Efficacy of first-line chemotherapy based on primary site of tumor versus etoposide-platinum in advanced gastroenteropancreatic neuroendocrine carcinoma

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Background: Gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) constitute a rare and aggressive group of malignancies usually with widespread disease. There are limited studies on GEP-NECs, and therefore, we aim to acquire more information on the clinical features, treatment regimens, and prognosis.

Methods: Data from advanced GEP-NECs patients who had not previously received systemic treatment for advanced disease at The First Affiliated Hospital of Nanjing Medical University from 2010 to 2022 were retrospectively collected. Relationships between clinical-pathological features, treatment regimens, and prognosis were investigated using Kaplan-Meier curves and cox regression models.

Results: A total of fifty-four patients were enrolled in the study. The median age was 65.5 years and 79.6% were male. At diagnosis, 51.9% and 3.7% of patients developed liver and brain metastasis respectively. Sixteen (29.6%) patients received chemotherapy according to primary site of tumor (PST), while thirty-eight (70.4%) were treated with etoposide-platinum (EP) regimen, which based on the first-line treatment of advanced small cell lung cancer (SCLC). No significant differences on progression-free survival (PFS) and response rate were observed between these two groups. Univariate survival analysis showed that liver metastasis, elevated baseline serum carcinoembryonic antigen, elevated baseline serum neuron-specific enolase, elevated baseline serum lactate dehydrogenase, and elevated baseline serum neutrophil-to-lymphocyte ratio (NLR) were associated with shorter PFS. After multivariate analysis, elevated NLR was the only factor that remained significantly associated with shorter PFS (P=0.01).

Conclusions: GEP-NECs are aggressive neoplasms, of which elevated NLR is proven to be an independent negative predictor. Treatment regimens based on PST are not inferior to regiments based on SCLC (EP) for GEP-NECs patients. Large-scale, prospective randomized controlled trials are required to establish the standard of care.

Keywords: Neuroendocrine carcinoma (NEC); chemotherapy; prognostic biomarkers

Introduction

Neuroendocrine tumors (NETs) are characterized by the expression of neuroendocrine proteins secreting peptide hormones or bio-amines, while highly aggressive and poorly differentiated neuroendocrine carcinomas (NECs) are usually accompanied by rapidly lethal disease (1). The incidence of NECs is increasing due to the emerging precise histopathologic diagnosis. NECs arise most commonly in the lung (91.3%) (2), while extrapulmonary NECs are mainly located along the gastrointestinal tract (3). According to the World Health Organization grading system, neuroendocrine neoplasms with mitotic count >20 per 10 high power fields (HPF) and/or Ki-67 index >20% are classified as NECs (4). Compared with well-differentiated NETs, NECs are more aggressive and are usually diagnosed at advanced stages. A Surveillance, Epidemiology, and End Results (SEER) database analysis of 162,983 cases disclosed that 60.8% have developed distant metastasis at diagnosis and median overall survival (OS) in untreated NEC patients is only 4–6 months (5,6).

Given that some of these neoplasms share similar immunohistochemical characteristics with small cell lung cancer (SCLC), chemotherapy of etoposide-platinum (EP), the standard of care for SCLC, is widely used in gastroenteropancreatic NECs (GEP-NECs) (7,8). Several retrospective studies evaluated the efficacy of EP as first-line chemotherapy in GEP-NECs and found a median

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Highlight box

Key findings
- Chemotherapy regimens based on primary site of tumor and small cell lung cancer (SCLC) are both optional for advanced gastroenteropancreatic neuroendocrine carcinomas (GEP-NECs) and elevated neutrophil-to-lymphocyte ratio (NLR) is an independent negative prognostic factor.

What is known and what is new?
- When making treatment decisions for advanced GEP-NECs, clinicians often follow the paradigm of SCLC due to morphological similarities. However, the outcomes were unsatisfying and effective prognostic factors are lacking.
- In this retrospective study, we found no statistical difference in treatment outcomes between patients receiving these two regimens. We also proved that elevated baseline NLR is an independent negative prognostic factor for advanced GEP-NECs.

What is the implication, and what should change now?
- Both regimens are optional and future studies are required to establish optimum treatment protocols for GEP-NECs.
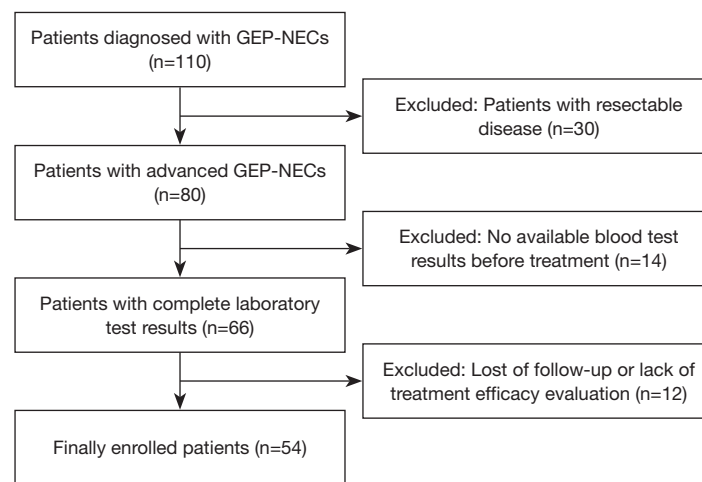
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response rate of 42.95% (28–62.5%), a median progression-free survival (PFS) of 5.65 months and a median OS of 11.67 months (9-11). However, according to National Comprehensive Cancer Network (NCCN) guidelines (12), the recommendation for EP regimen in GEP-NECs is only grouped into category 2A, which means the adoption of this regimen was based upon only low-level evidence, indicating that there is a lack of optimal treatment regimen for GEP-NECs. And the response rate and prognosis of GEP-NECs are even worse due to the molecular heterogeneity with SCLC (13). Other regimen, including temozolomide based chemotherapy, Folinic acid with fluorouracil and oxaliplatin (FOLFOX), Folinic acid with fluorouracil and irinotecan (FOLFIRI), were only covered in some small cohorts or under clinical trials (14-16). Immunotherapy and target therapy are feasible only in patients harboring certain gene mutations (12).

Meanwhile, it is noteworthy that in terms of cell morphology, not all GEP-NECs appear as pure small cells, adenocarcinoma or squamous cell carcinoma components could also be observed in GEP-NECs. In these so-called mixed neuroendocrine non-NECs (MiNECs) (4), squamous cell carcinoma components may exist in esophageal NECs while adenocarcinoma is found in gastric and colorectal NECs. This subtype and molecular differences between GEP-NECs and SCLC raise the problem of whether to adopt chemotherapy based on primary site of tumor (PST).

Prognostic factors have always been essential parts of clinical studies. Blood markers such as platelet count, neutrophil-to-lymphocyte (NLR) (17), lactate dehydrogenase (LDH) (5), and histopathological data such as Ki-67 proliferation index (5,6) have been confirmed useful in predicting treatment outcomes in lung, stomach and many other malignant tumors (18). However, the application value of these markers in GEP-NECs remains to be explored.

Given the paucity of cases and poor prognosis, the standard management and prognostic factors of GEP-NECs have not yet been defined. To improve our understanding of this rare tumor, we performed a retrospective and real-world study in our center to investigate the clinicopathological features of GEP-NEC patients. We also identified risk factors that influence prognosis and made a comparison of the effects of different first-line treatment regimens. We present this article in accordance with the TREND reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-64/rc).

Figure 1 Patient selection flow-chart. GEP-NECs, gastroenteropancreatic neuroendocrine carcinomas.

Methods

Study subject and data collection

This retrospective and real-world study was conducted based on the medical records from January 2010 to December 2022 in The First Affiliated Hospital of Nanjing Medical University. The inclusion criteria were as follows: (I) pathologically diagnosed with GEP-NECs from biopsied or surgically resected specimens; (II) diagnosed at an advanced stage or with recurrence at least six months after adjuvant chemotherapy; (III) received chemotherapy with/without target therapy and immunotherapy; (IV) no other primary malignancies. *Figure 1* summarizes the inclusion criteria of patients and the processing of data collected. Information on age, gender, symptoms at diagnosis, primary tumor location, stage at diagnosis, sites of metastases, morphology, baseline laboratory blood test results, treatment regimen, and clinical outcomes was reviewed. Tumor node metastasis (TNM) stage was assessed according to the seventh edition criteria of the American Joint Committee on Cancer (AJCC) staging system. Objective response rate (ORR; defined as the percentage of patients with complete or partial response), and disease control rate (DCR; defined as the percentage of patients with objective response and stable disease) were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. PFS was defined as the time from initiation of chemotherapy to confirmation of disease progression.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Affiliated Hospital of Nanjing Medical University (No. 2022-SR-706)

and individual consent for this retrospective analysis was waived.

Statistical analysis

The cut-off value of the NLR, platelet-to-lymphocyte ratio (PLR) and other factors for predicting PFS was calculated using R version 4.2.1 and the "survminer" package. PFS was estimated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate analyses by COX proportional hazard models were performed, and the hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) for PFS were calculated. $P<0.05$ was considered statistically significant. Statistical analysis was performed using R version 4.2.1 (The R Foundation, Vienna, Austria).

Results

Patient demographics

We retrospectively reviewed 54 patients diagnosed with GEP-NECs. The main clinicopathologic features of all enrolled patients in the study are summarized in *Table 1*. Forty-three (79.6%) patients were male and the median age at diagnosis was 65.5 (range, 35–81) years. The most common primary sites were esophagus (40.7%), followed by stomach (33.3%), colorectum (13.0%), and pancreas and hepatobiliary tract (13.0%). Forty-seven (87.0%) patients were diagnosed at stage IV and 7 (13.0%) recurred at least 6 months after adjuvant chemotherapy who previously

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Table 1 Demographic and clinical-pathological characteristics of all patients

Characteristic	Data, N=54
Age, years	65.5 [35–81]
Gender	
Female	11 (20.4)
Male	43 (79.6)
Location	
Esophagus	22 (40.7)
Stomach	18 (33.3)
Colorectum	7 (13.0)
Liver/gall bladder/pancreas	7 (13.0)
Clinical manifestation	
Abdominal pain or distention	20 (37.0)
Dysphagia	20 (37.0)
Gastrointestinal bleeding	5 (9.3)
Others/asymptomatic	13 (24.1)
Hormonal symptoms	0 (0)
Clinical stage at diagnosis	
Advanced	47 (87.0)
Recurrent[a]	7 (13.0)
Distant organ metastasis	
Liver	28 (51.9)
Lung	8 (14.8)
Bone	6 (11.1)
Brain	2 (3.7)
Pathology	
Pure NEC	45 (83.3)
MiNEC	9 (16.7)
Ki-67(%)	
≥80	30 (56.6)
<80	20 (37.0)
NA	4 (7.4)
Neuroendocrine markers	
Syn(+) (in 52 pts available)	51 (98.1)
CgA(+) (in 47 pts available)	27 (57.4)
CD56(+) (in 47 pts available)	40 (85.1)

Data are presented as n (%) or median [range]. [a], at least 6 months after last cycle of adjuvant chemotherapy. NEC, neuroendocrine carcinoma; MiNEC, mixed neuroendocrine non-NEC; Syn, synaptophysin; CgA, chromogranin A.

Table 2 Efficacy of first-line chemotherapy according to treatment regimen

Characteristic	SCLC	PST	P value
Total number	38 (70.4)	16 (29.6)	–
No. of cycles	4 [2–10]	4 [1–7]	0.75
PFS (months)	4.75 [1.57–21.5]	4.98 [1.27–12.5]	0.47
Response rate			–
CR	0 (0)	0 (0)	–
PR	10 (26.3)	4 (25.0)	–
SD	16 (42.1)	4 (25.0)	–
PD	12 (31.6)	8 (50.0)	–
DCR	68.4%	50.0%	0.20
ORR	26.3%	25.0%	>0.99

Data are presented as n (%) or median [range]. SCLC, small cell lung cancer; PST, primary site of tumor; PFS, progression-free survival; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; DCR, disease control rate; ORR, objective response rate.

underwent radical surgery. The most frequent site of distant metastasis was liver (51.9%) while brain metastasis was only seen in two patients. Among all the patients, no hormone-related symptoms were detected. Abdominal distention or pain (37.0%), dysphagia (37.0%), gastrointestinal bleeding (9.3%) and other clinical manifestations presented at diagnosis were related to tumor growth or metastases.

Histologically, the average and median Ki-67 proliferation index was 78% and 80% (range, 30–95%, available in 50 patients). Neuroendocrine markers were positive for synaptophysin (Syn) in 98.1% of the 52 patients with data, chromogranin (CgA) in 57.4% of the 47 with data, and cluster of differentiation 56 (CD56) in 85.1% of the 47 with data. All three markers were positive in 23 patients. In terms of pathological type, 9 (16.7%) patients had MiNEC.

Treatment patterns and response

The efficacy of first-line chemotherapy according to treatment regimen is shown in *Table 2*. The median PFS for all the patients was 4.85 months (*Figure 2*). Thirty-eight (70.4%) patients were managed with EP that used for reference to first-line chemotherapy in advanced SCLC, while 16 (29.6%) counterparts received first-line chemotherapy based on primary site of the tumor, e.g., capecitabine + oxaliplatin for colorectal NEC patients,

S1+oxaliplatin for gastric NEC patients, paclitaxel + platinum for esophageal NEC patients, etc. Median number of chemotherapy cycles was four for both cohorts. There were no statistically significant differences between these two regimens with regard to median PFS (4.75 *vs.* 4.98 months, P=0.47, *Figure 3A*), DCR (68.4% *vs.* 50.0%, P=0.20) and ORR (26.3% *vs.* 25.0%, P>0.99).
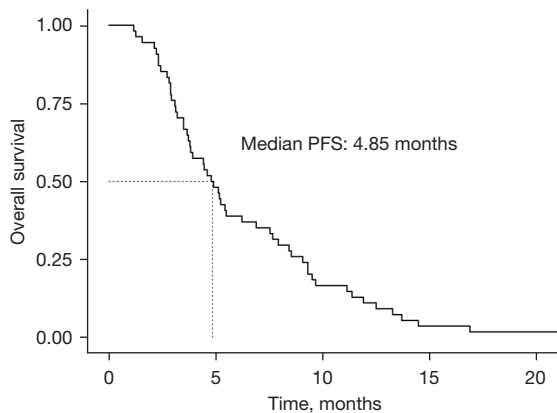

Figure 2 Median PFS in months among the whole population of patients with GEP-NECs. PFS, progression-free survival; GEP-NECs, gastroenteropancreatic neuroendocrine carcinomas.

Prognostic factors of PFS

Results of univariate and multivariate analyses of prognostic factors of the whole cohort are shown in *Table 3*. According to univariate analysis, liver metastasis (with *vs.* without, median 3.50 *vs.* 5.43 months, HR 1.841, P=0.03, *Figure 3B*), elevated baseline serum carcinoembryonic antigen (CEA) level [≥1 upper limit of normal value (ULN) *vs.* <1ULN, median 3.93 *vs.* 7.22 months, HR 2.081, P=0.01, *Figure 3C*], elevated baseline serum neuron-specific enolase (NSE) level (≥2ULN *vs.* <2ULN, median 3.83 *vs.* 6.90 months, HR 1.430, P=0.02, *Figure 3D*), elevated baseline serum LDH level (≥1ULN *vs.* <1ULN, median 3.78 *vs.* 5.20 months, HR 1.792, P=0.04, *Figure 3E*) and elevated baseline serum NLR level (≥2 *vs.* <2, median 4.13 *vs.* 8.43 months, HR 2.838, P=0.001, *Figure 3F*) were significantly associated with poorer PFS, while there was no significant difference in PFS in terms of Ki-67 index (≥80% *vs.* <80, median 4.14 *vs.* 4.85 months, P=0.69), baseline serum CA199 level (≥1ULN *vs.* <1ULN, median 4.34 *vs.* 4.90 months, P=0.055), baseline serum PLR level (≥105 *vs.* <105, median 4.18 *vs.* 6.90 months, P=0.62), baseline serum alkaline phosphatase (ALP) level (≥1ULN *vs.* <1ULN, median 4.63 *vs.* 5.17 months, P=0.06), and combination of target therapy and/

Table 3 Univariate and multivariate analysis of prognostic factor for progression-free survival

Characteristic	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (≥70 *vs.* <70 years)	1.193 (0.645–2.204)	0.57	–	–
Gender (male *vs.* female)	1.339 (0.685–2.619)	0.39	–	–
Liver metastasis (with *vs.* without)	1.841 (1.052–3.223)	0.03	1.595 (0.867–2.932)	0.13
Ki-67 index (≥80% *vs.* <80%)	1.122 (0.627–2.007)	0.69	–	–
Baseline serum CEA level (≥1ULN *vs.* <1ULN)	2.081 (1.146–3.780)	0.01	1.415 (0.737–2.716)	0.29
Baseline serum NSE level[a] (≥2ULN *vs.* <2ULN)	1.430 (1.039–1.969)	0.02	–	–
Baseline serum CA199 level (≥1ULN *vs.* <1ULN)	2.063 (0.984–4.323)	0.055	–	–
Baseline serum LDH level (≥1ULN *vs.* <1ULN)	1.792 (1.007–3.188)	0.04	0.926 (0.453–1.893)	0.83
Baseline serum NLR level (≥2 *vs.* <2)	2.838 (1.448–5.562)	0.001	2.705 (1.183–6.184)	0.01[b]
Baseline serum PLR level (≥105 *vs.* <105)	1.156 (0.646–2.067)	0.62	–	–
Baseline serum ALP level (≥1ULN *vs.* <1ULN)	1.857 (0.972–3.546)	0.06	–	–
Combination therapy[c] (with *vs.* without)	1.116 (0.454–1.769)	0.44	–	–

[a], baseline serum NSE level was excluded from multivariate analysis because of lack of data for 8 patients; [b], significant; [c], combination therapy includes target therapy and/or immunotherapy. HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; ULN, upper limit of normal value; NSE, neuron-specific enolase; CA199, carbohydrate antigen 19-9; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ALP, alkaline phosphatase.
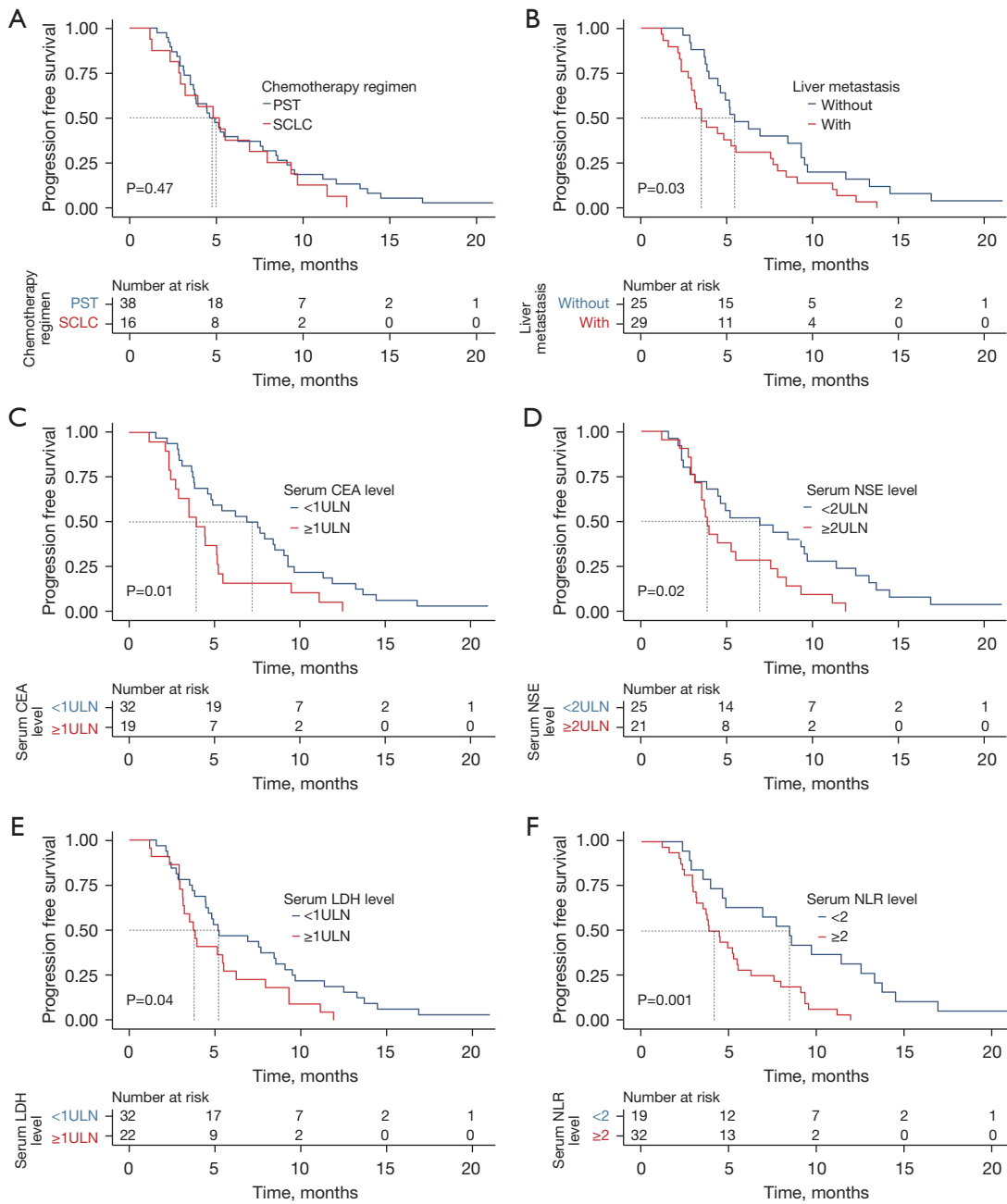
Figure 3 Kaplan-Meier curves of progression-free survival in patients with GEP-NECs, stratified by: (A) chemotherapy regimen, (B) liver metastasis, (C) serum CEA level, (D) serum NSE level, (E) serum LDH level, and (F) serum NLR level. GEP-NECs, gastroenteropancreatic neuroendocrine carcinomas; PST, primary site of tumor-like chemotherapy; SCLC, small cell lung cancer; CEA, carcinoembryonic antigen; ULN, upper limit of normal value; NSE, neuron-specific enolase; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio.

or immunotherapy (with *vs.* without, median 6.23 *vs.* 3.80 months, P=0.44).

A multivariate Cox proportion hazards model disclosed that elevated NLR (HR 2.705, 95% CI: 1.183–6.184, P=0.01) was a significant independent negative prognostic factor for GEP-NECs.

Discussion

The study aimed to analyze clinical and histological characteristics of GEP-NECs, as well as treatment regimens and several prognostic factors in a real-world setting.

Functional NETs have the ability to secret certain hormones like histamine and 5-hydroxytryptamine, thus inducing palpitation, flushing and many other carcinoid syndromes (19,20). However, the majority of NECs are clinically silent and are always presented with abdominal distention, bleeding and other gastrointestinal syndromes. Therefore, many patients may be wrongly treated as benign diseases or diagnosed at an advanced stage. These clinical characteristics also presented in our study: none of the patients complained of any hormone-related manifestations, which also attaches great importance to early diagnosis and surveillance.

Because of the rarity of disease and lack of large-scale prospective studies, there are no standard nor evidence-based chemotherapeutic recommendations for the treatment of GEP-NECs. When making treatment decisions, clinicians often follow the paradigm of SCLC due to morphological similarities. However, according to NCCN guideline (12), recommendation of chemotherapy regimen for EP is only classified as category 2A. Clinical data also show that even with the same regimen, parameters assessing clinical outcomes of NECs are much more unsatisfying than those in SCLC (13). The poor survival rate observed in locally advanced and metastatic settings challenges the treatment strategies, indicating that optimal therapy for GEP-NECs may be site-specific and different from SCLC (21). While in the current cohort, there is no statistical difference in treatment outcome indicators, such as PFS, DCR and ORR between patients receiving both chemotherapy strategies, suggesting that either regimen is optional.

On the other hand, only 2 (3.7%) patients in our study developed brain metastasis at diagnosis. However in SCLC, brain metastasis rates are much higher and carcinoid syndromes are more common (22). These features strongly suggest a certain degree of molecular divergence between GEP-NECs and SCLC.

Genomically, GEP-NECs disclose typical alterations of adenocarcinoma from the same sites of origin (23). For example in colorectal NECs, mutation rates of KRAS and BRAF range from 25% to 60% (24-26), making BRAF inhibitor a promising therapeutic strategy. GEP-NECs are highly vascularized tumors and are able to secrete vascular endothelial growth factor (VEGF), serving as a possible therapeutic target (27). A retrospective study conducted by Mishima *et al.* (28) focused on ramucirumab, a monoclonal antibody for VEGF receptor 2, which showed promising efficacy in gastric NECs, with ORR of 59% and median PFS of 7.7 months. In our cohort, however, the improvement of treatment outcomes could hardly be observed because only 13 (24.1%) patients received combination therapy of target and/or immunotherapy. Nonetheless, the combination therapy may serve as a promising treatment option according to the theory and mechanism mentioned above. As a result, the efficacy and safety of target therapy based on adenocarcinoma from the site of origin should be explored. Comprehensive tumor molecular profiling should be included in future large-scale prospective studies to identify novel therapeutic targets.

Apart from medical treatment, surgery and radiotherapy have been applied alone or in combination to improve survival in GEP-NECs patients. Surgery has been the primary curative treatment for early-stage malignant tumors (29). Even in metastatic diseases, palliative resection is indicated for preventing complications and reducing tumor burden (30). Liver metastasis is a negative prognostic factor in the current study, suggesting the significance of locoregional-directed therapy, including radiofrequency ablation and chemoembolization in cases with liver-predominant disease (29). To improve prognosis, a tailored treatment regimen is required for every single individual, thus precise pathological and molecular examinations are strongly recommended in the treatment of rare, advanced malignancies.

Furthermore, searching for prognostic factors is essential in the prediction of prognosis in malignant tumors, especially in highly-aggressive GEP-NECs. As a marker of cell proliferation, Ki-67 expression could predict prognosis to some extent. In the NORDIC study (5), PFS and OS in patients with Ki-67>55% significantly decreased while Lamarca *et al.* (31) identified 80% as a cut-off value for OS. In our cohort, given that the average and median Ki-67 index had already reached 78% and 80%, it was not statistically related to shortened PFS (P=0.607), reflecting the high aggressiveness of GEP-NECs.

Several studies have investigated serum markers as prognostic tools in other aggressive types of cancer (5,17,18,32). In our study, elevated baseline serum CEA, NSE, LDH and NLR levels were associated with shorter PFS. After multivariate analysis, elevated NLR level was the only independent negative prognostic factor. The

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inflammatory milieu within the tumor microenvironment plays a pivotal role in cancer development and progression, and NLR serves as a surrogate marker reflecting this delicate balance (33). Elevated NLR results from a relatively increased neutrophil count or depleted lymphocyte count and has been consistently linked to increased tumor aggressiveness, poorer response to therapy. Neutrophils may act as tumor-promoting leukocytes by secreting high levels of TGF-β, interleukin-18 (34), and VEGF (35), thus promoting invasion and angiogenesis. Conversely, diminished lymphocyte levels may compromise the anti-tumor immune response (36). The combination of these factors, as captured by NLR, offers a holistic view of the host's immune status and tumor microenvironment.

While this study has a number of advantages and certainly complements the current evidence base, there were some limitations. First, as this is a small-scale and retrospective study based on a real-world setting, statistics such as OS are not available, thus relationships between first-line chemotherapy and OS are unclear. Second, biological data, including neuroendocrine markers and blood tumor markers, are not available for all patients, which decreases the power of the multivariate analysis. Third, gene test results are absent, indicating that molecular analyses are unable to be performed, which prevents us from evaluating the efficacy of target therapy and/or immunotherapy. The representativeness and accuracy of statistical analysis are compromised given the small sample size of the study. All these deficiencies should be considered in future studies.

Conclusions

GEP-NECs are extremely aggressive tumors with poor prognosis, and elevated NLR is an independent negative prognostic factor. In terms of treatment, chemotherapy regimens based on PST and SCLC are both optional. Future studies are required to establish optimum treatment protocols for GEP-NECs.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-64/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-64/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-64/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-64/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Affiliated Hospital of Nanjing Medical University (No. 2022-SR-706) and individual consent for this retrospective analysis was waived.

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