ORIGINAL RESEARCH

Efficacy of Chemotherapy versus Transcatheter Arterial Chemoembolization in Patients with Advanced Primary Hepatic Neuroendocrine Carcinoma and an Analysis of the Prognostic Factors: A Retrospective Study

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Background: Primary hepatic neuroendocrine carcinoma (PHNEC) is a rare liver tumor, and there is no clear therapeutic recommendation for patients with advanced PHNEC. This study aims to compare the efficacy of platinum-based chemotherapy (etoposide combined with cisplatin/carboplatin, EP/EC) and transcatheter arterial chemoembolization (TACE) in patients with advanced PHNEC, and to evaluate the relevant prognostic factors.

Patients and Methods: The clinical data of 41 patients with advanced PHNEC from June 2014 to October 2019 were retrospectively reviewed.

Results: At a median follow-up time of 13.9 months, the median overall survival (OS) was 14.8 months in the EP/EC group and 12.2 months in the TACE group (P = 0.040). The median progression-free survival (PFS) was 4.4 months and 2.7 months in the EP/EC group and the TACE group, respectively (P = 0.005). No significant differences in the overall response rate and disease control rate were observed between the EP/EC group and the TACE group (26.1% vs 11.1%, P = 0.429; 73.9% vs 44.4%, P = 0.055, respectively). A univariate analysis indicated that the Eastern Cooperative Oncology Group performance status (ECOG PS), Ki-67, tumor number, and treatment options were prognostic factors for OS. A multivariate analysis further showed that ECOG PS (P < 0.001), Ki-67 (P = 0.003), and treatment options (P = 0.022) were independent prognostic factors for OS.

Conclusion: Ki-67, ECOG PS, and treatment options were the independent prognostic factors for OS in patients with advanced PHNEC. EP/EC may be a better choice for patients with advanced PHNEC.

Keywords: chemotherapy, transcatheter arterial chemoembolization, hepatic neuroendocrine carcinoma, prognosis

Introduction

Neuroendocrine neoplasms (NENs) are a heterogeneous group of tumors that originate from neuroendocrine cells. Neuroendocrine carcinoma (NEC) is defined as poorly differentiated NEN, with a mitotic rate > 20 per 2 mm^2 and/or Ki-67 $> 20\%$.[1] NEC typically occurs in the lungs and the gastrointestinal tract, and it often metastasizes to the liver. However, primary hepatic neuroendocrine carcinoma (PHNEC) is extremely rare, only accounting for 0.1% of NENs and 0.09–0.15% of malignant liver tumors.[2–9]

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Fewer than 150 cases of PHNEC have been described in English-language articles,[10] primarily in case reports.[11] Patients with PHNEC lack the typical clinical symptoms, and the most common initial symptoms are abdominal pain, liver mass without significant clinical manifestations, and jaundice. A definitive diagnosis relies on histopathological and immunohistochemical examinations. Due to the rarity of PHNEC, the efficacy of different treatment options in patients with advanced PHNEC is not clear. In this study, we retrospectively analyzed the clinicopathological characteristics, therapeutic approaches, and prognostic factors of 41 patients with advanced PHNEC, aiming to identify efficient treatment options and prognostic factors of advanced PHNEC.

Patients and Methods
Patients
We retrospectively reviewed the clinical data of patients who had been diagnosed with PHNEC in the Affiliated Cancer Hospital of Zhengzhou University from June 2014 to October 2019. The primary inclusion criteria were as follows: (1) histologically confirmed NEC with a hepatic primary location and unresectable or recurrent disease; (2) platinum-based chemotherapy (etoposide combined with cisplatin/carboplatin, EP/EC) or transcatheter arterial chemoembolization (TACE) as the first-line treatment; (3) an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; and (4) adequate organ function. Finally, 41 patients were included in the study. A response evaluation was performed according to the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 based on a computed tomographic (CT) scan of the abdomen. This study was approved by the Research Ethics Committee of the Affiliated Cancer Hospital of Zhengzhou University. All patients were admitted with a signed pan-informed consent form, which included consent to review their medical records.

End Point
Progression-free survival (PFS) was measured from the treatment initiation to disease progression or death from any cause. Overall survival (OS) was measured from the treatment initiation to death from any cause. The overall response rate (ORR) was defined as the proportion of patients with a confirmed complete (CR) or partial response (PR), while the disease control rate (DCR) was defined as the proportion of patients with CR, PR, or stable disease (SD). The primary end point was OS, while the secondary end points included PFS, ORR, and DCR.

Statistical Analysis
All of the statistical analyses were performed using IBM SPSS Advanced Statistics software (version 21; SPSS Inc., Chicago, IL, USA). Intergroup comparisons were conducted using a χ^2-test for the categorical variables. Survival rates were estimated using the Kaplan–Meier method and compared using the Log rank test. Prognostic factors were analyzed by searching all of the clinical variables in the univariate analysis. All of the variables with a P-value < 0.1 in the univariate analysis were entered into a multivariate Cox regression analysis. A two-sided P-value < 0.05 was considered to be significant, and 95% confidential intervals (CIs) were calculated.

Results
Patient Characteristics
Forty-one patients satisfying the eligibility criteria were included in the study. The study population was composed of 23 men (56.1%) and 18 women (43.9%). The median age of the patients was 61 years (range, 30–78 years). Abdominal pain was the most common clinical symptom (31.7% of the patients). Eleven patients (26.8%) had no obvious clinical symptoms. Other symptoms were abdominal distension (22.0%), jaundice (12.2%), and nausea or vomiting (7.3%). No hormone-related symptoms were observed. At baseline, 32 patients (78.0%) had an ECOG PS of 0 or 1, and nine patients (22.0%) had an ECOG PS of 2. Among the 41 patients, 23 patients (56.1%) received EP/EC treatment, while 18 patients (43.9%) received TACE treatment. In the EP/EC group, nine patients were treated with EC, and the remaining patients received EP chemotherapy. The median Ki-67 index was 70% (range, 30–90%). The positivity rates of chromogranin A (CgA) and synaptophysin (Syn) were 58.5% and 92.7%, respectively. The characteristics of the patients are presented in Table 1. No significant differences were observed between the two groups.

Response Evaluation and Survival
In our study, all of the patients were included in the response evaluation. No significant differences in the ORR and DCR were observed between the EP/EC group and the TACE group (ORR: 26.1% vs 11.1%, P = 0.429; DCR: 73.9% vs 44.4%, P =0.055). At the time of analysis, two patients were alive with a median follow-up time of 13.9 months (range,

Table 1 Baseline Patients' Characteristics

|	EP/EC	TACE	χ^2 value	P-value
	n=23	n=18		
Gender			0.327	0.567
Male	12	11		
Female	11	7		
Age, years			1.096	0.295
<60	9	10		
≥60	14	8		
ECOG PS			0.118	0.732
0–1	17	15		
2	6	3		
AST (U/L)			0.770	0.380
<80	15	14		
≥80	8	4		
ALT (U/L)			0.006	0.936
<80	18	13		
≥80	5	5		
HBV			0.004	0.951
Negative	13	10		
Positive	10	8		
Ki-67			0.891	0.345
<60%	8	3		
≥60%	15	15		
CgA			2.625	0.105
Positive	16	8		
Negative	7	10		
Syn			0.049	0.825
Positive	22	16		
Negative	1	2		
Tumor number			0.000	1.000
Single	3	3		
Multiple	20	15		
Metastasis			0.646	0.422
Yes	17	16		
No	6	2		

Abbreviations: EP, etoposide combined with cisplatin; EC, etoposide combined with carboplatin; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus; CgA, chromogranin A; Syn, synaptophysin.

3.4–21.2 months). According to the results of our study, the medians of the PFS and OS of the EP/EC group were 4.4 months (95% CI, 2.6–5.4 months) and 14.8 months (95% CI, 12.9–15.3 months), respectively. The medians of the PFS and OS of the TACE group were 2.7 months (95% CI, 1.9–3.5 months) and 12.2 months (95% CI, 7.6–14.3 months), respectively. A significant survival benefit was seen in the EP/EC group compared with the TACE group (PFS: P = 0.005, Figure 1A; OS: P = 0.040, Figure 1B). The medians of the PFS of patients who received EP and EC

chemotherapy were 4.0 months (95% CI, 2.4–5.7 months) and 3.3 months (95% CI, 3.0–3.6 months), respectively (P = 0.755, Supplementary Figure S1A). The median OS of patients who received EP and EC chemotherapy was 14.0 months (95% CI, 11.6–16.4 months) and 13.1 months (95% CI, 5.8–20.4 months), respectively (P = 0.892, Supplementary Figure S1B). Patients with ECOG PS 0–1 had a significantly longer PFS (4.2 vs 1.9 months, P < 0.001) (Figure 1C) and OS (13.7 vs 8.3 months, P = 0.002) (Figure 1D) than patients with ECOG PS 2. Similarly, patients with a single tumor of the liver had a significantly longer OS compared with those with multiple tumors of the liver (14.7 vs 12.1 months, P = 0.030) (Figure 1E). Patients with Ki-67 < 60% had a significantly longer OS than those with higher Ki-67 levels (15.7 vs 11.3 months, P = 0.003) (Figure 1F). Patients with Ki-67 ≥ 55% who received EP/EC had a significantly longer PFS compared with those who received TACE (5.0 vs 2.8 months, P = 0.001) (Supplementary Figure S2). A univariate analysis identified the ECOG PS (hazard ratio [HR] = 7.699; 95% CI, 2.836–20.899; P < 0.001) and treatment options (HR = 2.593; 95% CI, 1.294–5.196; P = 0.007) as prognostic factors for PFS. The ECOG PS (HR = 3.197; 95% CI, 1.462–6.992; P = 0.004), Ki-67 (HR = 3.358; 95% CI, 1.465–7.697; P = 0.004), tumor number (HR = 3.107; 95% CI, 1.062–9.087; P = 0.038), and treatment options (HR = 1.943; 95% CI, 1.017–3.713; P = 0.044) were the prognostic factors for OS. A multivariate analysis identified the ECOG PS (HR = 9.823; 95% CI, 3.453–27.946; P < 0.001) and treatment options (HR = 3.046; 95% CI, 1.520–6.105; P = 0.002) as the independent prognostic factors for PFS. The ECOG PS (HR = 6.104; 95% CI, 2.419–15.400; P < 0.001), Ki-67 (HR = 3.890; 95% CI, 1.581–9.573; P = 0.003), and treatment options (HR = 2.262; 95% CI, 1.128–4.538; P = 0.022) were significant prognostic factors for OS. The results of the univariate and multivariate regression analyses of the prognostic factors for survival are shown in Tables 2 and 3.

Adverse Events

The major adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 are summarized in Table 4. Regarding hematological adverse events, grade 3/4 adverse events occurred more frequently in the EP/EC group than in the TACE group (leukopenia, 17.4% vs 11.1%; neutropenia, 13.0% vs 5.6%; anemia, 13.0% vs 11.1%; and thrombocytopenia, 13.0% vs 5.6%; respectively). As for non-
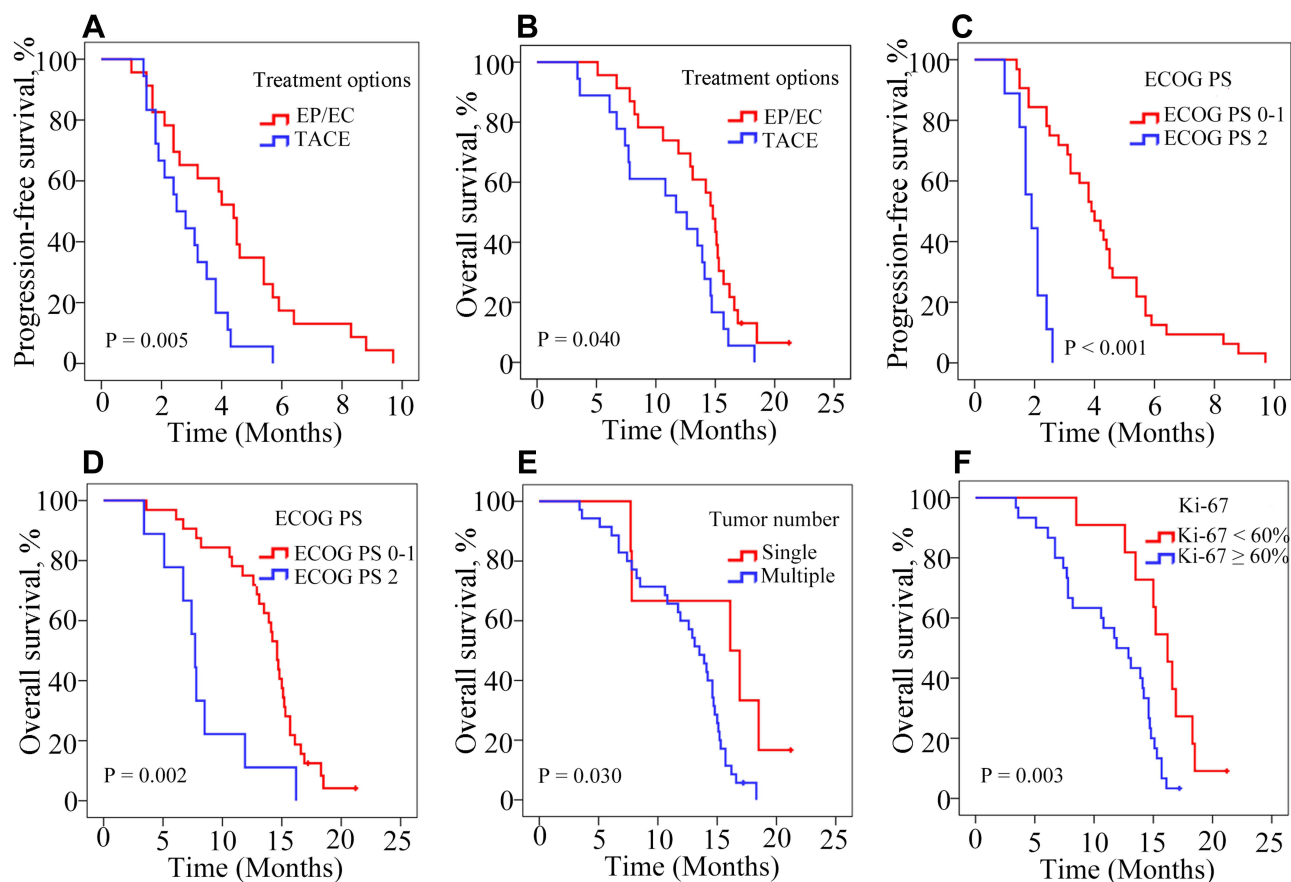
Figure 1 Progression-free survival and overall survival of patients according to treatment options (**A** and **B**) and ECOG PS (**C** and **D**); overall survival of patients according to tumor number (**E**) and Ki-67 index (**F**).
Abbreviations: EP, etoposide combined with cisplatin; EC, etoposide combined with carboplatin; TACE, transcatheter arterial chemoembolization; ECOG PS, Eastern Cooperative Oncology Group performance status.

hematological adverse events, grade 3/4 adverse events were observed more frequently in the EP/EC group than in the TACE group (nausea, 26.1% vs 16.7%; vomiting, 21.7% vs 16.7%; anorexia, 13.0% vs 0, respectively), whereas fatigue, post-embolization syndrome, and bleeding were more common in the TACE group. During the treatment period, no treatment-related death was observed in either of group.

Discussion

While the liver is a frequent site of gastrointestinal and lung NEC metastases, PHNEC is extremely rare, only accounting for 0.3–4.0% of all NECs.[12,13] Currently, surgical resection is the most effective therapy for PHNEC.[3,14,15] TACE, platinum-based chemotherapy (EP/EC), radiofrequency ablation (RFA), and liver transplantation have been used to treat PHNEC in previous cases.[3,6,11,16–18] However, a systematic analysis of the

treatment outcomes and prognostic factors in patients with PHNEC has not been conducted. In our study, 23 patients with advanced PHNEC received EP/EC, and 18 patients received TACE treatment. The European Society for Medical Oncology (ESMO) guideline recommends EP or EC as first-line chemotherapy for advanced NEC.[19] Sorbye et al found no significant differences in outcomes when comparing EP with EC treatments in patients with advanced gastrointestinal NEC.[20] Similarly, our study showed that survival did not differ between patients treated with EP and EC chemotherapy. ORR in the EP/EC group and the TACE group were 26.1% and 11.1% (P = 0.429), and DCR in the EP/EC group and the TACE group were 73.9% and 44.4% (P = 0.055).

Patients with advanced gastroenteropancreatic NEC and those with PHNEC[16,18,21–23] have a poor prognosis. In our study, the median PFS of the EP/EC group and the TACE group was 4.4 months vs 2.7 months, respectively

Table 2 Univariate and Multivariate Analyses of Clinicopathologic Factors and Treatment Options for Progression-Free Survival of Patients with Primary Hepatic Neuroendocrine Carcinoma

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender						
Male	1					
Female	0.706	0.373–1.337	0.286			
Age						
<60	1					
≥60	1.309	0.699–2.452	0.400			
ECOG PS						
0–1	1			1		
2	7.699	2.836–20.899	**<0.001**	9.823	3.453–27.946	**<0.001**
AST (U/L)						
<80	1					
≥80	0.611	0.305–1.223	0.164			
ALT (U/L)						
<80	1					
≥80	0.780	0.378–1.609	0.501			
HBV						
Negative	1					
Positive	1.332	0.697–2.545	0.386			
Ki-67						
<60%	1					
≥60%	0.636	0.307–1.316	0.223			
Tumor number						
Single	1					
Multiple	0.833	0.344–2.016	0.685			
Metastasis						
No	1					
Yes	1.938	0.847–4.434	0.117			
Treatment						
EP/EC	1			1		
TACE	2.593	1.294–5.196	**0.007**	3.046	1.520–6.105	**0.002**

Note: The bold font means the P-value was significant.
Abbreviations: HR, hazard ratio; CI, confidential interval; ECOG PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus; EP, etoposide combined with cisplatin; EC, etoposide combined with carboplatin; TACE, transcatheter arterial chemoembolization.

(P = 0.005), and the median OS was 14.8 months vs 12.2 months, respectively (P = 0.040). Furthermore, patients with Ki-67 ≥ 55% who received EP/EC had a significantly longer PFS than those who received TACE (5.0 vs 2.8 months, P = 0.001). This result is consistent with the observation of Sorbye et al that NENs with Ki-67 ≥ 55% display generally display a better response to platinum-based chemotherapy.[20] Iwasa et al included 21 patients with advanced NEC of the hepatobiliary tract and pancreas who received EP as the first-line chemotherapy. Their results showed that the median PFS was 1.8 months and the median OS was 5.8

months.[16] Similarly, Park et al reported that the median OS of four patients with advanced PHNEC who received chemotherapy was 11.3 months.[11] These results are consistent with our study. In addition, our data indicated that EP/EC was more effective than TACE in prolonging PFS and OS.

Our study identified ECOG PS, Ki-67, and treatment options as the independent prognostic factors for OS in univariate and multivariate regression analyses. Patients with ECOG PS 0–1 had significantly longer median PFS and OS than those with ECOG PS 2. Similarly, several studies reported poorer survival in NEC patients with

Table 3 Univariate and Multivariate Analyses of Clinicopathologic Factors and Treatment Options for Overall Survival of Patients with Primary Hepatic Neuroendocrine Carcinoma

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Gender						
Male	1					
Female	0.809	0.425–1.539	0.519			
Age						
<60	1					
≥60	1.021	0.984–1.060	0.264			
ECOG PS						
0–1	1			1		
2	3.197	1.462–6.992	**0.004**	6.104	2.419–15.400	**<0.001**
AST (U/L)						
<80	1					
≥80	1.406	0.705–2.805	0.333			
ALT (U/L)						
<80	1					
≥80	1.357	0.654–2.815	0.412			
HBV						
Negative	1					
Positive	0.640	0.333–1.230	0.181			
Ki-67						
<60%	1			1		
≥60%	3.358	1.465–7.697	**0.004**	3.890	1.581–9.573	**0.003**
Tumor number						
Single	1			1		
Multiple	3.107	1.062–9.087	**0.038**	2.188	0.751–6.376	0.151
Metastasis						
No	1					
Yes	1.960	0.853–4.499	0.113			
Treatment						
EP/EC	1			1		
TACE	1.943	1.017–3.713	**0.044**	2.262	1.128–4.538	**0.022**

Note: The bold font means the P-value was significant.
Abbreviations: HR, hazard ratio; CI, confidential interval; OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus; EP, etoposide combined with cisplatin; EC, etoposide combined with carboplatin; TACE, transcatheter arterial chemoembolization.

ECOG PS ≥ 2 than in those with ECOG PS 0–1.[20,24–26] Ki-67 is a cellular marker of proliferation.[27] In our study, the OS of patients with Ki-67 ≥ 60% was significantly shorter than that in patients with Ki-67 < 60% (11.3 vs 15.7 months, P = 0.003). This result is consistent with several studies that have shown that a high expression of Ki-67 is associated with a worse prognosis in NEC.[20,22,23,28,29] According to our study, EP/EC contributed to a significant survival benefit compared with TACE in patients with advanced PHNEC. In contrast, Sorbye et al and Yamaguchi et al reported that survival did not differ between gastroenteropancreatic NEC patients treated with different therapeutic options.[20,30] TACE is a specific local treatment applied only to liver tumors, and this is a different treatment modality from systemic chemotherapy. Our study was the first to evaluate the efficacy of systematic chemotherapy with EP/EC and local treatment with TACE in patients with PHNEC. These two previous studies only compared the efficacy of different platinum-based chemotherapy regimens. This may have led to disparate conclusions and deserves to be confirmed in future clinical trials. Similarly, our study showed that survival did not differ between patients treated with EP and EC chemotherapy.

Table 4 Treatment-Related Adverse Events

Adverse Events	EP/EC (n=23)		TACE (n=18)	
	All Grades	**Grade 3/4**	**All Grades**	**Grade 3/4**
Hematological				
Leukopenia	17 (73.9%)	4 (17.4%)	7 (38.9%)	2 (11.1%)
Neutropenia	7 (30.4%)	3 (13.0%)	2 (11.1%)	1 (5.6%)
Anemia	15 (65.2%)	3 (13.0%)	5 (27.7%)	2 (11.1%)
Febrile neutropenia	7 (30.4%)	1 (4.3%)	1 (5.6%)	1 (5.6%)
Thrombocytopenia	12 (52.2%)	3 (13.0%)	4 (22.2%)	1 (5.6%)
Non-hematological				
Bilirubin	9 (39.1%)	0	2 (11.1%)	0
AST	6 (26.1%)	2 (8.7%)	3 (16.7%)	0
ALT	7 (30.4%)	2 (8.7%)	3 (16.7%)	1 (5.6%)
Fatigue	7 (30.4%)	1 (4.3%)	4 (22.2%)	1 (5.6%)
Nausea	14 (60.9%)	6 (26.1%)	8 (44.4%)	3 (16.7%)
Vomiting	12 (52.2%)	5 (21.7%)	8 (44.4%)	3 (16.7%)
Anorexia	9 (39.1%)	3 (13.0%)	3 (16.7%)	0
Diarrhea	3 (13.0%)	0	0	0
Post-embolization syndrome	0	0	8 (44.4%)	3 (16.7%)
Bleeding	0	0	4 (22.2%)	1 (5.6%)

Abbreviations: EP, etoposide combined with cisplatin; EC, etoposide combined with carboplatin; TACE, transcatheter arterial chemoembolization; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

There are several limitations to our study. First, potential selection bias and unmeasured confounders may exist. Second, the sample size was relatively small. The treatment of patients with advanced PHNEC remains a challenge. Novel data on PHNEC are critically needed. The efficacy of EP/ EC vs TACE, and prognostic factors for patients with advanced PHNEC need to be tested in larger cohorts of patients.

In conclusion, Ki-67, ECOG PS, and treatment options are independent prognostic factors for OS in patients with advanced PHNEC. Patients with Ki-67 < 60% and ECOG PS 0–1 have a longer OS. Furthermore, EP/ EC may be a better choice for patients with advanced PHNEC, but further clinical studies are required to validate this conclusion.

Ethics Statement

This retrospective study was approved by the Research Ethics Committee of Affiliated Cancer Hospital of Zhengzhou University. We promise that all the data of the participants was maintained with confidentiality. The study protocol abided by the principles of the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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