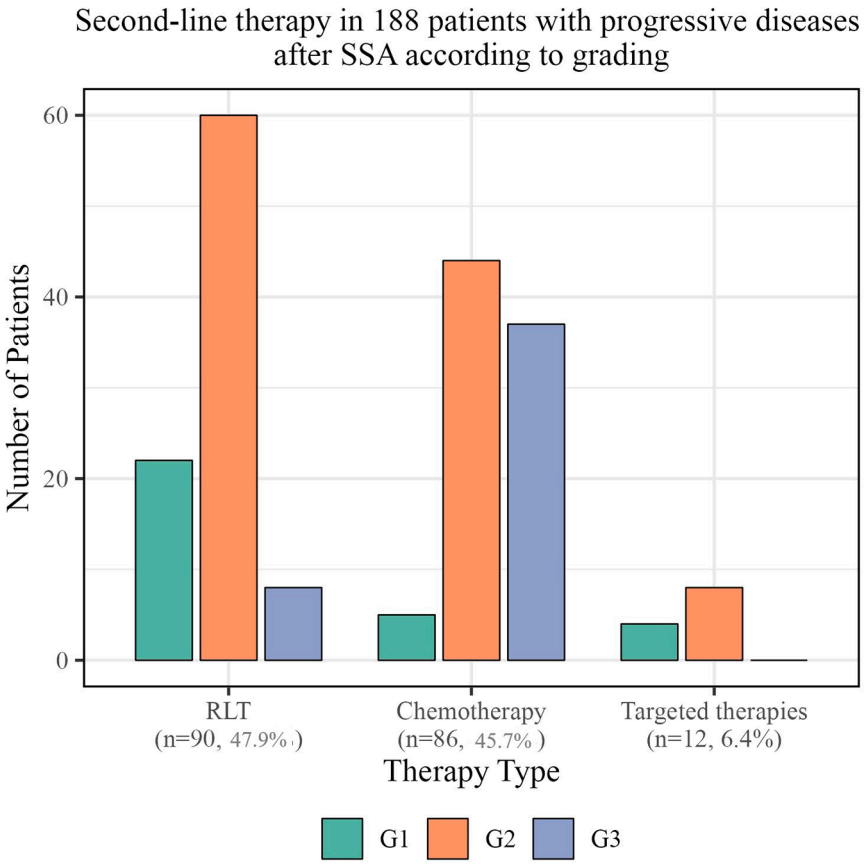

Fig. 2: **Distribution of second-line treatments in 188 patients with disease progression after SSA, stratified by tumour grade.** Bar chart showing the number and proportion of patients receiving radioligand therapy (RLT), chemotherapy, or targeted therapies as second-line treatment after progression on somatostatin analogues (SSA). Bars are coloured according to tumour grade (G1–G3). Percentages refer to the proportion of patients receiving each treatment among those progressing after SSA.

predominantly alkylating or antimetabolite-based in 57 patients (66.3%) and platinum-based in 29 (33.7%). Ninety patients (47.9%) received RLT, 34 (37.8%) with pancreatic and 56 (62.2%) with gastrointestinal primaries, including 22 (24.4%) G1, 60 (66.7%) G2, and 8 (8.9%) G3 tumours. Twelve patients (6.4%) received targeted agents (everolimus or sunitinib). Notably, 148 of 188 patients (78.7%) continued SSA in combination with the second-line regimen.

Survival data were available for 1271 patients. Among the 867 patients not included in the survival analysis, 578 were excluded because they were enrolled within 12 months before database lock, and 289 because they had indolent tumour subtypes for which longitudinal follow-up is not routinely performed. Over a median follow-up of 271 days (IQR 121–530), 62 deaths were observed (event rate 4.9%).

Overall survival differed markedly according to metastatic status. Patients with metastatic disease had significantly worse survival than non-metastatic patients (log-rank $\chi^2(1) = 46.05$, $p < 0.001$; Fig. 3). At 3 years, estimated OS was 95.5% in non-metastatic patients and 75.2% in metastatic patients, with corresponding RMST values of 1066 (95% CI 1050–1082) and 943 (95% CI 903–983) days, respectively. Similar results were observed in a supportive analysis based on ENETS stage, with worse survival in patients with stage IV disease compared with stage I–III (log-rank $\chi^2(1) = 32.5$, $p < 0.001$). At 3 years (1095 days), estimated overall survival was 93.0% (95% CI 91.0–97.8) for stage I–III disease and 75.1% (95% CI 66.4–85.0) for stage IV disease. Overall survival differed significantly across tumour grades (log-rank $\chi^2(3) = 76.11$, $p < 0.001$), with progressively worse outcomes from NET G1 to NET G3 and NEC. Compared with NET G1, patients with NET G2 showed a non-significant trend toward higher mortality (HR = 1.83, 95% CI 0.95–3.54, $p = 0.072$), whereas a substantially increased risk of death was observed for NET G3 (HR = 7.71, 95% CI 3.50–17.00, $p < 0.001$) and for neuroendocrine carcinomas (NEC; HR = 11.47, 95% CI 5.36–24.54, $p < 0.001$). Median overall survival was not reached for NET G1 and NET G2 within the available follow-up, reflecting the low event rates in these groups. At a

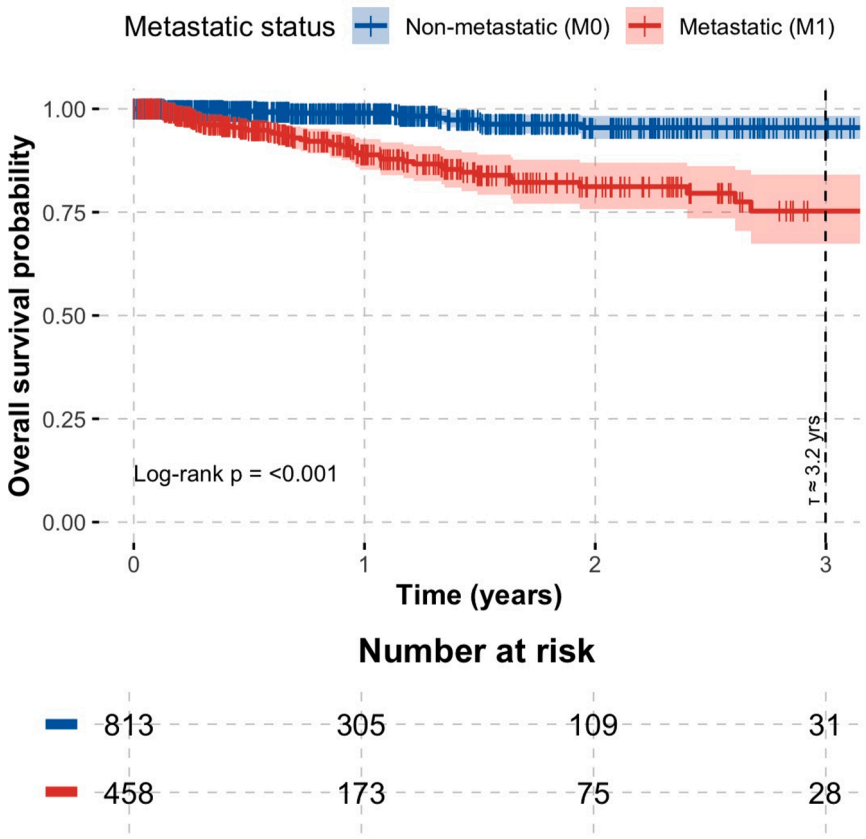

***Fig. 3:* Kaplan–Meier overall survival curves.** Kaplan–Meier curves of overall survival stratified by metastatic status at diagnosis (M0 vs M1). Advanced disease was associated with significantly worse overall survival (log-rank p < 0.001). Shaded areas indicate 95% confidence intervals; tick marks denote censored observations. Vertical dashed lines indicate truncation times ($\tau \approx 3.2$ and 3.3 years, respectively). Numbers at risk are shown below each panel.

clinically relevant time horizon of 3 years (τ = 1095 days), estimated overall survival probabilities were 95.0% (95% CI 91.8–98.3) for NET G1, 86.6% (95% CI 79.7–94.1) for NET G2, 57.3% (95% CI 36.8–89.2) for NET G3, and 52.1% (95% CI 34.4–78.8) for NEC. Consistent with these findings, RMST at 3 years decreased progressively across grading categories, from 1061 days in NET G1 and 1027 days in NET G2 to 832 days in NET G3 and 724 days in NEC.

Ki-67 was strongly associated with OS. Increasing proliferative activity was associated with higher mortality. Using an exploratory cut-off at 15%, patients with Ki-67 ≤ 15% had substantially better survival than those with Ki-67 > 15% (log-rank $\chi^2(1) = 98.9$, $p < 0.001$; Fig. 4). At 3 years, estimated overall survival was 93.0% and 48.8%, respectively, with an RMST difference of approximately 270 days (95% CI 177–363). Overall survival did not differ significantly between pancreatic and non-pancreatic NENs (log-rank $\chi^2(1) = 2.49$, $p = 0.115$), although lower 3-year survival estimates were observed in non-pancreatic tumours (84.1% vs 92.3%). In a multivariable Cox model including ENETS stage and Ki-67 as a continuous variable, both remained independently associated with overall survival (Table 2).

Progression-free survival analyses included 434 patients with metastatic disease at diagnosis (Cohort A), among whom 166 events (38.2%) were observed. Median follow-up was 210 days (IQR 104–410; maximum 1498 days). Estimated PFS was 60.7% at 1 year and 24.5% at 3 years, with a median PFS of 492 days and a 3-year RMST of 593 days (95% CI 544–643). PFS differed according to primary tumour site (log-rank $\chi^2 = 4.7$, $p = 0.03$). In univariable analysis, non-pancreatic primaries were associated with a lower risk of progression compared with pancreatic tumours (HR 0.70, 95% CI 0.51–0.97).

Recurrence-free survival was evaluated in 123 patients with non-metastatic disease who underwent curative-intent surgery (Cohort B), among whom 23 recurrences (18.7%) were observed. Estimated RFS was

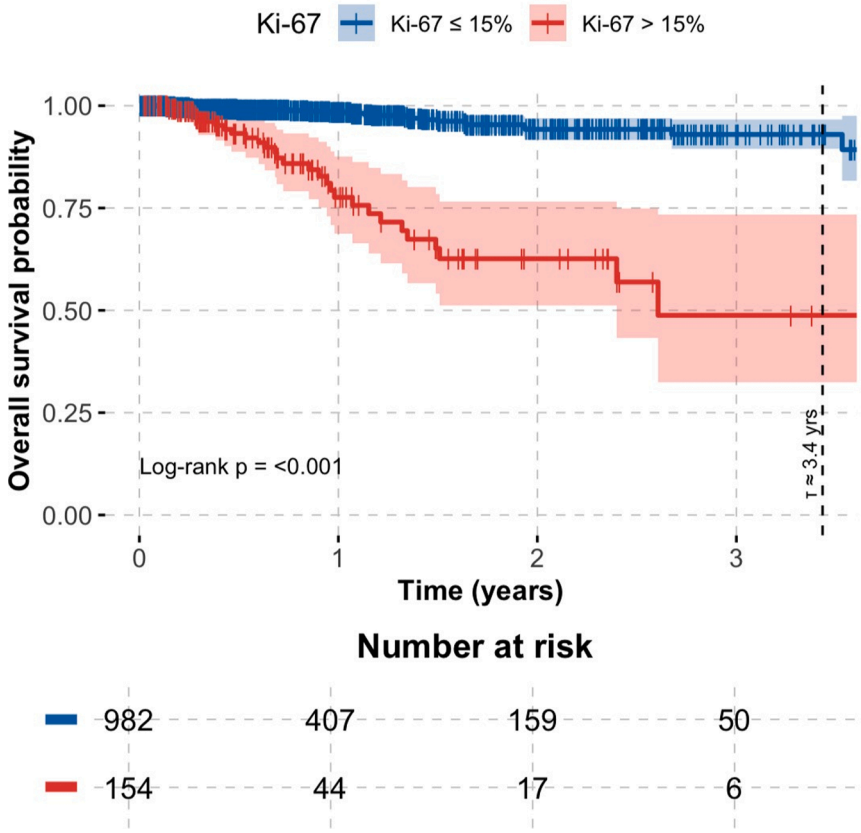

***Fig. 4:* Kaplan–Meier overall survival curves stratified by Ki-67.** Kaplan–Meier curves of overall survival stratified by Ki-67 using a 15% cutoff identified by maximally selected rank statistics. Patients with Ki-67 > 15% showed significantly worse overall survival compared with those with Ki-67 ≤ 15% (log-rank p < 0.001). Graphical conventions are as in Fig. 3.

75.4% at 1 year and 44.5% at 3 years, with a median RFS of 1048 days and a 3-year RMST of 788 days (95% CI 681–896). No significant differences in RFS were observed between pancreatic and non-pancreatic tumours (log-rank $\chi^2(1) = 0.2$, p = 0.65), and primary tumour site was not associated with recurrence risk in univariable analysis (HR 0.82, 95% CI 0.35–1.93).

Discussion

The epidemiology of GEP-NENs has been extensively described through population-based registries, most notably the US SEER database, which has consistently documented rising incidence and prevalence over recent decades.[1] Similar data have emerged from Japan, the UK, and selected European countries.[7,9,15,16] By

Variable	Comparison/unit	Univariable HR (95% CI)	p value	Multivariable[a] HR (95% CI)	p value
Metastatic status	M1 vs M0	6.35 (3.44–11.72)	<0.001	–	–
ENETS stage	IV vs I–III	4.99 (2.70–9.22)	<0.001	3.37 (1.69–6.70)	<0.001
Tumour grade	NET G2 vs G1	1.83 (0.95–3.54)	0.072	–	–
	NET G3 vs G1	7.71 (3.50–17.00)	<0.001	–	–
	NEC vs G1	11.47 (5.36–24.54)	<0.001	–	–
Ki-67 (continuous)	per 1% increase	1.03 (1.02–1.04)	<0.001	1.03 (1.02–1.04)	<0.001
Ki-67 (categorical)	>15% vs ≤ 15%	9.66 (5.59–16.69)	<0.001	–	–
Primary tumour site	Non-pancreatic vs pancreatic	1.57 (0.89–2.75)	0.118	–	–

[a]Multivariable Cox model included ENETS stage and Ki-67 as a continuous variable.

***Table 2:* Univariable and multivariable Cox regression analyses of overall survival.**

contrast, the recent attempt to establish a European registry was prematurely discontinued, yielding a fragmented dataset.[17] However, epidemiological data from these registries are often challenging to translate into clinical practice, as they may not accurately capture real-world management. To overcome these limitations, the ITANET national database was launched in 2019 to prospectively collect high-quality, real-world data on GEP-NENs.[13] Unlike earlier Italian reports, which revealed significant weaknesses in diagnostic accuracy and grading upon review,[12] the ITANET database provides systematically validated case-level data from a nationwide network of centres, generating original and reliable real-world data.

A key finding of the present study is the interval between symptom onset and diagnosis. Previous retrospective series had consistently reported a long delay, between 24 and 54 months, often referred to as the "diagnostic lag," which has historically characterised GEP-NENs.[18,19] In our prospective cohort, however, the median interval from first symptoms, whether related to hormonal syndromes in F NENs or non-specific manifestations in NF tumours, to diagnosis was 197 days (just over 6 months). Although not negligible, this interval is substantially shorter than that reported in previous studies. This discrepancy is likely multifactorial. First, the prospective design, with symptom onset explicitly captured in the CRF, ensured greater accuracy than retrospective data. Second, all Italian referral centres for NENs contributed to the study, and patients managed within this experienced national network plausibly benefited from earlier recognition and diagnosis, including several ENETS Centres of Excellence with high disease-specific expertise and structured diagnostic pathways. Most comparative data reporting longer diagnostic delays derive from earlier studies[18,19] and reflect diagnostic periods characterised by lower disease awareness and more limited access to specialised networks. These findings underscore the importance of centralising the management of patients with suspected or confirmed NENs within expert networks, a practice increasingly recognised as a quality criterion and a prerequisite for optimal care.[20]

Another relevant observation from our study is the high proportion of incidental diagnoses, accounting for 58.6% of all cases, with nearly half (44.4%) confined to the pancreas. The incidentally detected pancreatic NENs phenomenon has been steadily increasing and represents one of the most striking epidemiological trends of recent years. According to recent SEER data,[1] the incidence of pancreatic NENs is approximately 1.3 per 100,000, whereas prevalence approaches 0.3%, more than 200-fold higher, underscoring that pancreatic NENs are far from rare in clinical practice. These figures progressively approach those reported in autopsy or surgical series, where the likelihood of identifying a NEN in resected pancreatic specimens was approximately 1%.[21,22] The proportion of incidental diagnosis observed in this study may have been influenced by the participation of national high-volume referral centres for pancreatic diseases, possibly leading to an overestimation of incidental pancreatic NENs. Nonetheless, most gastric, duodenal, and rectal NENs are also diagnosed incidentally. The growing number of incidental NEN diagnoses suggests that these tumours may soon no longer fall within the definition of rare cancers, currently restricted to those with an incidence of fewer than 6 per 100,000.[23]

From a diagnostic perspective, most patients underwent ^{68}Ga-DOTA-peptide PET in addition to conventional imaging with abdomen-pelvis CE CT or MRI. Notably, ^{68}Ga-DOTA-peptide PET showed markedly superior diagnostic accuracy in small intestinal NENs (Fig. 1), whereas no significant difference was observed in pancreatic NENs, where all three modalities demonstrated similar sensitivity. This discrepancy is likely attributable to the greater difficulty of conventional radiology in detecting small intestinal lesions, highlighting the role of ^{68}Ga-DOTA-peptide PET in identifying the primary tumour in this setting, and the higher expression of somatostatin receptors in small bowel NENs compared to pancreatic NENs.[24] In pancreatic NENs, by contrast, ^{68}Ga-DOTA-peptide PET, beyond staging, mainly serves to assess receptor expression, which is crucial for prognostication and for guiding treatment with SSA or RLT.[25]

Regarding long-term outcomes, it is worth noting that follow-up in this cohort is still relatively short, and data on survival and treatment efficacy are not yet mature. However, in analysing patient outcomes, our study confirmed the crucial prognostic role of Ki-67, which has long been recognised as the most powerful predictor of prognosis, treatment response, and overall clinical course in NENs. Beyond reaffirming this established evidence, two additional observations emerge as noteworthy. First, the results highlight the value of considering Ki-67 as a continuous variable. Although the WHO grading system effectively stratifies prognosis, it relies on predefined cutoffs that inevitably compress biological heterogeneity, particularly within NET G2, where Ki-67 ranges widely from 3% to 20%.[3] In our series, each incremental 1% increase in Ki-67 was associated with a measurable increase in risk (+3.3%), providing a simple and clinically relevant tool for patient-level risk assessment that extends beyond the constraints of grading categories (Table 2). Second, our analysis identified 15% as a clinically meaningful cutoff for prognostic stratification. While previous retrospective series had suggested potential thresholds,[26,27] our analysis supports the identification of 15% as a potential threshold associated with prognostic stratification in this real-world cohort. This data-driven finding should be considered hypothesis-generating and does not support revision of WHO grading

criteria; longer follow-up is needed to clarify its prognostic implications. Despite the relatively short follow-up and the availability of treatment data for only a subset of patients, this study provides meaningful real-world insights into therapeutic strategies for advanced disease and second-line treatment after progression on first-line therapy. After progression on SSA, approximately half of patients received RLT and a similar proportion received chemotherapy, while targeted agents were used less frequently. These findings reflect real-world treatment patterns and are not intended to inform comparative efficacy or treatment selection. The choice of second-line therapy after progression on SSA remains an unsolved matter, particularly in pancreatic NENs.[28] In fact, robust evidence to guide the choice of optimal second-line therapy after progression on SSA is still lacking, and current guidelines recommend either chemotherapy- or RLT-based approaches. Nevertheless, retrospective data suggest a potential advantage of RLT over chemotherapy or targeted therapies,[29] a trend also reflected in recently updated guidelines.[4,5,30]

This study has several strengths, including its large sample size, prospective design, manual case-by-case centralised validation of data, and participation in a nationwide network encompassing all Italian referral centres for NENs. Nonetheless, some structural limitations must be acknowledged. First, diagnostic and therapeutic approaches were not standardised across centres, and although generally aligned with guidelines, they remained subject to local practice due to the observational nature of the study. Second, the contribution of participating sites varied, with high-volume centres potentially introducing some case-mix imbalances that may not fully reflect the national epidemiology. Third, despite the involvement of 38 centres, not all newly diagnosed patients were captured, as this non–population-based study was not designed to estimate incidence but represents a nationwide prospective cohort from referral centres. Although the study period overlapped with the COVID-19 pandemic, variations in enrolment primarily reflected the staggered activation of participating centres. Finally, the relatively short follow-up and the high proportion of recently enrolled patients limited the maturity of survival analyses and preclude assessment of long-term outcomes.

In conclusion, this study provides the most comprehensive prospective description of GEP-NENs in Italy, based on a large, systematically validated national database. The results illustrate presentation patterns, diagnostic pathways, prognostic markers, and therapeutic strategies across a nationwide referral network. Moreover, this experience may serve as a model for similar initiatives at the European level.

Contributors

FP, MR, and MF had full access to all the data in the study and verified the underlying data. FP and MF conceived and designed the study. FP, MR, and MF contributed to data acquisition and interpretation. MM performed the statistical analyses and drafted the manuscript with input from all coauthors. MR, FP, SP, and MF critically reviewed the manuscript for important intellectual content.

All authors had full access to the data, approved the final version of the manuscript, and were responsible for the decision to submit it for publication. FP and MF confirm that they have verified the data and take responsibility for the integrity and accuracy of the analysis.

Data sharing statement

De-identified individual participant data supporting the findings of this study will be made available from the corresponding author upon reasonable request.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author(s) used Grammarly-EDU for language editing and proofreading purposes only. No generative AI was employed to create the scientific content. After using this tool, the author(s) reviewed and edited the manuscript as needed and take full responsibility for the content of the published article.

Declaration of interests

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101684.

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