To Evaluate the Safety and Efficacy of Drug-eluting Beads Bronchial Arterial Chemoembolization Loaded with Pirarubicin in the Treatment of Advanced Non-small-cell Lung Cancer

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Research Article

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Abstract

Objectives

The control of solid tumors by drug-eluting beads has been recognized in clinical practice, but there are still few applications regarding drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) in lung cancer. To further investigate the role of DEB-BACE in patients with lung cancer. We evaluated the efficacy and safety of Pirarubicin-loaded CalliSpheres beads in patients treated for advanced non-small cell lung cancer (NSCLC).

Methods

From June 2017 to January 2018, 54 patients with advanced NSCLC received DEB-BACE with Pirarubicin-loaded CalliSpheres® beads. After the treatment, the progression-free survival (PFS) and overall survival (OS) were analyzed. Moreover, adverse events and complications were also reported.

Results

After DEB-BACE treatment, most of the adverse events and complications were CTCAE grade 1 or 2 (mild symptoms, no or local/noninvasive intervention indicated) . Of the 54 patients, 2 persons (4%) had grade-3 lung abscess and required percutaneous drainage, 1(2%) had a grade-3 pulmonary infection that caused difficulty breathing and required intravenous antibiotics and ventilator adjuvant therapy. Moreover, the patient's mean PFS was 7.828 months (95% CI: 6.614, 9.043), and the mean OS rates were 17.678 months (95% CI: 15.573, 19.783). Additionally, both univariate and multivariate cox regression indicated that the disease stage (stage III) seems related to better PFS in patients with advanced NSCLC (P=0.013).

Conclusions

The clinical effect of DEB-BACE with Pirarubicin-loaded CalliSpheres® beads on advanced NSCLC is probably significant and could improve the PFS, the adverse events and complications were tolerable.

Background

Lung cancer is one of the most common cancers, and also remains the leading cause of cancer-related mortality around the world[1]. There are 2.1 million new lung cancer cases worldwide, accounting for 11.6% of all new cancer cases[2]. So far, non-small cell lung cancer (NSCLC) is still the most common subtype of lung cancer, which leads to increased mortality. NSCLC accounts for more than 80%-85% of lung cancer, and the vast majority of patients are in an advanced stage and cannot accept surgical resection[3,4]. Unfortunately, patients with other comorbidities (cardiac disease, emphysema, or pulmonary fibrosis) are not amenable to surgical resection or systemic chemotherapy[3,5]. Furthermore, considering that the proximity of the tumor to vital organs, such as the aorta and heart, may increase the

risk of surgical resection with complications. Therefore, less invasive, more effective, and safer treatments are urgently sought.

Drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) is a safe and effective palliative treatment for lung cancer. The use of DEB-BACE with lung tumors can prolong the action time of chemotherapeutic drugs at the tumor, increase the drug concentration at the target site, and cause cancer cells to be more effectively inactivated[6]. Embolism also leads to obstruction of arterial blood flow, leading to tumor ischemia and necrosis. The results of the study by Shang et al[7]. demonstrated that the clinical effect of DEB-BACE in the treatment of lung cancer could be significant, which improves the short-term response (PFS and OS) of patients with stage II-IV lung cancer without increasing serious adverse reactions.

However, there are relatively few studies on BACE with drug-eluting beads as embolic materials in advanced NSCLC. To further verify the therapeutic effect of drug-eluting beads on such diseases. In this study, the CalliSpheres® beads (CB) loaded with pirarubicin were used to complete the embolization of bronchial artery chemotherapy of advanced NSCLC. The adverse events, PFS, OS and factors affecting PFS and OS were included in the study, which is summarized as follows.

Methods

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of The First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all patients.

Patients

In this retrospective study, we included 54 patients (58.1± 8.8 years; range 42-73 years) with advanced NSCLC received DEB-BACE with Pirarubicin-loaded CalliSpheres® beads. The patient characteristics are shown in (Table 1). The inclusion and exclusion criteria are listed in (Table 2).

Procedure

Preoperative preparation

After admission, all patients received routine laboratory tests (such as liver and kidney function, blood routine, coagulation function, tumor markers) according to clinical conditions. In addition, before performing the DEB-BACE procedure, conventional imaging examinations such as enhanced CT of the

lung and bone scan were performed to assess the status of the primary tumor and the extent of the tumor's blood supply.

DEB-BACE procedure

Under local anesthesia, a modified Seldinger technique was used to percutaneously puncture the right femoral artery. The 5F pigtail catheter (Terumo, Japan) was inserted into the thoracic aorta through the 5F vascular sheath to obtain an angiographic image of the thoracic aorta to confirm the blood supply range of the solid tumor. Then a 5F-Cobra catheter (Terumo, Japan) was introduced, and bronchial angiography was performed to further verify the tumor supplying artery. To avoid ectopic embolization, a 2.7F microcatheter (Terumo, Japan) was super-selectively advanced into the tumor supply artery through a coaxial hydrophilic guidewire to complete the embolization process. In detail, 40-50 mg of pirarubicin was filled into 2 mL (1000 mg/mL) CalliSpheres® beads (100-300 μm; Suzhou Hengrui Medical Co., Ltd., China). Mix the pirarubicin-loaded beads with the contrast agent to obtain 10 ml of the mixture. Under DSA fluoroscopy, the drug-loaded beads suspension was injected into the tumor blood supply artery through the microcatheter to completely embolize the offending vessels. Additionally, angiography of the internal thoracic artery, intercostal artery, and subclavian artery was completed to ensure the dense embolization of the lung cancer. (Figure 1) for treatment information.

Definitions and Evaluation of Data

The primary endpoint was PFS, which was defined as the interval from the start of DEB-BACE procedures to disease progression. The key secondary endpoint was OS, which was defined as the interval from the start of DEB-BACE procedures to death. Adverse events of treatment were evaluated based on the Common Terminology Criteria Adverse Events Version 4.0 (CTCAE v4.0) by National Cancer Institute.

Follow-up

One month after procedure, laboratory tests including tumor markers, liver/kidney function test, as well as imaging studies, i.e., enhanced CT or enhanced MR, were performed. Subsequently, the patients were followed-up every 3 months to monitor the recurrence after procedure.

Statistical analysis

Statistical analysis was conducted using the statistical software SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables are expressed as numbers or percentages (%), and continuous variables are expressed as the mean ± standard deviation (SD). Kaplan–Meier survival curves were used for survival analysis. Univariate and multivariate Cox proportional hazards regression analyses were used to predict prognostic factors of PFS and OS. A $P<0.05$ was considered for significant differences.

Results

Patient characteristics

The mean age of the patients was 58.1 ± 8.8 years (range, 34.1-71.5 years). Of the 54 patients, 35 (65%) were 60 years old or younger, 25 (46%) were male, and 30 (56%) of the advanced NSCLC patients were associated with adenocarcinoma, and 32 (59%) people have smoking backgrounds. In all of the patients, the mean target tumor size was 4.4 ± 1.9 (range, 2.9–6.8) cm, and 26 (48%) had tumors <3.5 cm in diameter. Additionally, 31 (57%) patients were considered to be stage III, while 23 (43%) were considered to be stage IV.

Treatment-related adverse events

Most of adverse events were CTCAE grade 1 or 2 (mild symptoms, no or local/noninvasive intervention indicated) (Table 3).The treatment-related adverse events included postembolization syndrome and common adverse reactions, such as nausea(3/6%), vomiting(6/11%) , cough(5/9%) ,fever(27/50%) and chest pain(22/41%). Of the 54 patients, 2 persons(4%) had grade 3 lung abscess and required percutaneous drainage, 1(2%) had grade 3 pulmonary infection that caused difficulty breathing and required intravenous antibiotics and ventilator adjuvant therapy. No toxin-induced death occurred in this study.

LTP and OS

After DEB-BACE treatment, the patient's mean progression-free survival (PFS) was 7.828 months (95% CI: 6.614, 9.043) and mean overall survival (OS) rates was 17.678 months (95% CI: 15.573, 19.783) (Figure 2); In detail , the 6- ,12- and 24-months PFS rates were 56.7% , 25.5% and 4.6% , respectively; The 6- ,and 12-months OS rates were 96.3% and 79.1%, respectively.

Factors affecting PFS and OS

After DEB-BACE treatment, the univariate Cox proportional hazard regression indicated that the age (>65 vs ≤ 65), sex (Male vs ≤ Female), histology (Adeno- vs Non-adeno), smoking history (smokers vs Non-smokers), and the ECOG(0-1 vs 2) were not associated with longer PFS and OS (both P□0.05). Additionally, univariate Cox regression showed that disease stage (stage III vs stage IV) and tumor diameter (□3.5cm vs ≥3.5cm) had no remarkable correlation with the better OS (both P□0.05). However, both univariate and multivariate cox regression further revealed that the disease stage (stage III) seems related to better PFS in patients with advanced NSCLC (P=0.013) (Table 4).

Discussion

For the advanced NSCLC patients with comorbidities, choosing an appropriate therapy is particularly important for improving the quality of life, reducing treatment-related complications, thereby prolonging the survival time of patients[8,9,10]. The advanced NSCLC with sensitive alterations (echinoderm microtubule–associated protein-like 4-anaplastic lymphoma kinase and epidermal growth factor receptor), ALK inhibitors and EGFR-tyrosine kinase inhibitors were widely used clinically as a first-line therapy[11,12,13]. But for advanced NSCLC without sensitive mutations expression, platinum-based doublet chemotherapy could be considered to be the effective and safe treatment for this disease[14]. At present, researches demonstrated that chemotherapy alone has reached a therapeutic plateau, to reduce the adverse reactions and complications caused by systemic chemotherapy, bronchial arterial chemoembolization (BACE) has gradually been accepted by some clinical institutions and obtained favorable therapeutic effects in the treatment process[15,16].

In comparison with conventional BACE, drug-eluting beads bronchial arterial chemoembolization (DEB-BACE) can first embolize the tumor-feeding artery, blocking the tumor's blood and nutrient supply. Meanwhile, these antineoplastic drugs can be slowly released from microspheres in solid tumors which would increase the local tumor drug concentration and prolong the drug residence time, thus reducing the systemic drug concentration and decreasing the incidence of adverse reactions. Therefore, DEB-BACE can effectively promote local tumor necrosis and improve clinical symptoms. The results of Bie et al[17]. found that for patients with NSCLC who are ineligible or refuse to receive standard treatment, the use of DEB-BACE may be a feasible and well-tolerated treatment. The PFS rates of patients at 6 months and 12 months were 66.7% and 16.7%, respectively. The median OS was 16.5 months (7-23 months), and the 3-month and 12-month OS rates were 100.0% and 66.7%, respectively. Besides, the quality of life of all patients during the 2-month follow-up period was remarkably improved ($P < 0.05$). A study involving 29 patients with stage III-IV lung cancer revealed that the PFS rates of patients at 3 -, 6 - and 12- months after DEB-TACE treatment were 70.2%, 50.1% and 27.1%, respectively. The median OS was 10.2 months (range 1.1-44.6 months), and the 3-, 6-, and 12-months OS rates were 87.9%, 68.6%, and 39.8%, respectively[18]. The study further illustrates that DEB-TACE is a safe and feasible treatment for patients with advanced lung cancer.

In this study, we treated 65 patients with advanced NSCLC who received DEB-BACE with Pirarubicin-loaded CalliSpheres® beads. The mean PFS of the patients was 7.828 months, and the mean OS was 17.678 months, which meets our treatment expectations, once again illustrating the potential and advantages of DEB-BACE in the treatment of advanced lung cancer. Additionally, most of the treatment-related adverse events in this study were CTCAE grade 1 or 2 (mild symptoms, no or local/noninvasive intervention indicated), and no serious life-threatening complications. Of note, both univariate and multivariate cox regression models indicated that the disease stage (stage III) in patients with advanced NSCLC seemed to be correlated with better PFS ($P = 0.013$).

We acknowledge that this study has several limitations. First, a single-center retrospective study with a limited sample size. Also, stage IV may not be similar to stage III in terms of biology and treatment effects, but because of the small sample size, the two stages are considered to have the same treatment

plan to include in the study may lead to biased results. Finally, the follow-up time of this study is short, and it may not be appropriate to include the cox regression model using the overall survival, but it can provide a reference for future studies.

Conclusion

PFS could be improved with advanced NSCLC who received DEB-BACE with Pirarubicin-loaded CalliSpheres® beads. In addition, the adverse events and complications were tolerable and could be managed with appropriate medical interventions. However, more studies are warranted to confirm these findings.

Abbreviations

DEB-BACE Drug-eluting beads bronchial arterial chemoembolization

BACE Bronchial arterial chemoembolization

NSCLC Non-small cell lung cancer

PFS Progression-free survival

OS Overall survival

CTCAE Common Terminology Criteria for Adverse Event

CB CalliSpheres® beads

Declarations

Data Availability

The clinical data were obtained from the interventional department of the First Affiliated Hospital of Zhengzhou University. The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Authors' Contributions

Zhaonan Li and Quanjing Chen contributed equally to this work.

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Tables

Table 1 Patient characteristics		
Characteristics	**(*n*=54)**	***Percentage(%)***
Age(years)	58.1± 8.8	
65	35	65
≥65	19	35
Sex		
Male	25	46
Female	29	54
Histology		
Adenocarcinoma	30	56
Non-adenocarcinoma	24	44
Smoking history		
smokers	32	59
Non-smokers	22	41
ECOG		
0-1	25	46
2	29	54
Disease stage		
III	31	57
IV	23	43
Primary tumor size(cm)	4.4 ± 1.9	
3.5cm	26	48
≥3.5cm	28	42
Primary tumor site		
Right lung	23	43
Left lung	31	57
ECOG, Eastern Cooperative Oncology Group		

Table 2

Inclusion and exclusion criteria

Inclusion criteria	***Exclusion criteria***
1.Age range: 18–75 years	1. Contraindications to endovascular treatment and contrast agent
2.Patients with lung cancer diagnosed by biopsy	2.Severe interstitial lung diseases
3.Patients with stage III–IV who were unable to tolerate or refused surgery, radiotherapy, or systemic chemotherapy	3.Diseases severely threatening patient's safety or influencing the patient's completion of this trial, as per investigator judgment
4.Patients with at least almost normal cardiopulmonary function	4.Cachexia or heart, lung, liver, or kidney failure
5. Liver and kidney function ≤1.5 times the upper limit of normal	5.Bronchial artery and spinal artery sharing the same trunk or with anastomosis in between, as detected by intraoperative angiography
6.Patients with white blood cells ≥3.0 × 109/L, neutrophils ≥1.5 × 109/L, hemoglobin ≥10.0 g/L, platelets ≥100 × 109/L	6.Contraindications to angiography such as serious bleeding tendency and iodine allergy
7. ECOG score≦2	
8.Patients could cooperate with follow-up	
9.A life expectancy of > 3 months	
Eastern Cooperative Oncology Group, ECOG	

Table 3

Adverse events and complications.

Categories	Grades	*N (%)*
	CTCAE	
Adverse events		
Nausea, no treatment	1	3(6)
Vomiting, no treatment	1	4(7)
Vomiting, requiring use antiemetics	2	2(4)
Cough, no treatment	1	2(4)
Cough, requiring use antitussives	2	3(6)
Fever, maximum 38°C, no treatment	1	19(35)
Fever, ≥ 38°C	2	8(15)
Mild pain, requiring nonopioid oral analgesic treatment	2	17(49)
Moderate pain, requiring opioid oral analgesic treatment	2	5(31)
Complications		
Lung abscess	3	2(4)
Pulmonary infection	3	1(2)

National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE version 4.03), uses Grades 1 through 5 to refer to the severity of the adverse events, based on general guidelines: Grade 1 mild - asymptomatic or mild symptoms, clinical or diagnostic observations only, intervention not indicated; Grade 2 moderate - minimal, local or noninvasive intervention indicated; Grade 3 severe - medically significant but not immediately life-threatening, hospitalization or prolongation of hospitalization indicated, disabling; Grade 4 life-threatening - urgent intervention indicated; Grade 5 death - related to adverse event.

Table 4

Factors affecting PFS and OS

Parameters	PFS			*P*	OS			*P*
	HR	*95%***CI**			***HR***	*95%**CI***		
		Lower	Higher			*Lower*	*Higher*	
Univariate Cox's regression								
Age (>65 vs ≤ 65)	1.108	0.608	2.017	0.738	0.932	0.520	1.668	0.812
Sex (Male vs ≤ Female)	0.889	0.500	1.579	0.687	0.957	0.541	1.691	0.880
Histology (Adeno- vs Non-adeno)	1.343	0.747	2.415	0.325	0.908	0.513	1.606	0.740
Smoking history (smokers vs Non-smokers)	0.683	0.490	1.595	0.885	1.218	0.681	2.177	0.507
ECOG(0-1 vs 2)	0.559	0.466	1.512	0.839	1.187	0.669	2.107	0.558
Disease stage (III vs IV)	2.108	1.160	3.832	**0.014**	1.036	0.584	1.836	0.904
Tumor diameter(≤3.5cm vs ≥3.5cm)	1.384	0.775	2.472	0.272	1.301	0.718	2.358	0.386
Multivariate Cox's regression								
Age (>65 vs ≤ 65)	1.237	0.639	2.392	0.528	0.866	0.457	1.640	0.659
Sex (Male vs ≤ Female)	0.754	0.386	1.471	0.407	0.861	0.460	1.612	0.640
Histology (Adeno- vs Non-adeno)	0.897	0.392	2.051	0.797	0.843	0.438	1.623	0.610
Smoking history (smokers vs Non-smokers)	0.934	0.480	1.819	0.841	1.323	0.695	2.515	0.394
ECOG(0-1 vs 2)	0.654	0.333	1.284	0.217	1.357	0.714	2.581	0.352
Disease stage (III vs IV)	2.820	1.242	6.403	**0.013**	1.181	0.598	2.332	0.632
Tumor diameter(≤3.5cm vs ≥3.5cm)	2.037	1.070	3.878	**0.030**	1.362	0.719	2.580	0.344

OS overall survival, HR hazard ratio, CI confidence interval, PFS progression free survival, ECOG Eastern Cooperative Oncology Group

Bold values indicate p<0.05

Figures

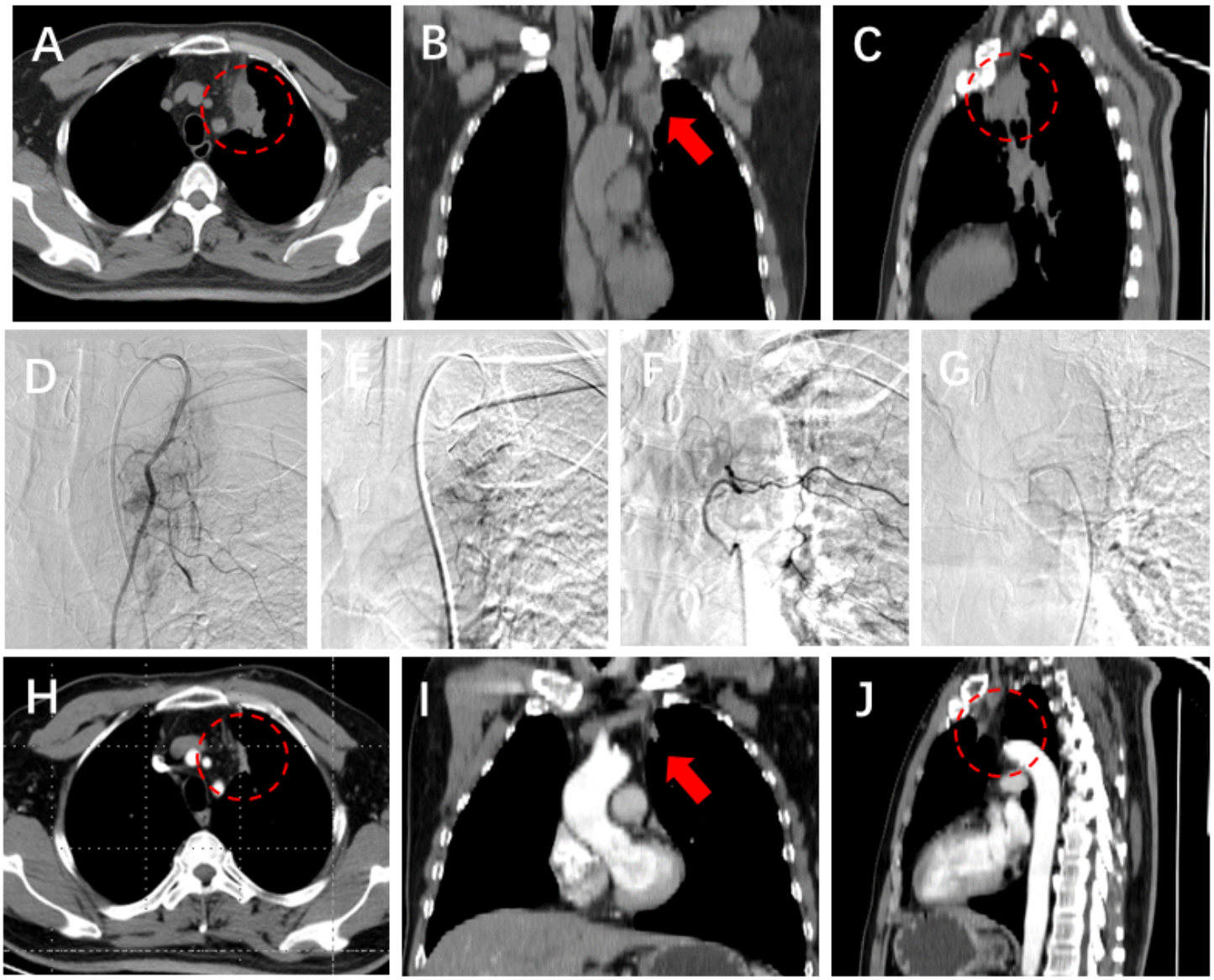

Figure 1

angiography of the internal thoracic artery, intercostal artery, and subclavian artery was completed to ensure the dense embolization of the lung cancer. (Figure 1) for treatment information.

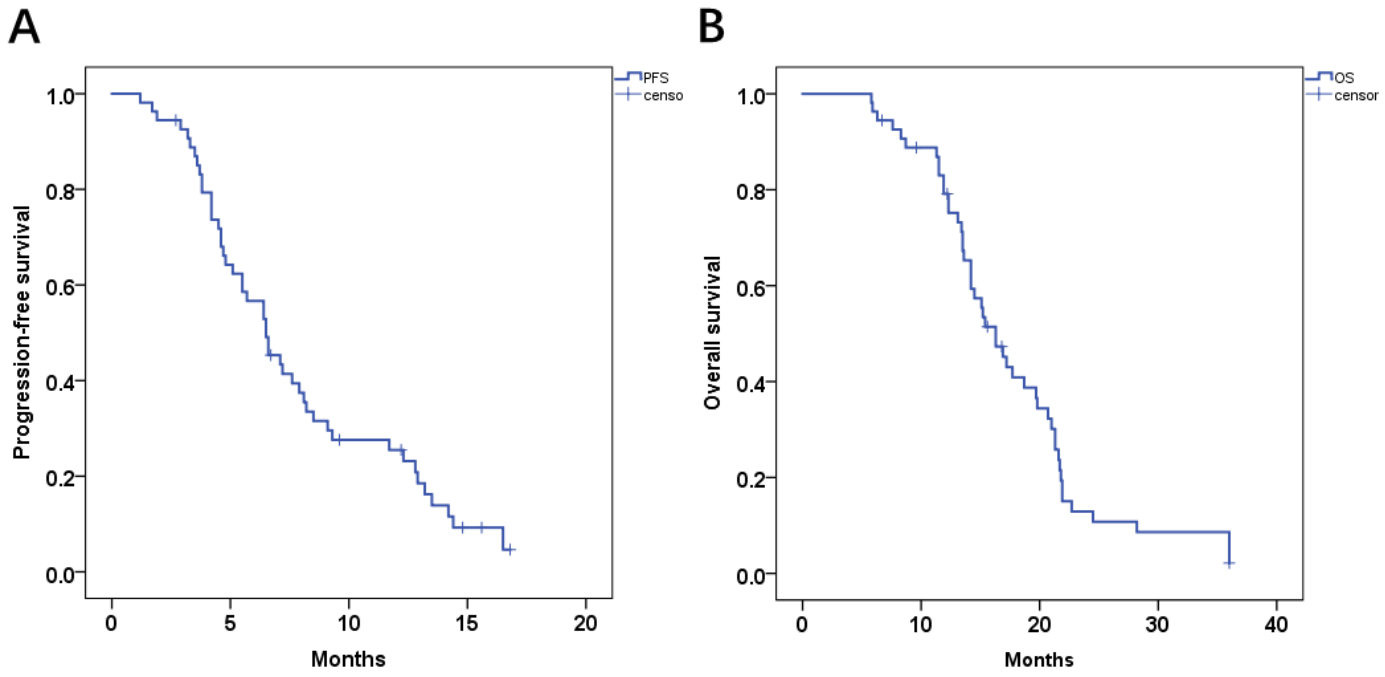

Figure 2

After DEB-BACE treatment, the patient's mean progression-free survival (PFS) was 7.828 months (95% CI: 6.614, 9.043) and mean overall survival (OS) rates was 17.678 months (95% CI: 15.573, 19.783) (Figure 2); In detail , the 6- ,12- and 24-months PFS rates were 56.7% , 25.5% and 4.6% , respectively; The 6- ,and 12-months OS rates were 96.3% and 79.1%, respectively.