Original Article

Efficacy of transcatheter arterial chemoembolization-based multimodal treatment in patients with neuroendocrine tumors involving the liver

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Background: Neuroendocrine tumors (NETs) are a group of heterogeneous diseases which have liver dominant involvement potency. The value of transcatheter arterial chemoembolization (TACE) treatment for NET patients in the era of somatostatin analogues (SSAs) and anti-proliferation agents needs further study. The study aimed to investigate the value of TACE-based treatment for NETs involving the liver.

Methods: A group of 29 NET patients received TACE-based multimodal treatment in the Department of Hepatic Oncology of Zhongshan Hospital, Fudan University was retrospectively collected. Baseline characteristics of included patients were analyzed. Kaplan-Meier analysis and Cox proportional hazards regression were used to investigate clinical and pathological parameters on overall survival (OS) and progression free-survival (PFS) in NET patients.

Results: The median OS and PFS were 20.0 [95% confidence interval (CI): 13.4–26.5] months and 11.0 (95% CI: 7.7–14.3) months, respectively. Tumor grade (P=0.001), number of TACE treatments (P=0.003), neutrophil to lymphocyte ratio (NLR) (P=0.005) and systemic treatment mode (P=0.007) were significantly associated with OS while tumor grade (P<0.001), number of TACE treatments (P=0.002), aspartate aminotransferase (AST) (P=0.01) and systemic treatment mode (P=0.001) were of significance to PFS in multivariate Cox regression analyses.

Conclusions: TACE-based multimodal treatment is beneficial for NETs involving the liver. The sequence and timing of local treatment and systemic treatment allocation need further investigation.

Keywords: Neuroendocrine tumors (NETs); transcatheter arterial chemoembolization (TACE); overall survival (OS); progression-free survival (PFS)

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Introduction

Neuroendocrine tumors (NETs) consist of a group of heterogeneous neoplasms arising from neuroendocrine cells, and the most affected organs vary geographically (1,2). The incidence of NETs increases gradually with the advancement of imaging technology and health care system (1,2). NETs can be categorized as functional and non-functional. Functional NETs may cause symptoms such as flushing, diarrhea, hyper- or hypoglycemia mediated by hormonal abnormality while nonfunctional NETs only demonstrate nodular imaging change.

Metastasis is common in NETs even in low propagating entity such as G1 or G2. Liver is the primary site of metastasis and liver metastasis affects patient quality of life and overall survival (OS). While surgery is only indicated in a minority of metastatic patients (3,4), liver directed therapy is of hot interest. Trans-arterial therapies such as transcatheter arterial chemoembolization (TACE), transcatheter arterial embolization (TAE) and transcatheter arterial radioembolization (TARE) have been showed to be effective in alleviating symptoms and reducing tumor bulk (5-7). In the era of systemic treatments such as somatostatin analogues (SSAs), anti-proliferation agents such as everolimus, chemotherapy, targeted and peptide receptor radionuclide therapy (PRRT) (8-10), the role of liver directed treatment especially TACE in the treatment of NET liver metastases is being redefined and continuously re-evaluated. Timing of TACE in the course of the disease and sequencing with other therapies remain under active investigation. In this retrospective study, we analyzed the OS and progression-free survival (PFS) of 29 NETs patients involving the liver and tried to interpret the factors affecting outcome. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2482/rc).

Highlight box

Key findings

- Transcatheter arterial chemoembolization (TACE)-based multimodal treatment can prolong survival of patients with neuroendocrine tumors (NETs) involving the liver.

What is known and what is new?

- NETs are a group of heterogeneous diseases which have liver dominant involvement potency, and their treatment options vary according to the tumor differentiation and grade.
- In this study, we show that TACE-based multimodal treatment is beneficial for NETs involving the liver.

What is the implication, and what should change now?

- TACE may be an integral part of the combinational treatment strategy for the patients with NETs involving the liver.

Methods

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2020-117R) and individual consent for this retrospective analysis was waived. From September 2016 to February 2021 at Zhongshan Hospital of Fudan University, 29 NETs patients with liver dominance who underwent TACE treatments were enrolled in this study. Written consents for the TACE procedure and systemic therapy were obtained from each patient. Demographic, clinical, and survival data of patients were retrieved from electronic medical records. All the patients had biopsy confirmed NETs. Tumor was graded in accordance with the latest version of World Health Organization (WHO) standard (11). The primary end point of the study was the death of any cause. Patients were evaluated from the date of their first TACE treatment to either the date of last clinical follow-up or death.

TACE procedure

All procedures were performed by the physicians who had more than 10 years of experience in interventional oncology. After local anesthesia, the common femoral artery was punctured by the Seldinger's technique, and a 4F RH catheter (Cook, Bloomington, USA) was introduced under fluoroscopic guidance, and arteriography of the celiac trunk and superior mesenteric artery were performed. After detection of the tumor and identification of the hepatic artery feeding the tumor, the angiography catheter or a microcatheter was advanced into the tumor feeding artery. Lipiodol-based TACE or drug eluting beads TACE (DEB-TACE) was carried out in according to the angiography pattern of the tumor and the operator's preference. In lipiodol TACE, 30–40 mg epirubicin hydrochloride was mixed with 6–15 mL lipiodol (Lipiodol ultra-fluide, Guerbet, France) according to the size of the tumor and patient's tolerance, and gelatin sponge of 150–350 or 350–560 μm size was subsequently used to reach the embolization endpoint. In DEB-TACE, 50–70 mg epirubicin hydrochloride was loaded to one bottle of

beads in accordance with guidance of protocol, and the size adopted in the study was 150–300 or 300–500 μm. Following the treatment, the catheter and microcatheter were removed. TACE was repeated on demand until tumor progression, unacceptable toxicities, or clinical deterioration.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (range) where appropriate and compared using the unpaired *t*-test. Categorical data were presented as number (percentage) and compared using the χ^2 test or the Fisher's exact test. Survival curves were plotted by the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazards model was used to assess the factors affecting survival. All variables with P value <0.1 on the univariate analysis were sequentially entered into the multivariate analysis model. All statistical analyses were performed using SPSS software (version 25.0, IBM Corp., NY, USA). A P value <0.05 was considered statistically significant.

Results

Patient characteristics

From September 2016 to February 2021, a total of 29 NET patients were treated in the Department of Hepatic Oncology of Zhongshan Hospital, Fudan University. The baseline patient characteristics are summarized in *Table 1*. There were 17 males (58.6%) and 12 females (41.4%). The median age of the patients was 60 years (range, 29–88 years). The majority of the tumors were metastatic (24/29, 82.8%) and multiple liver tumor nodules was the predominant form (22/29, 75.9%). As to the tumor grade, the well differentiated entity (G1/G2) and the poor differentiated entity [G3/neuroendocrine carcinoma (NEC)] each had a relative ratio (14/15). Besides, 10 patients had received other treatments previously such as chemotherapy, surgery, and SSAs and the rest 19 NET patients were diagnosed and treated for the first time. In addition to TACE, other treatment methods were also adopted such as chemotherapy (11/29, 37.9%), SSA (7/29, 24.1%), anti-vascular therapy (8/29, 27.6%). Ablation (4/29, 13.8%) and immune checkpoint inhibitor (3/29, 10.3%) were later adopted in a few cases while 3 patients received only TACE treatment. In our analysis, more than one systemic treatment was defined as combination treatment, and no systemic or only one systemic treatment was defined as mono-treatment.

Survival outcome

To the date of February 29, 2024, the median follow-up time was 70.0 months [95% confidence interval (CI): 27.2–112.8]. During the follow-up period, 22 (75.9%) patients died. Overall, the median OS and PFS were 20.0 (95% CI: 13.4–26.5) months and 11.0 (95% CI: 7.7–14.3) months, respectively (*Figure 1*).

Prognostic factors for OS and PFS

The univariate and multivariate Cox regression analyses of prognostic factors for OS and PFS are outlined in *Tables 2*,*3*. The univariate analysis showed that tumor grade (P=0.003), number of TACE treatments (P=0.02), and neutrophil-to-lymphocyte ratio (NLR) (P=0.03) were statistically significantly associated with OS, with systemic treatment mode (P=0.07) showed marginal significance (*Figure 2*). As for PFS, tumor grade (P=0.003), alanine aminotransferase (ALT) (P=0.02) and number of TACE treatments (P=0.02) were of statistical significance, with aspartate aminotransferase (AST) (P=0.052) and systemic treatment mode (P=0.08) having marginal significance (*Figure 3*). In the subsequent multivariate analysis, tumor grade (P=0.001), number of TACE treatments (P=0.003), NLR (P=0.005) and systemic treatment mode (P=0.007) were all significantly associated with OS, whereas tumor grade (P<0.001), number of TACE treatments (P=0.002), AST (P=0.01) and systemic treatment mode (P=0.001) were of significance for PFS.

Safety profiles

TACE was routinely carried out in our department and we had well planned protocol in the entire procession. There were 109 TACE procedures in the 29 patients, and among 29 patients, 4 patients had DEB-TACE and the rest 25 received conventional lipiodol-TACE. No patient had procedure-related death, and most of the side effects were grade 1/2 which included post embolization syndrome, leucopenia, and other abnormal laboratory tests. To be noted, in our group of patients, DEB-TACE were found to be associated with high grade (G3) side effects which included fever and abnormal laboratory tests (data not shown).

Table 1 Demographic and clinical characteristics of the NET patients

Variables	Value
Gender	
Male	17 (58.6)
Female	12 (41.4)
Age (years)	60.9±13.1
TB (μmol/L)	10.8±10.9
Albumin (g/L)	42.0±3.8
ALT (U/L)	28.2±16.6
AST (U/L)	37.1±37.5
ALP (U/L)	145.2±119.8
GGT (U/L)	149.4±185.5
CRP (mg/L)	9.3±18.2
NLR	3.1±2.4
Tumor origin	
Liver	5 (17.2)
Gastrointestinal	17 (58.6)
Others	7 (24.1)
Tumor size (cm)	8.6±11.4
Liver tumor number	
Singular	5 (17.2)
Multiple	22 (75.9)
Diffuse	2 (6.9)
Tumor grade	
G1	1 (3.4)
G2	13 (44.8)
G3	6 (20.7)
NEC	9 (31.0)
Number of metastatic organs	
One	16 (55.2)
Two	9 (31)
Three and more	4 (13.8)
Previously treated	
No	19 (65.5)
Yes	10 (34.5)
Combined treatment	
Chemotherapy	11 (37.9)
SSA	7 (24.1)
Anti-vascular	8 (27.6)
Ablation	4 (13.8)
Immune checkpoint inhibitor	3 (10.3)

Data are presented as No. (%) or mean ± standard deviation. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; NLR, neutrophil-to-lymphocyte ratio; SSA, somatostatin analogues; TB, total bilirubin.

Discussion

NETs are diverse in their malignancy which have a propensity to target the liver with their metastasis accounting for majority of the mortality. TACE has been documented in literature to be effective in the palliative treatment of NETs in that NETs have rich blood supply from hepatic artery. In the meantime, systemic treatments have gained enormous advancement in recent decades. Thus, choice and timing of TACE in the course of the disease, sequencing with other therapies call for further investigation.

We report here a group of 29 NET patients with liver involvement treated with TACE-based multimodal treatment. The median OS was 20.0 months (95% CI: 13.4–26.5), which is in line with several studies. And tumor grade, number of TACE treatments, NLR and systemic treatment mode were all significantly associated with OS in multivariate analysis. To be noted, tumor proliferation according to Ki-67 proportion which is defined as tumor grade has been proved to affect NET survival expectancy (12,13). And in our group of 29 patients, 15 (51.7%) were highly proliferating NETs that are less sensitive to TACE which may in part explain the relative short median OS. The number of TACE treatments was found to be associated with patient survival in that those patients who withstood more TACE treatment procedures were more likely to be well differentiated G1 and G2, which are proved to be more responsive to TACE treatment and SSAs (14).

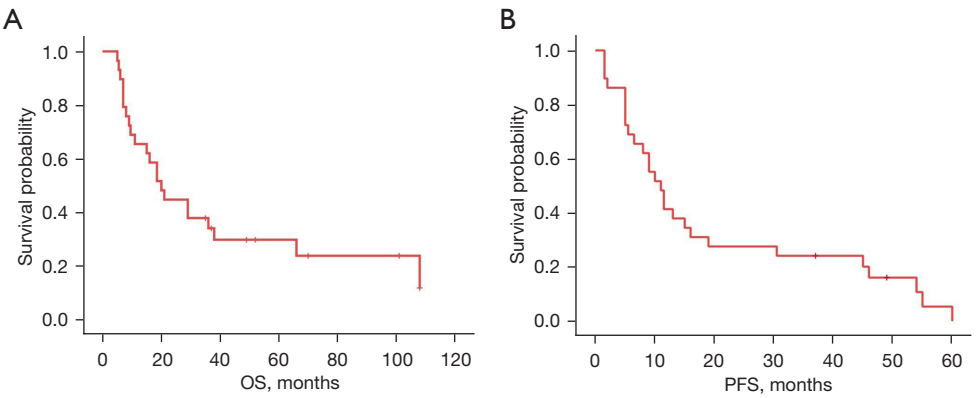

Figure 1 Kaplan-Meier curves of OS (A) and PFS (B) of the 29 NET patients. The median OS and PFS were 20.0 and 11.0 months, respectively. NET, neuroendocrine tumor; OS, overall survival; PFS, progression-free survival.

Table 2 Univariate and multivariate analysis of the factors related to OS in our group of NETs

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Gender	1.113	0.728–1.701	0.62	–	–	–
Age	2.165	0.752–6.647	0.17	–	–	–
Comorbidity	0.826	0.541–1.261	0.38	–	–	–
TB	24.430	0.050–11,849.982	0.31	–	–	–
Albumin	1.096	0.423–2.840	0.85	–	–	–
ALT	3.459	0.802–14.920	0.10	–	–	–
AST	2.290	0.670–7.825	0.19	–	–	–
ALP	22.051	0.003–15,094.286	0.49	–	–	–
GGT	1.971	0.659–5.892	0.23	–	–	–
NLR	2.703	1.118–6.535	0.03	4.003	1.508–10.626	0.005
CRP	1.264	0.543–2.941	0.59	–	–	–
Tumor origin	1.108	0.529–2.322	0.79	–	–	–
Tumor size	2.987	0.691–12.991	0.14	–	–	–
Tumor number	1.124	0.632–1.999	0.47	–	–	–
Tumor metastatic organs	1.533	0.844–2.785	0.16	–	–	–
Tumor grade	2.145	1.290–3.567	0.003	2.542	1.444–4.474	0.001
Previous treatment	1.232	0.775–1.959	0.38	–	–	–
Number of TACE treatment	0.227	0.066–0.782	0.02	0.129	0.003–0.500	0.003
Systemic treatment mode	0.358	0.120–1.066	0.07	0.203	0.063–0.653	0.007

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; NETs, neuroendocrine tumors; OS, overall survival; TB, total bilirubin; TACE, transcatheter arterial chemoembolization.

Table 3 Univariate and multivariate analysis of the factors related to PFS in our group of NETs

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Gender	1.072	0.224–1.720	0.86	–	–	–
Age	1.651	0.653–4.175	0.29	–	–	–
Comorbidity	1.065	0.479–2.365	0.88	–	–	–
TB	25.812	0.132–5,065.605	0.23	–	–	–
Albumin	1.051	0.433–2.553	0.91	–	–	–
ALT	4.303	1.272–14.550	0.02	–	–	–
AST	3.342	0.991–11.147	0.052	5.389	1.458–20.018	0.01
ALP	22.514	0.010–52,085.286	0.43	–	–	–
GGT	1.640	0.612–4.392	0.33	–	–	–
NLR	1.754	0.757–4.064	0.19	–	–	–
CRP	1.232	0.565–2.689	0.60	–	–	–
Tumor origin	0.856	0.466–1.573	0.88	–	–	–
Tumor size	2.259	0.758–6.736	0.14	–	–	–
Tumor number	1.124	0.632–1.999	0.68	–	–	–
Tumor metastatic organs	1.250	0.745–2.097	0.45	–	–	–
Tumor grade	14.203	NA	0.003	2.983	1.706–5.283	<0.001
Previous treatment	1.113	0.909–1.364	0.25	–	–	–
Number of TACE treatment	0.324	0.127–0.829	0.02	0.140	0.041–0.487	0.002
Systemic treatment mode	0.471	0.201–1.009	0.08	0.120	0.033–0.437	0.001

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CRP, C-reactive protein; GGT, γ-glutamyl transpeptidase; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; NA, not available; NETs, neuroendocrine tumors; PFS, progression-free survival; TB, total bilirubin; TACE, transcatheter arterial chemoembolization.

In addition, higher NLR was found to be associated with worse survival of NET patients in that inflammation state is documented to be connected with cancer prognosis (15-17). In our analysis, pretreatment NLR more than 2.8 was associated with worse outcome, which is in line with previous report (18). In our group of patients, concomitant treatment with two or more systemic treatment method such as SSA, chemotherapy, antiproliferation or anti-vascular treatment was defined as combination treatment while no or only one method of systemic treatment was defined as mono-treatment. And interestingly, combination treatment was found to be associated with better OS and PFS, which can be explained by synergistic antitumor effect of the agents which show less toxicities (19,20), yet the sequence of the introduction of each agent needs further study.

Several limitations of our study should be acknowledged. This was a single-center, retrospectively designed study, and the number of patients included was rather small. It should also be mentioned that our results need external validation, ideally prospective validation. In addition, it would be ideal to enroll NET patients treated by various treatments and compare the efficacy of systemic treatment with or without TACE to determine the effects of TACE on NET patient's prognosis. Indeed, it was not easy to collect a substantial number of representative rare tumors, especially in the era of targeted therapeutic agents and PRRT. Although we selected the NLR cutoff for group division by first assessing NLR as a continuous variable, our cutoff could not be

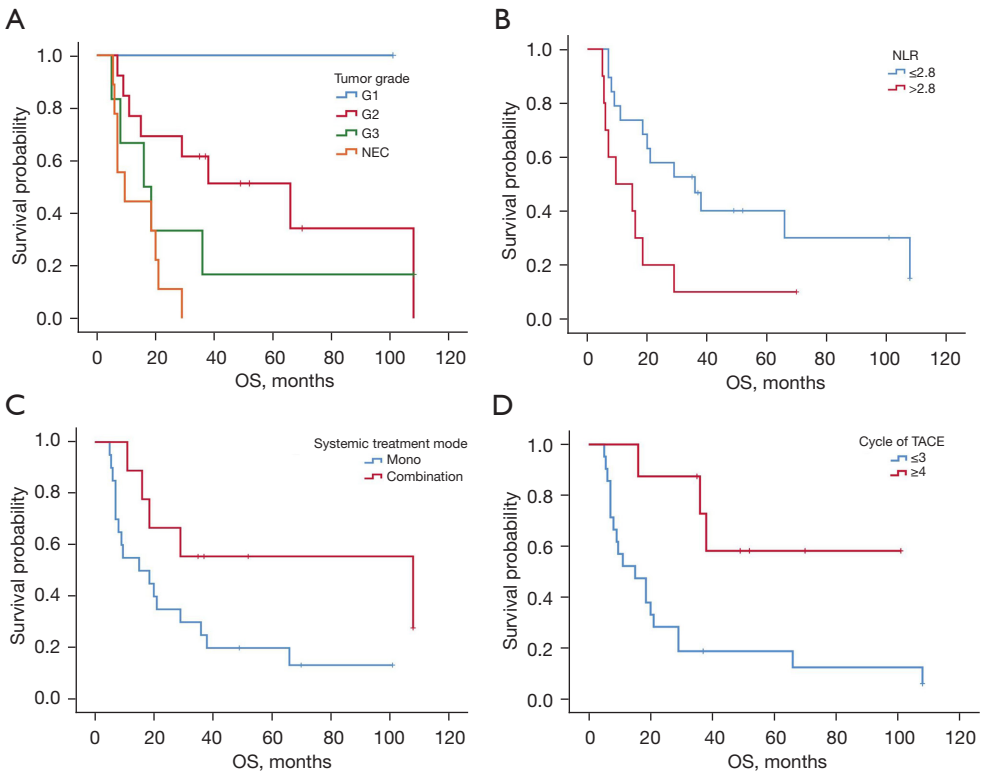

Figure 2 Kaplan-Meier curves of OS of the 29 NET patients stratified by various risk factors in univariate Cox regression analysis. (A) OS of patients according to the tumor grade. Tumor grade was statistically significantly associated with OS (P=0.003). (B) OS of patients according to the NLR. NLR was statistically significantly associated with OS (P=0.03) (C) OS of patients according to the systemic treatment mode. Systemic treatment mode was marginally significantly associated with OS (P=0.07). (D) OS of patients according to the number of TACE treatments. The number of TACE treatments was statistically significantly associated with OS (P=0.02). NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; TACE, transcatheter arterial chemoembolization.

optimal for assessment. Nevertheless, our NLR cutoff is consistent with published literature on use of NLR as a predictive tool for outcomes.

Conclusions

In conclusion, tumor grade, number of TACE treatments, NLR and systemic treatment options are independent prognostic factors for OS in liver metastatic NET patients receiving TACE-based treatments. Patients with G1 and G2 and NLR ≤2.8 have a longer OS. Furthermore, combined systemic treatment may be a better choice for patients with liver metastatic NETs, but further clinical studies are required to validate this conclusion.

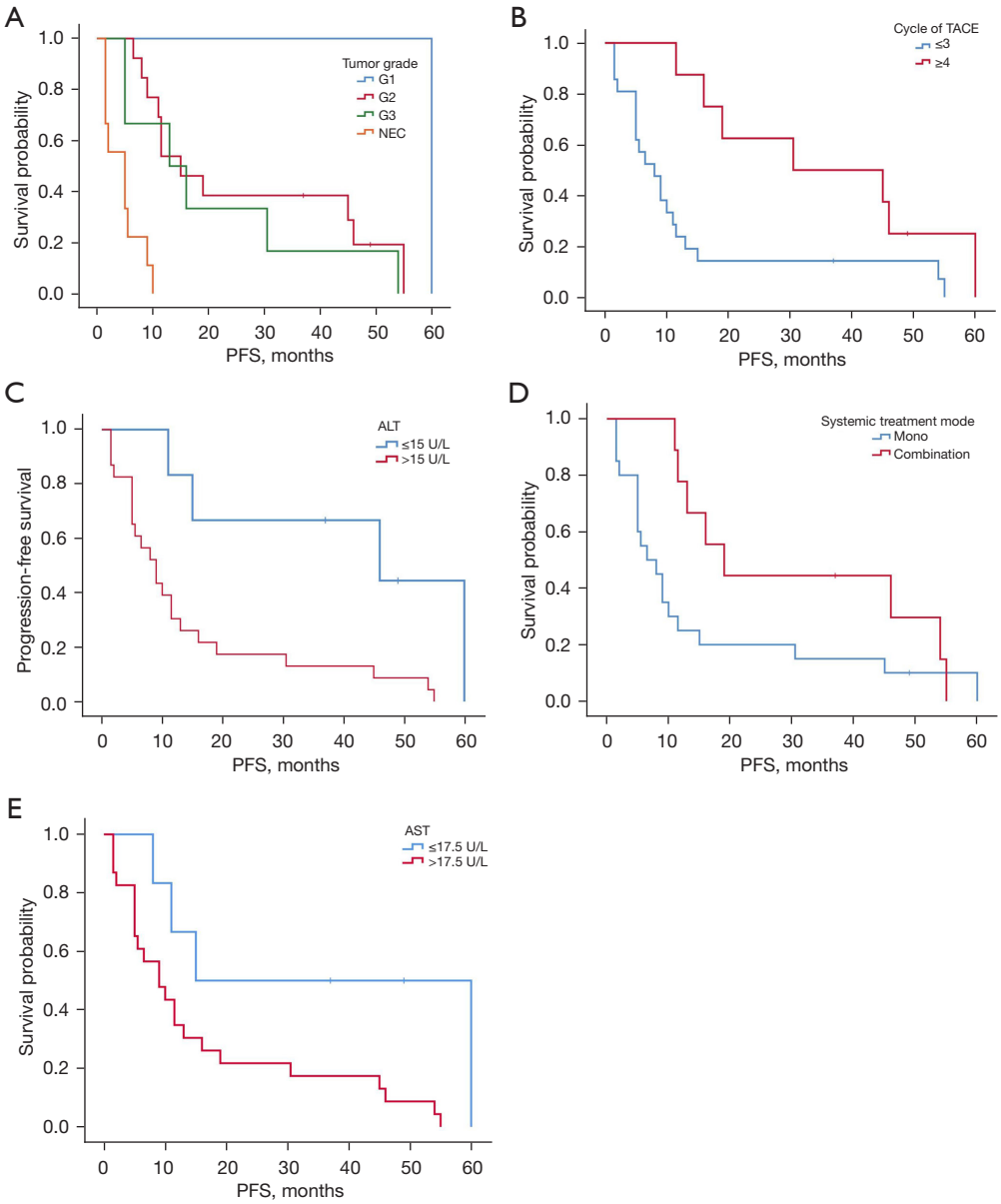

Figure 3 Kaplan-Meier curves of PFS of the 29 NET patients stratified by various risk factors in univariate Cox regression analysis. (A) PFS of patients according to the tumor grade. Tumor grade was statistically significantly associated with PFS (P=0.003). (B) PFS of patients according to the number of TACE treatments. The number of TACE treatments was statistically significantly associated with PFS (P=0.02). (C) PFS of patients according to the ALT level. ALT was statistically significantly associated with PFS (P=0.02). (D) PFS of patients according to the systemic treatment mode. Systemic treatment mode was marginally significantly associated with PFS (P=0.08). (E) PFS of patients according to the AST level. AST was marginally significantly associated with PFS (P=0.052). ALT, alanine aminotransferase; AST, aspartate aminotransferase; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; PFS, progression-free survival; TACE, transcatheter arterial chemoembolization.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2482/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2482/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2482/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 and its subsequent amendments. The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (No. B2020-117R) and individual consent for this retrospective analysis was waived.

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