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Perioperative chemotherapy and long-term cure in resected grade 3 gastroenteropancreatic neuroendocrine carcinomas: The GETNE SOUTH-NEC Study

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ABSTRACT

Background: In resected stage I–III gastroenteropancreatic neuroendocrine carcinomas (GEP-NEC), whether perioperative chemotherapy eradicates residual disease or merely delays relapse is unknown, since Cox models cannot distinguish these effects.

Methods: We analysed 162 patients with resected stage I–III GEP-NEC from the GETNE registry. Event-free (EFS), recurrence-free (RFS) and overall survival (OS) were modeled by Cox regression with chemotherapy as a time-dependent exposure, adjusted for age, sex, performance status, stage, Ki-67 and site, and by a Bayesian promotion-time cure model that separates a clonogenic (cure) component from a kinetic (relapse timing) component.

Results: Seventy-four patients (46%) received chemotherapy; median follow-up was 93 months. Chemotherapy was associated with longer EFS (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.40–0.96) and RFS (HR, 0.59; 95% CI, 0.37–0.93), but not clearly with OS (HR, 0.73; 95% CI, 0.46–1.15). On EFS, the cure model attributed the association to a lower clonogenic burden (ratio, 0.67; 95% credible interval [CrI], 0.40–1.11; posterior probability, 94%) rather than to slower kinetics (ratio, 0.93); on RFS both components contributed. The population cure fraction was 22.7% (95% CrI, 15.9–29.6) for EFS and 28.6% (21.9–35.7) for RFS, matching the Kaplan-Meier plateaus. No Ki-67 by chemotherapy interaction was detected.

Conclusion: In resected grade 3 GEP-NEC, perioperative chemotherapy is associated with longer EFS and RFS and, on the composite endpoint, with a higher probability of long-term cure rather than delayed recurrence. These

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associations are observational and the cure-versus-delay decomposition is descriptive. Cure models add information beyond conventional survival metrics.

1. Introduction

Gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) are poorly differentiated, high-grade neuroendocrine neoplasms with aggressive clinical behavior, poor prognosis, and usually high Ki-67 indices, distinct from well-differentiated grade 3 neuroendocrine tumors (NET G3) [1]. In the metastatic setting, systemic chemotherapy remains the standard of care, yet median overall survival (OS) ranges from 7 to 11 months and has not substantially improved over the past few decades [2,3]; in recent randomized trials of first-line etoposide–cisplatin versus irinotecan–cisplatin, median OS was 10–13 months [4,5]. In contrast, surgical resection with curative intent is the cornerstone of treatment for nonmetastatic disease. However, recurrence is common, typically within 2 years, and 5-year event-free survival (EFS) rarely exceeds 20%-40% [6,7].

The role of perioperative systemic therapy in resected GEP-NEC is still debated. Platinum-etoposide, the most common regimen in advanced disease, has been adopted in the perioperative setting without evidence from randomized trials, and current NANETS and ENETS guidelines acknowledge the limited supporting data [7,8]. Retrospective series have reported inconsistent results, with some suggesting benefit in selected subgroups and others showing no independent association after adjustment for clinicopathologic variables [9–14]. Interpretation of these findings is constrained by small sample sizes, treatment heterogeneity, selection bias, and immortal time bias.

In addition, most prior studies have relied on Cox proportional hazards models, which summarize treatment effects as hazard ratios (HR) [15]. In settings where some patients may achieve long-term cure, this framework is informative but inherently limited [16–18]: the HR cannot distinguish between delaying recurrence among patients destined to relapse (a kinetic effect) and complete eradication of residual disease in a subset of patients who become truly cured (a curative effect) [16,19]. The shape of Kaplan-Meier curves in resected GEP-NEC, with an early decline followed by a plateau, is what one would expect when a curable subgroup exists, as previously shown for pancreatic neuroendocrine neoplasms [20].

Promotion-time cure models were developed to address this question [21]. Unlike conventional time-to-event methods, they define the survival function by modeling the unobservable number of residual clonogenic cells after treatment and the time required for these cells to produce a detectable recurrence [22,23], which separates treatment effects on residual clonogenic burden from effects on recurrence dynamics. To our knowledge, this approach has not yet been applied to nonmetastatic GEP-NEC.

In this context, the SOUTH-NEC (Survival Outcomes Under Therapy in High-grade NECs) study aimed to assess the association of perioperative systemic therapy with survival outcomes and the probability of cure in early-stage GEP-NEC, applying a Bayesian promotion-time cure model alongside conventional Cox models.

2. Materials and methods

2.1. Study design and population

Data were obtained from the Spanish National Neuroendocrine Neoplasm (NEN) Registry (RGETNE), a multi-institutional, hospital-based database coordinated by the Spanish Group of Neuroendocrine Tumors (GETNE) that has enrolled consecutive patients diagnosed with neuroendocrine neoplasms since 2000. Investigators from more than 60 academic and community sites across Spain (Supplementary Appendix 1) enter comprehensive clinical, pathological, therapeutic and outcome data through a centralized web platform (https://e-crd.net/), as previously described [24–26]. The registry protocol and informed-consent documents (Supplementary Appendix 2) were approved by a National Scientific and Ethical Committee, and all procedures conformed to the 1964 Helsinki Declaration and its later amendments.

All registered patients were screened for eligibility, of whom 262 had stage I–III grade 3 neuroendocrine neoplasms; quality control included double-checking all variables of interest and monitoring discrepancies and missing data. Eligibility required a histologically confirmed NEC of digestive origin, a Ki-67 proliferation index $>$ 20%, and local or locoregional disease (TNM stage I, II, or III) at diagnosis; mixed histologies and well-differentiated grade 3 tumors were excluded after cross-checking the successive WHO classifications recorded in the registry. Because the study question concerns perioperative treatment, the analysis population comprises the 162 patients who underwent resection of the primary tumor (Fig. 1). Patients were treated according to standard clinical practice.

2.2. Variables and outcomes

Recorded variables included epidemiological (age, sex), clinical (Eastern Cooperative Oncology Group [ECOG] performance status, primary tumor site, TNM stage at diagnosis, mode of presentation, and initial treatment approach), and pathological characteristics (tumor differentiation, Ki-67 index, and neuron-specific enolase and chromogranin A expression when available), together with the dates of diagnosis, surgery, relapse or progression, and last visit or death, and the cause of death. The data cut-off was September 2026. Primary tumor sites were grouped as pancreas, colorectal, gastric, or other according to the distribution of the sample.

Time zero for all analyses was the date of primary surgery. EFS, the prespecified registry endpoint, was defined as the time from surgery to recurrence or death from any cause, whichever came first. Recurrence-free survival (RFS) was defined as the time from surgery to the first documented recurrence. Overall survival (OS) was defined as the time from surgery to death from any cause. Patients without an event were censored at last follow-up.

Covariates for the multivariable Cox models were selected a priori, accounting for the number of available events [27]: age (restricted cubic spline with three knots at 49, 71 and 83 years, the 10th, 50th and 90th percentiles), sex, ECOG performance status (0, 1, or $\geq$2, with unknown status retained as an explicit category), TNM stage (I, II, or III), Ki-67 index (restricted cubic spline with three knots at 30%, 70% and 90%), and primary tumor site group (colorectal, pancreas or other). Ki-67 was available as an exact value in 137 patients and as a reported range in 16, for which the midpoint was used; Ki-67 was missing in 9 patients and age in 4, and both were handled by multiple imputation as described below.

2.3. Promotion-time cure model

The promotion-time cure model is grounded in stochastic carcinogenesis theory [21,22]. After primary treatment, a patient may harbor a finite, unobserved number of residual clonogenic foci, each capable of remaining dormant or undergoing stochastic activation that yields a detectable recurrence; this latent number is a model-implied quantity inferred from the population survival curve, not a measured count. The expected residual burden is modeled as a Poisson parameter θ, so that the population survival function is $S(t) = \exp\{-\theta \cdot F(t)\}$, where $F(t)$ is the distribution of the time for one focus to relapse, and the cure probability

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equals exp(−θ). Covariates act on θ (incidence, or cure, component) or on the timing of recurrence among uncured patients (latency, or kinetics, component). The promotion time followed a Weibull distribution.

The model was fitted in a fully Bayesian framework using Hamiltonian Monte Carlo sampling in Stan [28], following Chen, Ibrahim and Sinha [23,29]. Covariate assignment followed biological rationale: age, TNM stage and primary tumor site (colorectal vs other) entered the incidence component only, whereas Ki-67 (as the same restricted cubic spline used in the Cox models) and perioperative chemotherapy were allowed to act in both components, chemotherapy as a time-dependent switch that, from the start of treatment, multiplies the residual clonogenic burden by a clonogenic ratio and the activation kinetics of the remaining foci by a kinetic ratio. To resolve the near-identifiability that arises when a covariate influences both components, we placed weakly informative Normal(0, 2.5) priors on the standardized incidence coefficients and tighter Normal(0, 0.25) priors on the latency coefficients. This asymmetric choice is not neutral: it privileges attribution of shared effects to the cure component when the data do not separate the two mechanisms, encoding the assumption that recurrence kinetics are relatively stable while a cytotoxic regimen acts mainly on residual burden. Any attribution to cure is therefore contingent on this prior structure, which was examined under six prior specifications (Supplementary Table A1) and is revisited in the Discussion. The model was fitted to EFS and to RFS, with a posterior predictive check against the Kaplan-Meier curve; the full specification, identifiability diagnostics and computational settings are provided in Supplementary Appendix 3.

2.4. Statistical analysis

EFS, RFS and OS were estimated by the Kaplan-Meier method by treatment group, TNM stage, primary tumor site and Ki-67 category as descriptive summaries; because the treatment groups in these curves are defined at baseline, they are subject to immortal time and are not used for inference. Median follow-up was estimated by the reverse Kaplan-Meier method. Perioperative chemotherapy entered all models as a time-dependent exposure switched on at the date of first administration (time zero for neoadjuvant chemotherapy), which removes immortal time; the immortal person-time and the bias it would induce under the null were quantified by simulation (Supplementary Appendix 3). Multivariable Cox proportional hazards models were fitted for EFS, RFS and OS with the prespecified covariates, and the proportional-hazards assumption was checked with Schoenfeld residuals. Missing Ki-67 and age values were handled using multiple imputation by chained equations (20 imputations, combined using Rubin's rules) in the Cox models, whereas in the Bayesian cure model they were estimated jointly with the model parameters under bounded prior distributions (Supplementary Appendix 3).

Interactions of chemotherapy with Ki-67 and age were tested in the Cox models, with each potential effect modifier modeled as a linear continuous variable, as a restricted cubic spline, and dichotomized at 55% for Ki-67 or 70 years for age. The Ki-67 × chemotherapy interaction was also evaluated in the clonogenic component of the cure model. Sensitivity analyses (fixed-exposure and landmark models, complete-case analysis, imputation of ECOG status, linear specifications of Ki-67 and age, diagnostic era, exclusion of esophageal and rectal primaries, surgical covariates recorded in subsets, and E-values with an empirical calibration against the measured covariates) are detailed in Supplementary Appendix 3. Analyses were performed in R (version 4.3.2) with the survival and mice packages [30] and in Stan with rstan (version 2.32). The complete source code is available in a public GitHub repository archived via Zenodo (https://github.com/alberto-carm/south_nec; DOI: 10.5281/zenodo.19602317).

3. Results

3.1. Baseline characteristics

Table 1 describes the 162 resected patients. Median age was 71 years (interquartile range [IQR], 61–79), and 106 (65%) were male. Among patients with available data, ECOG performance status was 0–1 in 113 of 122 (93%). Disease stage at diagnosis was stage III in 96 patients (59%), stage II in 45 (28%), and stage I in 21 (13%). Median Ki-67 index was 70% (IQR, 40–80); it was not recorded in 9 patients. The most frequent primary tumor sites were the colon (n = 53, 33%), pancreas (n = 34, 21%), rectum (n = 28, 17%), and stomach (n = 27, 17%). Patients who

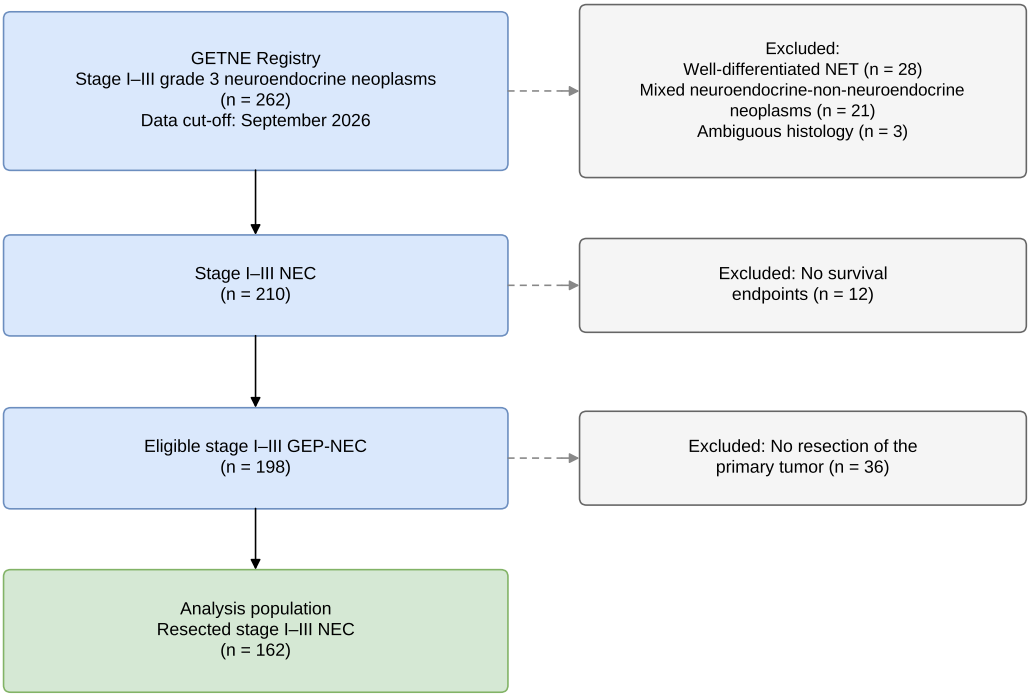


Fig. 1. Flowchart of study population selection.

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Table 1
Baseline characteristics of the 162 resected patients (GETNE Registry), overall and by perioperative chemotherapy (not received, n = 88; received, n = 74). Percentages for each variable were calculated using the number of cases with available data for the corresponding variable as the denominator. Continuous variables are presented as median (IQR); categorical variables as n (%). The expression status of neuron-specific enolase and chromogranin A refers to immunohistochemical staining of the primary tumor. Ki-67 was not recorded in 9 patients and age in 4; both were multiply imputed in the analyses. Abbreviations: N, number of patients; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group performance status; Ki-67, proliferation index; TNM, Tumor–Node–Metastasis staging system; GETNE, Spanish Group of Neuroendocrine Tumors.

Characteristic	Overall, N = 162	No perioperative chemotherapy, N = 88	Perioperative chemotherapy, N = 74
Age, years, Median (IQR)	71 (61, 79)	75 (66, 80)	67 (58, 76)
Unknown	4	4	0
Sex, n (%)			
Female	56 (35%)	32 (36%)	24 (32%)
Male	106 (65%)	56 (64%)	50 (68%)
ECOG performance status, n (%)			
0	46 (38%)	19 (32%)	27 (43%)
1	67 (55%)	35 (59%)	32 (51%)
≥2	9 (7%)	5 (8%)	4 (6%)
Unknown	40	29	11
TNM stage at diagnosis, n (%)			
I	21 (13%)	13 (15%)	8 (11%)
II	45 (28%)	22 (25%)	23 (31%)
III	96 (59%)	53 (60%)	43 (58%)
Ki-67 index, %, Median (IQR)	70 (40, 80)	60 (36, 80)	75 (55, 90)
Unknown	9	4	5
Primary tumor site, n (%)			
Colon	53 (33%)	29 (33%)	24 (32%)
Rectum	28 (17%)	14 (16%)	14 (19%)
Pancreas	34 (21%)	19 (22%)	15 (20%)
Stomach	27 (17%)	17 (19%)	10 (14%)
Esophagus	4 (2%)	2 (2%)	2 (3%)
Small bowel	7 (4%)	4 (5%)	3 (4%)
Other	8 (5%)	3 (3%)	5 (7%)
Unknown primary site	1 (1%)	0 (0%)	1 (1%)
Primary tumor site group, n (%)			
Colorectal	81 (50%)	43 (49%)	38 (51%)
Pancreas	34 (21%)	19 (22%)	15 (20%)
Other	47 (29%)	26 (30%)	21 (28%)
Neuron-specific enolase (primary tumor), n (%)			
Positive	31 (20%)	17 (20%)	14 (19%)
Negative	6 (4%)	2 (2%)	4 (5%)
Not reported	120 (76%)	65 (77%)	55 (75%)
Unknown	5	4	1
Chromogranin A (primary tumor), n (%)			
Positive	111 (70%)	63 (73%)	48 (66%)
Negative	31 (19%)	14 (16%)	17 (23%)
Not reported	17 (11%)	9 (10%)	8 (11%)
Unknown	3	2	1
Clinical presentation, n (%)			
Non-secretory symptoms, primary tumor	132 (85%)	71 (87%)	61 (82%)
Incidental finding	20 (13%)	8 (10%)	12 (16%)
Secretory symptoms	4 (3%)	3 (4%)	1 (1%)
Unknown	6	6	0

received perioperative chemotherapy were younger (median age, 67 vs 75 years) and had higher proliferative activity (median Ki-67, 75% vs 60%) than those who did not, with similar distributions of the remaining baseline variables (Table 1).

3.2. Treatment and perioperative management

All 162 patients underwent resection of the primary tumor, with curative radical intent recorded in 154 (95%). Seventy-four patients (46%) received perioperative chemotherapy: 56 received adjuvant chemotherapy only and 18 received neoadjuvant chemotherapy, with or without postoperative treatment; adjuvant chemotherapy started a median of 1.6 months after surgery (IQR, 1.4–2.0). Etoposide plus platinum was the predominant regimen (52 patients, 70%), followed by other platinum-based combinations (11, 15%), capecitabine plus temozolomide (2, 3%), other regimens (5, 7%) and unspecified regimens (4, 5%); the median recorded duration of perioperative chemotherapy was 3.3 months (IQR, 2.4–4.2; 42 patients with complete dates; Supplementary Table A2). Perioperative treatment rates were similar across stages and primary sites, and higher in tumors with Ki-67 ≥ 55% than below (52% vs 32%; P = .03).

3.3. Outcomes

Median follow-up was 93 months. At the time of analysis, 115 patients (71%) had an EFS event, 107 had recurred, and 97 (60%) had died. Median EFS, RFS and OS were 13.0, 13.1 and 35.9 months (Tables 2 and 3 and Supplementary Table A3). Patients who received perioperative chemotherapy had longer EFS (median, 17.0 vs 9.6 months; five-year EFS, 38% vs 21%), RFS (median, 17.5 vs 9.7 months; five-year RFS, 41% vs 21%) and OS (median, 56.6 vs 23.6 months; five-year OS, 48% vs 39%; Supplementary Figure A1). Both EFS and RFS curves reached a plateau: the last EFS event occurred at 150 months, with the curve at 19.7% (95% CI, 13.1–29.6) beyond that point and 11 patients at risk beyond 10 years, and the last RFS event at 116 months, with a plateau of 26.8% (95% CI, 19.7–36.5).

3.4. Multivariable Cox proportional hazards models

In multivariable Cox models with chemotherapy as a time-dependent exposure (n = 162), perioperative chemotherapy was independently associated with longer EFS (HR, 0.61; 95% CI, 0.40–0.96; P = .031) and RFS (HR, 0.59; 95% CI, 0.37–0.93; P = .023), whereas the association with OS was weaker and not significant (HR, 0.73; 95% CI, 0.46–1.15; P = .17; Supplementary Table A4 and Supplementary Figure A2). Stage I and II disease and colorectal primaries were associated with better EFS, Ki-67 showed a positive but imprecise association (HR for 80% vs 40%, 1.30; 95% CI, 0.88–1.92), and the hazard rose with age up to about 70 years and did not rise further beyond (HR for 79 vs 61 years, 0.95; 95% CI, 0.65–1.37; test of nonlinearity, P = .018). The fixed-exposure estimate was stronger, as expected from immortal time, which represented 5.3% of the treated person-time (Supplementary Appendix 3). The complete-case analysis (n = 149) gave similar results (HR, 0.60, 0.56 and 0.71 for EFS, RFS and OS).

3.5. Promotion-time cure model

The cure model converged on both endpoints (maximum R-hat, 1.002; no divergent transitions), and its implied marginal survival reproduced the observed Kaplan-Meier curves, including the late plateau (Supplementary Figure A3). Posterior estimates are reported in Table 4.

The population cure fraction, the average over patients of their own cure probability under their observed exposure, was 22.7% (95% CrI, 15.9–29.6) for EFS and 28.6% (95% CrI, 21.9–35.7) for RFS, in agreement with the Kaplan-Meier plateaus of 19.7% and 26.8%.

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Table 2
Event-Free Survival by Perioperative Chemotherapy and Key Clinical Characteristics in the Resected Cohort (n = 162). Note: The table presents event-free survival (EFS) stratified by perioperative chemotherapy, and disaggregated by TNM stage, primary tumor site (colorectal, pancreas, gastric, other) and Ki-67 proliferation index (<55% vs ≥55%; not available in 9 patients). Values are presented as number of patients (N), observed events, and Kaplan-Meier median survival with 95% confidence interval (CI) in months (Greenwood variance, log transformation). NR = not reached. Treatment groups are defined at baseline and the estimates are descriptive; the adjusted estimates with chemotherapy as a time-dependent exposure are given in the text and in Supplementary Table A4. Abbreviations: N, number of patients; CI, confidence interval; NR, not reached; EFS, event-free survival; GETNE, Spanish Group of Neuroendocrine Tumors.

	All resected patients			No perioperative chemotherapy			Perioperative chemotherapy		
	N	Events	Median (95% CI)	N	Events	Median (95% CI)	N	Events	Median (95% CI)
Total	162	115	13.0 (9.7–16.8)	88	67	9.6 (7.2–14.0)	74	48	17.0 (14.2–87.2)
Disease stage									
Stage I	21	10	72.2 (14.8–NR)	13	7	72.2 (13.0–NR)	8	3	NR (14.8–NR)
Stage II	45	29	16.8 (11.6–107.3)	22	16	9.6 (6.6–NR)	23	13	49.6 (16.8–NR)
Stage III	96	76	9.2 (7.2–14.0)	53	44	7.0 (4.6–12.0)	43	32	13.1 (8.7–36.2)
Primary tumor site									
Colorectal	81	53	15.1 (9.7–40.6)	43	31	12.8 (7.2–32.3)	38	22	20.0 (9.7–NR)
Pancreas	34	26	14.7 (8.1–49.6)	19	14	7.5 (6.0–NR)	15	12	16.8 (14.8–NR)
Gastric	27	19	9.2 (3.0–NR)	17	13	8.4 (2.7–NR)	10	6	63.6 (3.0–NR)
Other	20	17	12.2 (9.6–53.2)	9	9	12.8 (8.4–NR)	11	8	11.6 (9.6–NR)
Ki-67 index									
<55%	53	33	16.5 (10.0–53.2)	36	23	14.0 (9.2–72.2)	17	10	16.8 (9.3–NR)
≥55%	100	77	11.6 (8.7–16.1)	48	42	6.8 (4.4–12.8)	52	35	17.5 (14.2–87.2)
Not available	9	5	56.2 (8.0–NR)	4	2	56.2 (3.8–NR)	5	3	9.2 (8.0–NR)

Table 3
Recurrence-Free Survival by Perioperative Chemotherapy and Key Clinical Characteristics in the Resected Cohort (n = 162). Note: The table presents recurrence-free survival (RFS; time from surgery to the first documented recurrence) stratified by perioperative chemotherapy, and disaggregated by TNM stage, primary tumor site (colorectal, pancreas, gastric, other) and Ki-67 proliferation index (<55% vs ≥55%; not available in 9 patients). Values are presented as number of patients (N), observed events, and Kaplan-Meier median survival with 95% confidence interval (CI) in months (Greenwood variance, log transformation). NR = not reached. Treatment groups are defined at baseline and the estimates are descriptive; the adjusted estimates with chemotherapy as a time-dependent exposure are given in the text and in Supplementary Table A4. Abbreviations: N, number of patients; CI, confidence interval; NR, not reached; RFS, recurrence-free survival; GETNE, Spanish Group of Neuroendocrine Tumors.

	All resected patients			No perioperative chemotherapy			Perioperative chemotherapy		
	N	Events	Median (95% CI)	N	Events	Median (95% CI)	N	Events	Median (95% CI)
Total	162	107	13.1 (10.0–17.5)	88	63	9.7 (7.4–14.0)	74	44	17.5 (14.2–NR)
Disease stage									
Stage I	21	8	NR (15.1–NR)	13	6	NR (13.0–NR)	8	2	NR (NR–NR)
Stage II	45	29	16.8 (11.6–107.3)	22	16	9.6 (6.6–NR)	23	13	49.6 (16.8–NR)
Stage III	96	70	9.2 (7.5–14.0)	53	41	7.2 (5.0–12.8)	43	29	13.1 (8.7–NR)
Primary tumor site									
Colorectal	81	48	15.1 (9.7–NR)	43	29	12.8 (7.2–32.3)	38	19	20.0 (9.7–NR)
Pancreas	34	25	14.7 (8.1–50.4)	19	14	7.5 (6.0–NR)	15	11	17.0 (15.4–NR)
Gastric	27	17	9.2 (5.0–NR)	17	11	8.4 (2.7–NR)	10	6	63.6 (3.0–NR)
Other	20	17	12.2 (9.6–53.2)	9	9	12.8 (8.4–NR)	11	8	11.6 (9.6–NR)
Ki-67 index									
<55%	53	32	16.5 (10.0–53.2)	36	22	14.0 (9.2–NR)	17	10	16.8 (9.3–NR)
≥55%	100	70	12.8 (8.7–17.0)	48	39	7.0 (4.4–12.8)	52	31	19.7 (14.2–NR)
Not available	9	5	56.2 (8.0–NR)	4	2	56.2 (3.8–NR)	5	3	9.2 (8.0–NR)

Perioperative chemotherapy was the only modifiable covariate (Table 4). On EFS it was associated with a lower clonogenic burden (ratio, 0.67; 95% CrI, 0.40–1.11), with a posterior probability of 94% that the burden is reduced, whereas the posterior probability of a post-exposure change in recurrence kinetics was 60% (kinetic ratio, 0.93; 95% CrI, 0.54–1.59). At the mean covariate profile, the cure probability was 14.5% (95% CrI, 6.4–25.6) without chemotherapy and 26.8% (95% CrI, 15.6–38.7) with adjuvant chemotherapy started at the median delay of 1.6 months (cure odds ratio, 2.16; 95% CrI, 0.83–6.05). The posterior correlation between the clonogenic and kinetic chemotherapy estimates was 0.53, indicating that the data separate the two mechanisms only partially. On RFS (Supplementary Table A5), the clonogenic ratio was 0.73 (95% CrI, 0.44–1.21; posterior probability, 89%), the kinetic ratio 1.24 (95% CrI, 0.76–1.95; posterior probability, 81%), and the probability of never recurring rose from 22.6% to 33.0% at the mean profile (cure odds ratio, 1.68; 95% CrI, 0.73–4.01): on this endpoint the two components contributed comparably. In the EFS model, stage III carried about three times the clonogenic burden of stage I (ratio, 2.93; 95% CrI, 1.53–6.15), colorectal primaries had a lower burden than other sites (ratio, 0.61; 95% CrI, 0.42–0.89), and the burden was highest in the seventh decade and lower at younger and older ages (ratio for 79 vs 61 years, 0.97; 95% CrI, 0.69–1.35).

The Ki-67 index showed a positive but imprecise association with clonogenic burden (ratio for 80% vs 40%, 1.33; 95% CrI, 0.84–2.11; posterior probability, 88%) and no clear association with recurrence kinetics. Fig. 2 displays, for RFS, the model-implied clonogenic burden, probability of never recurring and median time to relapse across the Ki-67 range (panels A to C) and, from the model with a Ki-67 × chemotherapy term, the odds ratio of never recurring for chemotherapy and the probability of never recurring by treatment group (panels D and E): the odds ratio increased with Ki-67, but its credible intervals included 1 throughout the range.

There was no clear evidence that Ki-67 modified the association between perioperative chemotherapy and outcome. In the cure model, the posterior probability of direction for the Ki-67 × chemotherapy interaction was 72% for EFS and 83% for RFS. Similarly, in the Cox models, no significant interaction was observed when Ki-67 was modeled as a linear continuous variable (P = .56 and .31), as a restricted

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Table 4

Bayesian promotion-time cure model with perioperative chemotherapy as a time-dependent exposure: posterior estimates for event-free survival in the resected cohort (N = 162; 115 events, 71%). The model used four MCMC chains with 4000 iterations each (2000 warmup). In the clonogenic submodel, coefficients are on the log scale: a positive coefficient increases the model-implied clonogenic burden and simultaneously reduces the probability of cure; the exponential of the coefficient represents the multiplicative effect on clonogenic burden. In the kinetic submodel, coefficients are on the log scale of the Weibull scale parameter: a negative coefficient indicates faster relapse among uncured patients. Ki-67 enters both submodels and age the clonogenic submodel as restricted cubic splines, shown as the contrasts between 80% and 40% and between 79 and 61 years (interquartile ranges of the cohort). Perioperative chemotherapy enters as a switch at the start of treatment: the clonogenic ratio applies to the foci still dormant at that time and the kinetic ratio to their activation kinetics. Missing Ki-67 (n = 9) and age (n = 4) values were treated as bounded parameters of the model. Covariates were centered and scaled prior to estimation; priors were Normal(0, 2.5) on the standardized clonogenic coefficients and Normal(0, 0.25) on the kinetic coefficients. The probability of direction (pd) reflects the posterior probability that a coefficient has the sign of its median estimate (*** pd > 99%; ** pd > 95%; * pd > 90%). The model converged (R-hat ≤ 1.002) with zero divergent transitions. The corresponding model for recurrence-free survival is given in Supplementary Table A5. Abbreviations: CrI, credible interval; pd, probability of direction; MCMC, Markov chain Monte Carlo. *Primary model with additive covariate structure and time-dependent chemotherapy exposure. N = 162; 115 events (71%). Four MCMC chains, 4000 iterations each (2000 warmup).*

Covariate	Coefficient	95% CrI	exp (coef)	P(direction)	Interpretation
Clonogenic submodel (log theta): model-implied clonogenic burden (cure component)					
Stage II (vs I)	0.445	−0.266, 1.235	1.56	pd = 88.5%	
Stage III (vs I)	1.075	0.423, 1.816	2.93	pd = 100.0% ***	
Site: colorectal (vs other)	−0.497	−0.878, −0.116	0.61	pd = 99.4% ***	
Ki-67 (80% vs 40%; restricted cubic spline)	0.282	−0.179, 0.746	1.33	pd = 88.4%	Interquartile contrast (25th to 75th percentile)
Age (79 vs 61 years; restricted cubic spline)	−0.032	−0.374, 0.303	0.97	pd = 57.3%	Interquartile contrast (25th to 75th percentile)
Perioperative chemotherapy (time-dependent, from its start date)	−0.404	−0.908, 0.101	0.67	pd = 94.3% *	Clonogenic burden still dormant when chemotherapy starts is reduced by 33%
Kinetic submodel (log lambda): activation kinetics among uncured patients					
Ki-67 (80% vs 40%; restricted cubic spline)	0.158	−0.335, 0.630	1.17	pd = 73.9%	
Perioperative chemotherapy (time-dependent; post-exposure kinetics)	−0.070	−0.609, 0.462	0.93	pd = 60.1%	Ratio of the activation-time scale after chemotherapy; > 1 = slower relapse
Global parameters					
alpha (Weibull shape)	1.03	0.88, 1.18			~ 1: constant activation hazard
Cure probability, untreated, other covariates at their means	14.5%	6.4%, 25.6%			
Cure probability, chemotherapy started at 1.6 months, other covariates at their means	26.8%	15.6%, 38.7%			
Cure odds ratio, chemotherapy at 1.6 months vs none	2.16	0.83, 6.05		P(OR > 1) = 94.3%	
Population-average cure probability (mean of individual probabilities)	22.7%	15.9%, 29.6%			

Model specification. The promotion-time (bounded cumulative hazard) cure model assumes each patient carries $N \sim \text{Poisson}(\theta)$ latent clonogenic foci, each with an independent Weibull-distributed activation time. Population survival is $S(t) = \exp\{-\theta\,[1 - S_0(t)]\}$, where $S_0(t) = \exp[-(t/\lambda)^{\alpha}]$ is the baseline Weibull survival. Cure occurs when $N = 0$, with probability $P(\text{cure}) = \exp(-\theta)$. Covariates enter via $\log(\theta) = \beta_0 + X\beta$ (clonogenic submodel) and $\log(\lambda) = \gamma_0 + Z\gamma$ (kinetic submodel). Perioperative chemotherapy enters as a time-dependent switch: from its start date s, the burden of the foci still dormant is multiplied by $\exp(\delta)$ and their activation-time scale by $\exp(\eta)$, so that follow-up before s contributes as in an untreated patient.

Coefficient interpretation. In the clonogenic submodel, coefficients are on the log-θ scale: a positive coefficient increases the model-implied clonogenic burden and reduces the probability of cure. exp(coef) gives the multiplicative effect on clonogenic burden (e.g., $\exp(1.075) = 2.93$ means 2.9 × the burden). In the kinetic submodel, coefficients are on the log-λ scale: a negative coefficient reduces λ (the Weibull scale), meaning faster relapse among uncured patients.

Prior distributions. Covariates were centered and scaled prior to estimation. Clonogenic coefficients: Normal(0, 2.5) on the standardized scale. Kinetic coefficients: Normal(0, 0.25). Intercepts: Normal(0, 2.5). Weibull shape α: Gamma(2, 1). Missing Ki-67 and age values: Normal prior centered on the observed mean and standard deviation, bounded by the registry category or by the definition of NEC (Ki-67) and by 18 and 100 years (age). The asymmetric priors regularize the weakly identified kinetic component and privilege attribution of shared effects to the cure component, as stated in Methods; the results under six prior specifications are given in Supplementary Table A1.

Clinical interpretation of the sign. In the clonogenic submodel, positive coefficients indicate greater model-implied clonogenic burden and therefore lower probability of cure (e.g., advanced stage is adverse); negative coefficients indicate protection (e.g., perioperative chemotherapy or a colorectal primary). In the kinetic submodel, negative coefficients denote faster time-to-relapse among uncured patients.

Convergence diagnostics. All R-hat ≤ 1.002; minimum effective sample size 2662; zero divergent transitions; all Pareto k < 0.7 on leave-one-out cross-validation. Incremental censoring test: cure fraction stable within 0.1 percentage points when follow-up was truncated to 70% of its maximum. Posterior predictive check in Supplementary Figure A3.

CrI = credible interval; θ = model-implied clonogenic burden (expected number of clonogenic foci); λ = Weibull scale (time-to-activation); α = Weibull shape; pd = probability of direction.

cubic spline (P = .72 and .48), or dichotomized at 55% (P = .32 and .19; Supplementary Table A6). Stratifying at the 55% threshold associated with platinum sensitivity in advanced disease [3], the hazard ratio for chemotherapy was 0.55 (0.33–0.91) for EFS and 0.49 (0.29–0.84) for RFS at Ki-67 ≥ 55%, about two thirds of the cohort, and 0.92 (0.39–2.16) and 0.98 (0.42–2.31) below 55%, where only 17 treated patients with a recorded Ki-67 were available (Tables 2 and 3 and Supplementary Table A6): the observed gradient may reflect the greater concentration of information in the Ki-67 ≥ 55% subgroup rather than true effect modification. The association did not vary with age either (interaction P = .26–.78; Supplementary Table A6).

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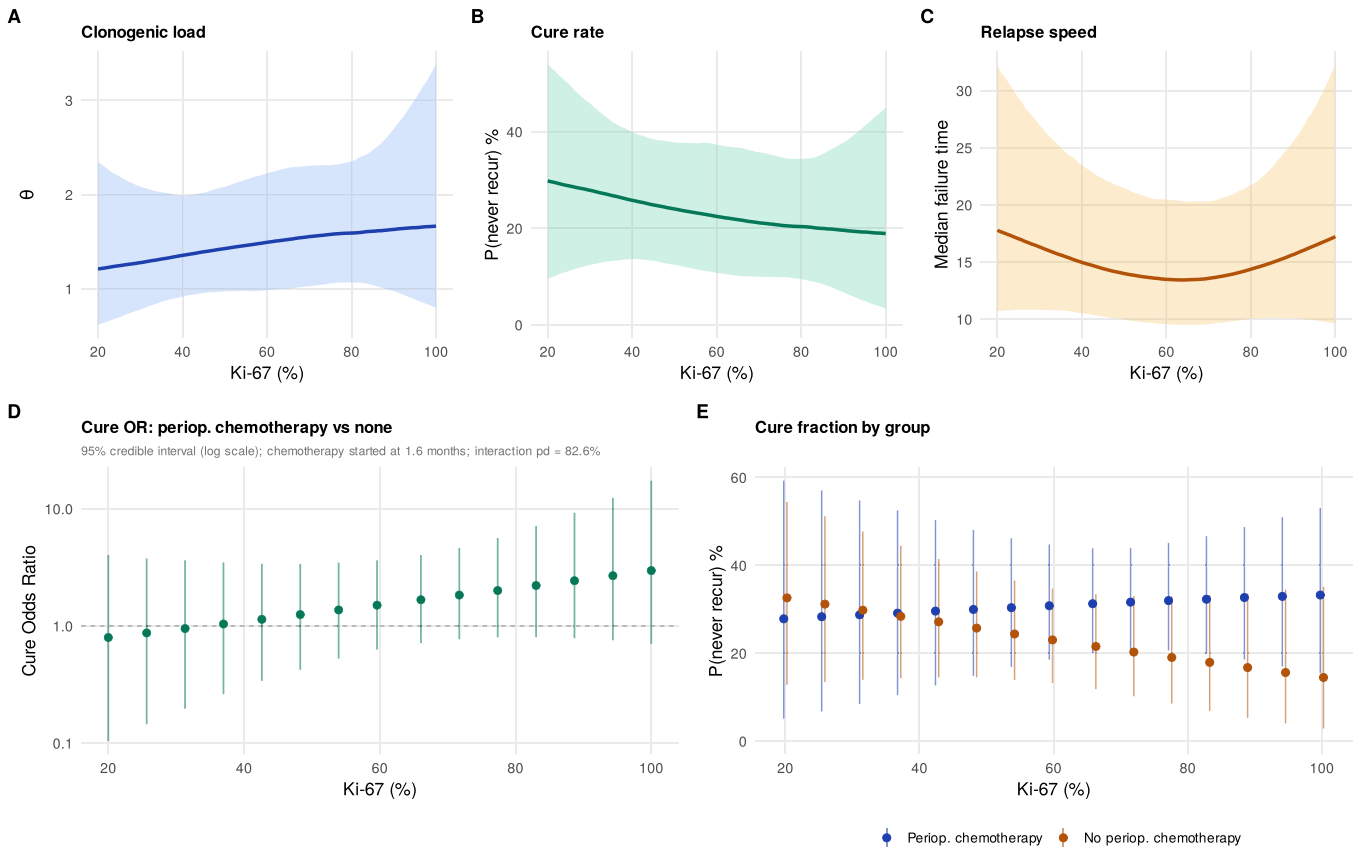


Fig. 2. Bayesian promotion-time cure model estimates across the Ki-67% proliferation index for recurrence-free survival in the resected cohort (n = 162). Panels (A) to (C) show model-estimated quantities as a function of Ki-67%, for untreated patients with the other covariates (age, stage and site) at their means, each with its 95% credible band: (A) the expected residual clonogenic burden (θ); (B) the probability of never recurring; and (C) the median time to relapse among uncured patients (kinetic component). (D) Odds ratio of never recurring for perioperative chemotherapy started at the median observed delay (1.6 months after surgery) versus no perioperative chemotherapy, from the model with a Ki-67 × chemotherapy term, plotted on a logarithmic scale across Ki-67% values with points and 95% credible intervals; the dashed line marks an odds ratio of 1.0. (E) Estimated probability of never recurring by treatment group across Ki-67% values from the same model: blue markers denote patients who received perioperative chemotherapy and orange markers those treated with surgery alone, each with its 95% credible interval. The interaction term is not supported (posterior probability of direction, 83%), so the odds ratio does not vary credibly with Ki-67; the corresponding estimates for event-free survival are given in Table 4 (additive model) and Supplementary Table A6 (interaction term).

3.6. Sensitivity analyses

The chemotherapy association was similar across the prespecified sensitivity analyses (Supplementary Tables A1 and A7–A11; Supplementary Figures A4 and A5). Landmark analyses at 3 and 6 months gave EFS HRs of 0.58 and 0.67. Linear specifications of Ki-67 and age (Supplementary Table A11), the complete-case analysis, multiple imputation extended to ECOG status, adjustment for or stratification by diagnostic era, and exclusion of esophageal and rectal primaries (HR, 0.64; 95% CI, 0.38–1.06; n = 130) gave EFS hazard ratios between 0.57 and 0.67, and in the subsets with resection margin, lymphadenectomy or pathological nodal status recorded, adding each factor did not materially change the chemotherapy estimate within the corresponding subset. Across six prior specifications (asymmetric, symmetric and mirrored), the clonogenic ratio ranged from 0.67 to 0.74 (posterior probability, 90%–94%) and the population cure fraction from 20.4% to 22.7%. E-values and their empirical calibration are given in Supplementary Table A7.

4. Discussion

In this multi-institutional registry analysis of resected grade 3 GEP-NEC, perioperative chemotherapy, analyzed as a time-dependent exposure and adjusted for age, sex, performance status, stage, Ki-67 and primary site, was independently associated with longer EFS and RFS, with a weaker and not significant association with OS. On the composite endpoint, the Bayesian promotion-time cure model attributed the association to a higher probability of long-term cure rather than to a delay in recurrence among uncured patients, with population cure fractions of 22.7% for EFS and 28.6% for RFS that coincide with the Kaplan-Meier plateaus; on RFS, the two components contributed comparably. We found no evidence that the association depended on the Ki-67 index. To our knowledge, this is the first cure-model-based analysis of long-term outcome in nonmetastatic GEP-NEC.

The study's main strength is the convergence of two complementary approaches. In the multivariable Cox model, perioperative chemotherapy remained independently associated with longer EFS and RFS; yet a Cox model cannot tell whether this reflects fewer patients relapsing, later recurrence among those who do, or both [15]. Cure-model approaches resolve this by jointly modeling the proportion who never relapse and the timing of recurrence in those who do [21,31,32]. Here, on EFS, the benefit operated mainly through the clonogenic (cure) pathway, whereas on RFS, which censors deaths unrelated to the disease, the data did not separate cure from delay. The data are therefore compatible with, but do not establish, eradication of micrometastatic disease in a subset of patients: the decomposition is descriptive and depends on the prior structure discussed below.

The magnitude of the association is consistent with other surgical NEC cohorts. Two independent US National Cancer Database analyses reported lower mortality with adjuvant chemotherapy (HR 0.73 [95%

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CI, 0.64–0.84] in resected colorectal NEC [14]; HR 0.58 [95% CI, 0.49–0.68] in a broader gastrointestinal high-grade cohort [33]), and the RGETNE-HERACLES study and Mao et al. reported greater adjuvant benefit in left-sided colorectal tumors [14,34].

Ki-67 was not identified as an effect modifier in these data: none of the Ki-67 × chemotherapy interaction specifications in either the Cox or cure models provided clear evidence of interaction. Although the estimated chemotherapy association appeared stronger in tumors with Ki-67 $\geq$ 55%, the threshold associated with platinum sensitivity in advanced disease [3], this subgroup comprised approximately two thirds of the cohort and most treated patients, and the contrast between strata may therefore partly reflect the distribution of information rather than true heterogeneity of treatment effect. The weak independent prognostic signal of Ki-67 may likewise be related to the cohort's enrichment for highly proliferative tumors (median Ki-67 70%), limited variability, and partial overlap of its prognostic information with stage. Whether proliferative activity can identify patients more likely to benefit from perioperative treatment remains a hypothesis for prospective study.

Against a limited and inconsistent retrospective literature, none of which separated a kinetic from a curative effect [13,14,35,36], the present study cannot remove the uncertainty inherent to observational data, but it adds three elements prior work lacked: the association with EFS and RFS persisted after adjustment for age, sex, performance status, stage, Ki-67 and primary site with a time-dependent exposure that removes immortal time; the cure model attributes it, on the composite endpoint, to a higher cure fraction rather than to a purely kinetic effect, and its implied survival reproduces the observed plateau; and the association was similar across the prespecified sensitivity analyses.

A site-specific consideration applies to esophageal and anorectal primaries, for which definitive chemoradiotherapy is an organ-preserving alternative to resection: in limited-stage small cell esophageal carcinoma, a pooled analysis of 127 patients found longer survival with chemoradiotherapy than with surgery plus chemotherapy (median OS, 33.0 vs 17.5 months) [37], and a series of 22 patients with locally advanced esophageal NEC treated with definitive chemoradiotherapy reported a median OS of 37.5 months [38]. Every patient in this study underwent primary resection, so our results apply to patients in whom resection was chosen and cannot inform the comparison with definitive chemoradiotherapy. The cohort contained only 4 esophageal and 28 rectal primaries; the chemotherapy association was similar after their exclusion, but for these sites the findings should be interpreted with additional caution.

Several limitations should be acknowledged. First, the registry-based observational design precludes causal inference, and residual confounding by indication cannot be excluded [39]: treated patients were younger and had higher Ki-67 values; both were adjusted for, and an unmeasured confounder would need to be associated with both treatment and outcome with risk ratios of about 2.2 to explain the association away, a strength that none of the measured covariates approaches, but a confounder of the strength of age could move the confidence interval to include the null (Supplementary Table A7); resection margin, lymphadenectomy and pathological nodal status were available only in subsets, and comorbidity and treatment completion are not reliably recorded. Second, immortal time was addressed by modeling chemotherapy as a time-dependent exposure, but attribution bias in the retrospective coding of treatment intent cannot be excluded. Third, there was no central pathological review, and histology was recorded under successive WHO classifications. Fourth, the sample had limited power for OS, where the association was weaker and not significant; regimen heterogeneity precluded regimen-specific analyses; and the study period spans changes in classification and practice, although adjustment for and stratification by diagnostic era did not alter the results. Finally, the cure-incidence decomposition relies on an asymmetric prior structure that mitigates the weak identifiability intrinsic to promotion-time cure models with shared covariates and encodes the assumption that platinum-etoposide acts mainly on the residual clonogenic burden; it is informative about how the benefit is apportioned between cure and timing, not about its existence or magnitude, and the posterior correlation of 0.53 between the two chemotherapy coefficients and the results across six prior specifications show that the data separate the two mechanisms only partially. The decomposition is therefore descriptive, and the treatment effect is interpreted as associative and hypothesis-generating.

Beyond the treatment question, two messages stand out. Clinically, a distinct cured fraction challenges the assumption that recurrence is inevitable and argues against the therapeutic nihilism that may limit surgical candidacy. This interpretation is supported by registry data in which resection of nonmetastatic poorly differentiated GEP neuroendocrine neoplasms was associated with longer survival than nonoperative management (adjusted HR, 0.42; 95% CI, 0.36–0.50, in 2245 patients) [40]. Among patients selected for resection, our findings are also consistent with combining surgery with perioperative chemotherapy, a strategy that deserves prospective evaluation; they do not inform the comparison with definitive chemoradiotherapy for esophageal and anorectal primaries. Methodologically, cure models recover information that median survival and Cox hazard ratios miss [15,31]: in rare aggressive tumors, where outcome may hinge on a cured subgroup, whether treatment changes the chance of definitive eradication is the pertinent question.

Author contributions

R.G.C.: conceptualization, methodology, project administration, data curation, investigation, review and editing of the manuscript and original draft writing. A.C.B.: conceptualization, methodology, project administration, data curation, investigation, formal analysis, review and editing of the manuscript and original draft writing. P.J.F.: conceptualization, methodology, project administration, original draft writing, data curation, investigation, and review and editing of the manuscript. J.C.: data curation, investigation, review and editing of the manuscript. V.A.: data curation, investigation, review and editing of the manuscript. M.B.: data curation, investigation, review and editing of the manuscript. C.L.L.: data curation, investigation, review and editing of the manuscript. J.C.R.: data curation, investigation, review and editing of the manuscript. G.C.: data curation, investigation, review and editing of the manuscript. L.N.: data curation, investigation, review and editing of the manuscript. M.S.R.G.: data curation, investigation, review and editing of the manuscript. G.M.: data curation, investigation, review and editing of the manuscript. J.H.: data curation, investigation, review and editing of the manuscript. M.M.A.: data curation, investigation, review and editing of the manuscript. A.C.: data curation, investigation, review and editing of the manuscript.

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Alberto Carmona-Bayonas: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Paula Jimenez-Fonseca:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Jaume Capdevila:** Writing – review & editing, Investigation, Data curation. **Vicente Alonso:** Writing – review & editing, Investigation, Data curation. **Marta Benavent:** Writing – review & editing, Investigation, Data curation. **Carlos Lopez-Lopez:** Writing – review & editing, Investigation, Data curation. **José Carlos Ruffinelli:** Writing – review & editing, Investigation, Data curation. **Guillermo Crespo:** Writing – review & editing, Investigation, Data curation. **Laura Nosti:** Writing – review & editing, Investigation, Data curation. **Maria San-Roman-Gil:** Writing – review & editing, Investigation, Data curation. **Gema Marin:** Writing – review & editing, Investigation, Data curation. **Jorge Hernando:** Writing – review & editing, Investigation, Data curation. **Monica Marazuela Azpiroz:** Writing – review & editing,

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Investigation, Data curation. **Angel Castaño:** Writing – review & editing, Investigation, Data curation. **Rocio Garcia-Carbonero:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Research involving human participants

All procedures were in accordance with the ethical standards of the responsible committee on human research (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients before inclusion in the study.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.117773.

Data availability

Data from this study are available upon reasonable request to the corresponding author.

References

[1] Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. Nat Med 2017;23:664–73. https://doi.org/10.1038/nm.4341.

[2] Dasari A, Wallace K, Halperin DM, Maxwell J, Kunz P, Singh S, et al. Epidemiology of neuroendocrine neoplasms in the US. JAMA Netw Open 2025;8:e2515798. https://doi.org/10.1001/jamanetworkopen.2025.15798.

[3] Sorbye H, Hjortland GO, Vestermark LW, Ladekarl M, Svensson J, Sundlöv A, et al. Characteristics and treatment outcome in a prospective cohort of 639 advanced high-grade digestive neuroendocrine neoplasms (NET G3 and NEC). The NORDIC NEC 2 study. Br J Cancer 2025;133:316–24. https://doi.org/10.1038/s41416-025-03054-w.

[4] Morizane C, Machida N, Honma Y, Okusaka T, Boku N, Kato K, et al. Effectiveness of etoposide and cisplatin vs irinotecan and cisplatin therapy for patients with advanced neuroendocrine carcinoma of the digestive system: the TOPIC-NEC phase 3 randomized clinical trial. JAMA Oncol 2022;8:1447–55. https://doi.org/10.1001/jamaoncol.2022.3395.

[5] Zhang P, Li J, Li J, Zhang X, Zhou J, Wang X, et al. Etoposide and cisplatin versus irinotecan and cisplatin as the first-line therapy for patients with advanced, poorly differentiated gastroenteropancreatic neuroendocrine carcinoma: a randomized phase 2 study. Cancer 2020;126(Suppl 9):2086–92. https://doi.org/10.1002/cncr.32750.

[6] Garcia-Carbonero R, Anton-Pascual B, Modrego A, Del Carmen Riesco-Martinez M, Lens-Pardo A, Carretero-Puche C, et al. Advances in the treatment of gastroenteropancreatic neuroendocrine carcinomas: are we moving forward? Endocr Rev 2023;44:724–36. https://doi.org/10.1210/endrev/bnad006.

[7] Eads JR, Halfdanarson TR, Asmis T, Bellizzi AM, Bergsland EK, Dasari A, et al. Expert consensus practice recommendations of the North American Neuroendocrine Tumor Society for the management of high grade gastroenteropancreatic and gynecologic neuroendocrine neoplasms. Endocr Relat Cancer 2023;30:e220206. https://doi.org/10.1530/ERC-22-0206.

[8] Sorbye H, Grande E, Pavel M, Tesselaar M, Fazio N, Reed NS, et al. European Neuroendocrine Tumor Society (ENETS) 2023 guidance paper for digestive neuroendocrine carcinoma. J Neuroendocrinol 2023;35:e13249. https://doi.org/10.1111/jne.13249.

[9] Pellat A, Walter T, Augustin J, Hautefeuille V, Hentic O, Do Cao C, et al. Chemotherapy in resected neuroendocrine carcinomas of the digestive tract: a national study from the French group of endocrine tumours. Neuroendocrinology 2020;110:404–12. https://doi.org/10.1159/000502825.

[10] Shen C, Chen H, Chen H, Yin Y, Han L, Chen J, et al. Surgical treatment and prognosis of gastric neuroendocrine neoplasms: a single-center experience. BMC Gastroenterol 2016;16:111. https://doi.org/10.1186/s12876-016-0505-5.

[11] Sørbye H, Westre B, Horn A. Curative surgery after neoadjuvant chemotherapy in metastatic poorly differentiated neuroendocrine carcinoma. Eur J Surg Oncol 2007;33:1209–10. https://doi.org/10.1016/j.ejso.2007.01.030.

[12] Dasari A, Shen C, Devabhaktuni A, Nighot R, Sorbye H. Survival according to primary tumor location, stage, and treatment patterns in locoregional gastroenteropancreatic high-grade neuroendocrine carcinomas. Oncologist 2022;27:299–306. https://doi.org/10.1093/oncolo/oyab039.

[13] Schmitz R, Mao R, Moris D, Strickler JH, Blazer DG. Impact of postoperative chemotherapy on the survival of patients with high-grade gastroenteropancreatic neuroendocrine carcinoma. Ann Surg Oncol 2021;28:114–20. https://doi.org/10.1245/s10434-020-08730-0.

[14] Mao R, Li K, Cai J-Q, Luo S, Turner M, Blazer D, et al. Adjuvant chemotherapy versus observation following resection for patients with nonmetastatic poorly differentiated colorectal neuroendocrine carcinomas. Ann Surg 2021;274:e126–33. https://doi.org/10.1097/SLA.0000000000003562.

[15] Msaouel P, Jimenez-Fonseca P, Lim B, Carmona-Bayonas A, Agnelli G. Medicine before and after David Cox. Eur J Intern Med 2022;98:1–3. https://doi.org/10.1016/j.ejim.2022.02.022.

[16] Andersson TM, Dickman PW, Eloranta S, Lambert PC. Estimating and modelling cure in population-based cancer studies within the framework of flexible parametric survival models. BMC Med Res Methodol 2011;11:96. https://doi.org/10.1186/1471-2288-11-96.

[17] Mateos L, Jiménez-Fonseca P, Gallego J, Lecumberri A, Custodio A, Martínez De Castro E, et al. Does perioperative FLOT increase cure rates in resectable esophageal adenocarcinoma? A mixture cure model analysis. Br J Cancer 2026;134:414–27. https://doi.org/10.1038/s41416-025-03264-2.

[18] Carmona-Bayonas A, Álvarez-Escolá C, Ballester Navarro I, Hernando Cubero J, Mangas Cruz MÁ, Garcia-Centeno R, et al. Does adjuvant mitotane impact cure rates in adrenocortical carcinoma? Insights from the ICARO-GETTHI/SEEN registry. J Clin Endocrinol Metab 2025;110:3155–67. https://doi.org/10.1210/clinem/dgaf082.

[19] Amico M, Van Keilegom I. Cure models in survival analysis. Annu Rev Stat Appl 2018;5:311–42. https://doi.org/10.1146/annurev-statistics-031017-100101.

[20] Ricci C, Casadei R, Taffurelli G, Campana D, Ambrosini V, Pacilio CA, et al. Is radical surgery always curative in pancreatic neuroendocrine tumors? A cure model survival analysis. Pancreatology 2018;18:313–7. https://doi.org/10.1016/j.pan.2018.02.008.

[21] Yakovlev AY, Tsodikov AD, Asselain B. Stochastic models of tumor latency and their biostatistical applications. Singapore: World Scientific; 1996.

[22] Tsodikov A. A proportional hazards model taking account of long-term survivors. Biometrics 1998;54:1508–16.

[23] Chen M-H, Ibrahim JG, Sinha D. A new Bayesian model for survival data with a surviving fraction. J Am Stat Assoc 1999;94:909–19. https://doi.org/10.2307/2670006.

[24] Garcia-Carbonero R, Capdevila J, Crespo-Herrero G, Díaz-Pérez JA, Martínez Del Prado MP, Alonso Orduña V, et al. Incidence, patterns of care and prognostic factors for outcome of gastroenteropancreatic neuroendocrine tumors (GEP-NETs): results from the National Cancer Registry of Spain (RGETNE). Ann Oncol 2010;21:1794–803. https://doi.org/10.1093/annonc/mdq022.

[25] Carmona-Bayonas A, Jiménez-Fonseca P, Lamarca Á, Barriuso J, Castaño Á, Benavent M, et al. Prediction of progression-free survival in patients with advanced, well-differentiated, neuroendocrine tumors being treated with a somatostatin analog: the GETNE-TRASGU Study. J Clin Oncol 2019;37:2571–80. https://doi.org/10.1200/JCO.19.00980.

[26] Nuñez-Valdovinos B, Carmona-Bayonas A, Jimenez-Fonseca P, Capdevila J, Castaño-Pascual Á, Benavent M, et al. Neuroendocrine tumor heterogeneity adds uncertainty to the World Health Organization 2010 classification: real-world data

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from the Spanish tumor registry (R-GETNE). Oncologist 2018;23:422–32. https://doi.org/10.1634/theoncologist.2017-0364.
[27] Harrell FE. Regression modeling strategies: with applications to linear models, logistic and ordinal regression, and survival analysis. 2nd ed. New York: Springer; 2015.
[28] Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, et al. Stan: a probabilistic programming language. J Stat Softw 2017;76. https://doi.org/10.18637/jss.v076.i01.
[29] Ibrahim JG, Chen MH, Sinha D. Bayesian semiparametric models for survival data with a cure fraction. Biometrics 2001;57:383–8. https://doi.org/10.1111/j.0006-341x.2001.00383.x.
[30] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2023.
[31] Lambert P, Bremhorst V. Estimation and identification issues in the promotion time cure model when the same covariates influence long- and short-term survival. Biom J 2019;61:275–89. https://doi.org/10.1002/bimj.201700250.
[32] Gressani O, Faes C, Hens N. Laplacian-P-splines for Bayesian inference in the mixture cure model. Stat Med 2022;41:2602–26. https://doi.org/10.1002/sim.9373.
[33] Alese OB, Jiang R, Shaib W, Wu C, Akce M, Behera M, et al. High-grade gastrointestinal neuroendocrine carcinoma management and outcomes: a national cancer database study. Oncologist 2019;24:911–20. https://doi.org/10.1634/theoncologist.2018-0382.
[34] Iglesias Álvarez G, Capdevila J, Garcia-Carbonero R, Jimenez-Fonseca P, Benavent M, Vicente MÁ, et al. Proximal-to-distal gradient and its implications in differentiation and prognosis in colorectal neuroendocrine neoplasms: the RGETNE-HERACLES study. Neuroendocrinology 2026. https://doi.org/10.1159/000552234.
[35] Lin J-P, Zhao Y-J, He Q-L, Hao H-K, Tian Y-T, Zou B-B, et al. Adjuvant chemotherapy for patients with gastric neuroendocrine carcinomas or mixed adenoneuroendocrine carcinomas. Br J Surg 2020;107:1163–70. https://doi.org/10.1002/bjs.11608.
[36] Ma F, Wang B, Xue L, Kang W, Li Y, Li W, et al. Neoadjuvant chemotherapy improves the survival of patients with neuroendocrine carcinoma and mixed adenoneuroendocrine carcinoma of the stomach. J Cancer Res Clin Oncol 2020;146:2135–42. https://doi.org/10.1007/s00432-020-03214-w.
[37] Meng MB, Zaorsky NG, Jiang C, Tian LJ, Wang HH, Liu CL, et al. Radiotherapy and chemotherapy are associated with improved outcomes over surgery and chemotherapy in the management of limited-stage small cell esophageal carcinoma. Radiother Oncol 2013;106:317–22. https://doi.org/10.1016/j.radonc.2013.01.008.
[38] Honma Y, Nagashima K, Hirano H, Shoji H, Iwasa S, Takashima A, et al. Clinical outcomes of locally advanced esophageal neuroendocrine carcinoma treated with chemoradiotherapy. Cancer Med 2020;9:595–604. https://doi.org/10.1002/cam4.2708.
[39] Carmona-Bayonas A, Jimenez-Fonseca P, Fernández-Somoano A, Álvarez-Manceñido F, Castañón E, Custodio A, et al. Top ten errors of statistical analysis in observational studies for cancer research. Clin Transl Oncol 2018;20:954–65. https://doi.org/10.1007/s12094-017-1817-9.
[40] Thornblade LW, Warner SG, Melstrom L, Ituarte PHG, Chang S, Li D, et al. Does surgery provide a survival advantage in non-disseminated poorly differentiated gastroenteropancreatic neuroendocrine neoplasms? Surgery 2021;169:1417–23. https://doi.org/10.1016/j.surg.2021.01.026.

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