Prediction of Veristrat Test in First-Line Therapy of Pemetrexed Based Regimen for Advanced Lung Adenocarcinoma Patients

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Abstract

Background

Although advanced non-squamous non-small cell lung cancer (NSCLC) patients have significantly better survival outcome on pemetrexed based treatment, a subset of patients still show intrinsic resistance and progress rapidly. Therefore we aim to use a blood-based protein signature (VeriStrat, VS) to analyze whether VS could identify the subset of patients who had poor efficacy on pemetrexed therapy.

Methods

This study retrospectively analyzed 72 advanced lung adenocarcinoma patients who received first-line pemetrexed/platinum or combined with bevacizumab treatment.

Results

Plasma samples from these patients were analyzed using VS and classified as Good (VS-G) or Poor (VS-P) group. The relationship between efficacy and VS status was further investigated. Of 72 patients included in this study, 35 (48.6%) were treated with pemetrexed plus platnum and 37 (51.4%) were treated with pemetrexed/platinum combined with bevacuzumab. Among all patients, 60 (83.3%) and 12 (16.7%) patients were classified as VS-G and VS-P, respectively. VS-G patients had significantly better median PFS (Unreached vs. 4.2 months; P0.001) than VS-P patients. Besides, partial response (PR) rate was higher in VS-G than that in VS-P group (46.7% vs 25.0%, P=0.212). Subgroup analysis showed that PFS was also significantly longer in the VS-G than that in VS-P group no matter for patients received chemotherapy alone or chemotherapy plus bevacizumab.

Conclusions

Our study indicates that VS could be considered as a novel and valid method to predicit efficacy of pemetrexed based therapy and identify a subset of advanced lung adenocarcinoma patients who have intrinsic resistance to pemetrexed based regimen.

1. Introduction

Lung cancer is the most common cancer worldwide and most patients are diagnosed with advanced stage. [1, 2]. Over the past decades, although the treatment for non-small cell lung cancer (NSCLC) patients has been improved noticeably, especially a significant progress has been made in immunotherapy and targeted therapy, but chemotherapy remains the cornerstone for advanced NSCLC patients.

Pemetrexed based therapy has been the standard first-line chemotherapy regimen for advanced non-squamous NSCLC patients without epidermal growth factor receptor (EGFR) sensitizing mutations, anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 receptor kinase (ROS1) rearrangement. First-line

pemetrexed based chemotherapy showed significant better outcomes than other chemotherapy regimens for these patients especially with gemcitabine/platinum[3–5]. However some patients still showed primary resistance to pemetrexed regimen and progressed rapidly. It is unclear why these patients responded heterogeneously and it is necessary to find a method to predict the efficacy of pemetrexed therapy, and identify a subset of patients who might resistant to pemetrexed based regimen. Therefore these patients could have a chance to receive other treatment methods such as immunotherapy, targeted therapy, and other chemotherapy regimens.

VeriStrat (VS), a blood-based test could divide patients into either VS Good (VS-G) or VS Poor (VS-P) group, which might potentially help oncologists in a puzzle about the matter in their clinical practice.. Previous studies have shown that VS was a valid method to predict the efficacy of chemotherapy or targeted therapy[6–10]. However, so far there has been no study using VS method for the prediction of first-line pemetrexed based chemotherapy for Chinese advanced lung adenocarcinoma patients without EGFR sensitizing mutations, ALK or ROS1 rearrangement. Therefore we conducted a study to explore whether VS could be used in the first-line setting to identify advanced adenocarcinoma patients who have better outcomes or resistance on pemetrexed chemotherapy.

2. Materials And Methods

2.1 Patents

Patients were enrolled in this study if they had stage IIIB or IV lung adenocarcinoma, had no previous systemic anticancer therapy and showed measurable lesions. All patients received chemotherapy or combined with bevacizumab. Chemotherapy regimens include pemetrexed (500 mg/m2 q21d) in combination with cisplatin (75 mg/m2 q21d) or carboplatin (AUC = 5 q21d). The dose of bevacizumab was 7.5 mg/kg, q21d. The primary endpoint was progression free survival (PFS). Other endpoints include partial response and objective response rate (ORR). PFS was calculated from the date of initiation of chemotherapy to the date of progression or death from any cause. The tumor response was assessed by RECIST version 1.1.

2.2. Samples and Veristrat test

Serum samples were collected and stored frozen. Samples were anonymized and shipped to Bioyong (Beijing,China). VeriStrat analysis was conducted on 72 serum samples by Bioyong (Beijing, China) in a blinded to clinical and treatment data. VeriStrat (VS)testing was performed as described.[6, 11]This test use Clin-TOFII mass spectrometer(based on MALDI mass spectrometry) (Bioyong,Beijing,China). Samples were thawed on ice and diluted 1:10 in HPLC-grade water, then combined with equal volume of matrix solution.(25 mg/ml sinapinic acid prepared in 50% acetonitrile/0.1% trifluoroacetic acid).Spot 2 uL sample-matrix mixture on polished stainless steel MALDI plates three times. Acquire data on Clin-TOFII Mass Spectrometer (Bioyong,Beijing,China)in linear mode. Export ASCII files from spectra, and run VeriStrat Algorithm on ASCII files. A Vetistrat label of Good or Poor was produced for each sample when all replicates from a sample gave the same classification. An indeterminate classification status was

assigned to samples with discordant findings in the replicates. Only patients with classifications of VeriStrat good (VSG) or VeriStrat Poor(VSP) were included in this study cohort. Complete details of the method are described elsewhere.

2.3. Statistical analysis

Baseline characteristics between VS-G and VS-P group were compared using T test for age or using X2 test for all other variables. Tumor response was compared using X2 test in two groups. PFS was compared using univariate analysis. A Cox model was used to adjust differences in PFS between groups for other confounding variables (gender, stage, smoking status, and treatment).

3. Results

3.1. Patient Characteristics

Table 1 shows the patients' clinical characteristics in this study. Of the 72 patients, 60 (83.3%) were classified as VS-G and 12 (16.7%) as VS-P. Patients' characteristics were well balanced between VS-G and VS-P group ($P > 0.05$ for all).

Table 1
Patients' Characteristics according to VS Classification

	All Patients (%)	VS-G (%)	VS-P (%)	P[1]
Age (years)				0.682
Median (range)	58 (34–81)	58 (34–81)	58 (46–74)	
Gender				1.000
Female	24 (33.3)	20 (33.3)	4 (33.3)	
Male	48 (66.7)	40 (66.7)	8 (66.7)	
ECOG				1.000
0	42 (58.3)	35 (58.3)	7 (58.3)	
1	30 (41.7)	25 (41.7)	5 (41.7)	
Stage				1.000
IIIB	14 (19.4)	12 (20.0)	2 (16.7)	
IV	58 (80.6)	48 (80.0)	10 (83.3)	
Smoking				0.595
Yes	41 (56.9)	35 (58.3)	6 (50.0)	
No	31 (43.1)	25 (41.7)	6 (50.0)	
Treatment				0.916
Chemotherapy	35 (48.6)	29 (48.3)	6 (50.0)	
Chemotherapy + Bevacizumab	37 (51.4)	31 (51.7)	6 (50.0)	
[1]Two groups were compared using T test for age or using X^2 test for all other characteristics.				

3.2.Tumor Response

Table 2 illustrates the tumor response in two groups. The partial response (PR) rate was higher in VS-G group than that in VS-P group (46.7% vs 25.0%, P = 0.212). For patients who received chemotherapy alone, PR rate was 31.0% and 0.0% in VS-G and VG-P groups respectively. For patients with chemotherapy and bevacizumab treatment, PR rate was also higher in VS-G than that in VG-P groups (61.3% for VS-G vs. 50.0% for VS-P). The difference did not reach a statistical significance likely because of the limited number of patients in this study (Table 2).

Table 2
Tumor response according to VS Classification

	VS-G (%)			VS-P (%)		P[1]
PR	28 (46.7)			3 (25.0)		0.212
SD	28 (46.7)			8 (66.7)		0.343
PD	3 (5.0)			1 (8.3)		0.526
PR + SD	56 (93.3)			11 (91.7)		1.000
	Chemotherapy		P[1]	Chemotherapy + Bevacizumab		P[1]
	VS-G(%)	VS-P(%)		VS-G(%)	VS-P(%)	
PR	9 (31.0)	0 (0.0)	0.304	19 (61.3)	3 (50.0)	0.670
SD	17 (58.6)	5 (83.3)	0.377	11 (35.5)	3 (50.0)	0.653
PD	2 (6.9)	1 (16.7)	0.442	1 (3.2)	0 (0.0)	1.000
PR + SD	26 (89.7)	5 (83.3)	0.546	30 (96.8)	6 (100.0)	1.000

[1]Tumor response was compared using X^2 test in two groups.

3.3. Survival

Of 72 patients in this study, 25 patients experienced disease progression. The median follow-up time for all patients was 7.4 months (0.9–18.8 months). A significant improved median PFS was observed for patients in VS-G group compared with that in VS-P group (Unreached vs. 4.2 months; P□0.001) (Fig. 1). Median OS was not reached in either group. For 35 patients received chemotherapy, median PFS was significantly superior for patients in VS-G than that in VS-P group (Unreached vs. 4.0 months; P□0.001) (Fig. 2). For 37patients treated with chemotherapy and bevacizumab, median PFS was also significantly longer in the VS-G than that in VS-P group (Unreached vs. 4.8 months, p = 0.042) (Fig. 3). Interaction between PFS and VS classification was tested using the Cox model. After adjusting for gender, stage, smoking status and treatment by multivariate analysis, the interaction between PFS and VS classification was also statistically significant (P = 0.011) (Table 3).

Table 3
Association of Treatment with Progression-free Survival (PFS)

	Univariate Analysis	Multivariate Analysis	
	P[1]	HR (95% C.I.)	P[2]
Treatment			
Chemotherapy vs. Chemotherapy + bevacizumab	0.890	0.734 (0.325–1.656)	0.457
Gender			
Male vs. Female	0.344	0.998 (0.262–3.803)	0.998
Smoking Status			
Smoking vs. Non-smoking	0.379	0.646 (0.201–2.077)	0.463
Stage			
IV vs. IIIB	0.059	0.265 (0.061–1.150)	0.076
VeriStrat			
Good vs. Poor	0.001	0.214 (0.088–0.522)	0.011

[1]P-value was estimated by univariate analysis. [2]Hazard ratio (HR), 95% confidence interval (C.I.) and P-value were estimated in Cox proportional hazards model.

4. Discussion

This is the first study indicating that a blood-based protein signature (VS) could be considered as a novel and valid method to predict efficacy of pemetrexed/platinum or combined with bevacizumab in the first-line treatment for Chinese advanced lung adenocarcinoma patients.

Pemetrexed is a third generation cytotoxic agent. It can inhibit cell replication and tumor growth by disrupting folate-dependent normal cellular metabolism. Several clinical trials demonstrated that first-line pemetrexed based therapy was associated with significant better survival outcome than other chemotherapy regimens for advanced lung adenocarcinoma patients. Besides, the combination of bevacizumab could further imporve survival for these patients. Therefore, pemetrexed/platinum combined with bevacizumab has been the standard first-line chemotherapy regimen for advanced non-squamous NSCLC patients. But some patients still showed poor response to pemetrexed based regimen[12, 13]. Currently, for lacking of clinical evidence, no specific biomarkers have been applied in

clinical practice Therefore it is urgently needed to find promising biomarkers to predict efficacy of cytotoxic agents.

In 2007, David Carbone etc initially established a VeriStrat method that can be used to predict the first-line efficacy of EGFR tyrosine kinase inhibitor (TKI) for advanced NSCLC patients who did not receive EGFR mutation test before treatment. In this study, the median survival was 306 days in VS-G group of 69 patients, far more than 107 days in VS-P group of 27 patients[4]. A series of follow up studies demonstrated that VS is predictor of therapeutic benefit from EGFR TKI therapy[14]. In PROSE study, VS method was utilized to predict second-line single-drug chemotherapy for advanced lung cancer (pemetrexet/docetaxel). The results show that among the 129 patients receiving single-drug chemotherapy, OS and PFS were significantly lower in VS-P group than in VS-G group [15]. Another study examined the performance of VeriStrat in three independent clinical trials from 481 patients treated with platinum-based chemotherapy in first line. Patients classified as VS-G had significantly longer PFS and OS than VS-P patients. These results demonstrated that VS is a strong predictive test in NSCLC patients treated with platinum-based regimens in the first line. 9However, so far there has been no study using this VS method for the prediction of first-line pemetrexed plus platinum-based chemotherapy or combined with bevacizumab for Chinese advanced lung adenocarcinoma patients.

To address these issues, we conducted a retrospective analysis of plasma samples from lung adenocarcinoma patients with stage IIIB or IV, who recieved first-line pemetrexed based chemotherapy. Our study showed that median PFS was unreached in VS good group, significantly superior than that in VS poor group, the PFS of which was 4.2 months. For 35 patients received chemotherapy, an improved PFS was still observed for patients in VS-G vs. VS-P group (median PFS: Unreached vs. 4.0 months) A recent study included 76 non-squamous patients treated with a combination of carboplatin or cisplatin with pemetrexed. Patients classified as VS-G had longer PFS and OS than VS-P: 6.5 vs 1.6 months and 10.8 vs 3.4 months, respectively.10 The PFS in our study was longer than previously reported data likely because pemetrexed maintainence therapy was administered in our study. It has been demonstrated that continuation maintenance therapy with pemetrexed is an effective and well tolerated treatment option for patients with advanced non-squamous NSCLC with good performance status who have not progressed after induction therapy with pemetrexed plus cisplatin. 16In PAROMOUNT study, the median PFS was 4.1 months for pemetrexed and 2.8 months for placebo.17 The result in our study was consistent with that in PAROMOUNT study.

In POINTBREAK study, PFS was significantly improved with pemetrexed/carboplatin plus bevacizumab and pemetrexed/bevacizumab maintenance therapy (median PFS, 6.0 v 5.6 months; $P = 0.012$)[18]. In AVAPEAL study, bevacizumab plus pemetrexed maintenance was also associated with a significant PFS benefit compared with bevacizumab alone (median, 3.7 v 7.4 months; $P < 0.001$)[19]. Updated survival analysis of the AVAPERL study showed maintenance with bevacizumab-pemetrexed was associated with a nonsignificant increase in OS over bevacizumab alone[20]. A recent study (WJOG 5610L) reported in 2019 American Society of Clinical Oncology annual meeting demonstrated that bevacizumab and pemetrexed maintenance therapy could not prolong OS compared with bevacizumab maintencance

therapy alone (median, 23.3 vs 19.6 months; P = 0.069). In our study, for 37 patients treated with chemotherapy and bevacizumab, PFS was also significantly longer in the VS-G compared with VS-P group (median PFS: Unreached vs. 4.8 months). Our study indicated that VS is also predictive for chemotherapy and bevacizumab combined therapy. Although this study clearly identified patients who might have worse outcome on pemetrexed based therapy. These data are not compelling enough to deny pemetrexed therapy to VS-P patients. But perhaps in these VS-P patients, alternative treatment approaches could be considered.

Several limitations of our study are worthy of note. First, 72 were eligible for inclusion and analysis,and only a small subset of participants (12/72, 16.7%) tested as VS-P. This limited the power of the analysis we performed. Further, OS data was not available. Because OS is typically not calculated until more than 50% of patients experienced events, and median OS was not reached in either group. But our study still indicates that VS could be considered as a novel and valid method to predicit efficacy of pemetrexed based therapy and identify a subset of advanced lung adenocarcinoma patients who have intrinsic resistance to pemetrexed based regimen.

5. Conclusions

Our study indicates that VS could be considered as a novel and valid method to predicit efficacy of pemetrexed based therapy with Chinese advanced lung adenocarcinoma patients and identify a subset of patients who have intrinsic resistance to pemetrexed based regimen.

Declarations

Ethics approval and consent to participate The study was approved by the Medical Ethics Committee of Peking University Cancer Hospital. All patients signed "Informed consent of obtaining the patient sample to conduct a scientific study" and all authors had no access to patient's identities.

Consent for publication: All authors have read and agreed to the published version of the manuscript.

Availability of data and material The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

Competing interests: Authors Song Cui, Rong Zhang, Qingwei Ma were employed by the company Bioyong Technologies Inc. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contributions: Conceptualization, B.J. and ZP.W.; methodology, XH.Z, S.L., JF.L., ML.M., C.C., S.C., R.Z. and QW.M; formal analysis, B.J.; investigation, B.J., J.F. and ZP.W.; data curation, Z.D., D.W., J.Z., MN.W., TT.A., YY.W., ML.Z., JJ.L., Y.W., J.Z., X.Y., J.Z., HX.C., JJ.W.,YJ.C., and XY.Z.; writing—original draft preparation, B.J.; writing—review and editing, B.J.; supervision, ZP.W.; project administration, ZP.W.; funding acquisition, ZP.W.

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Figures

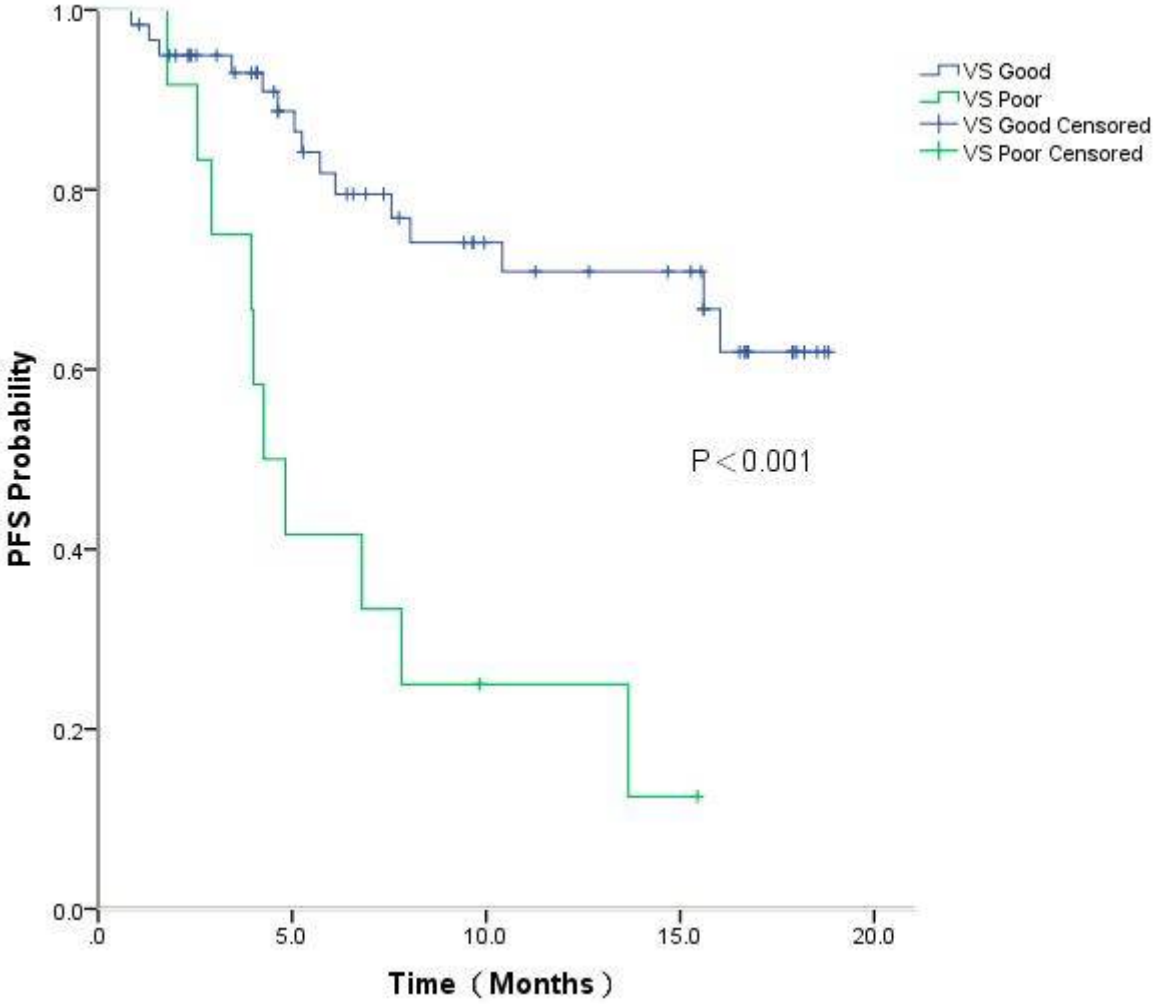

Figure 1

Progression-free Survival (PFS) by VS Classification for all patients

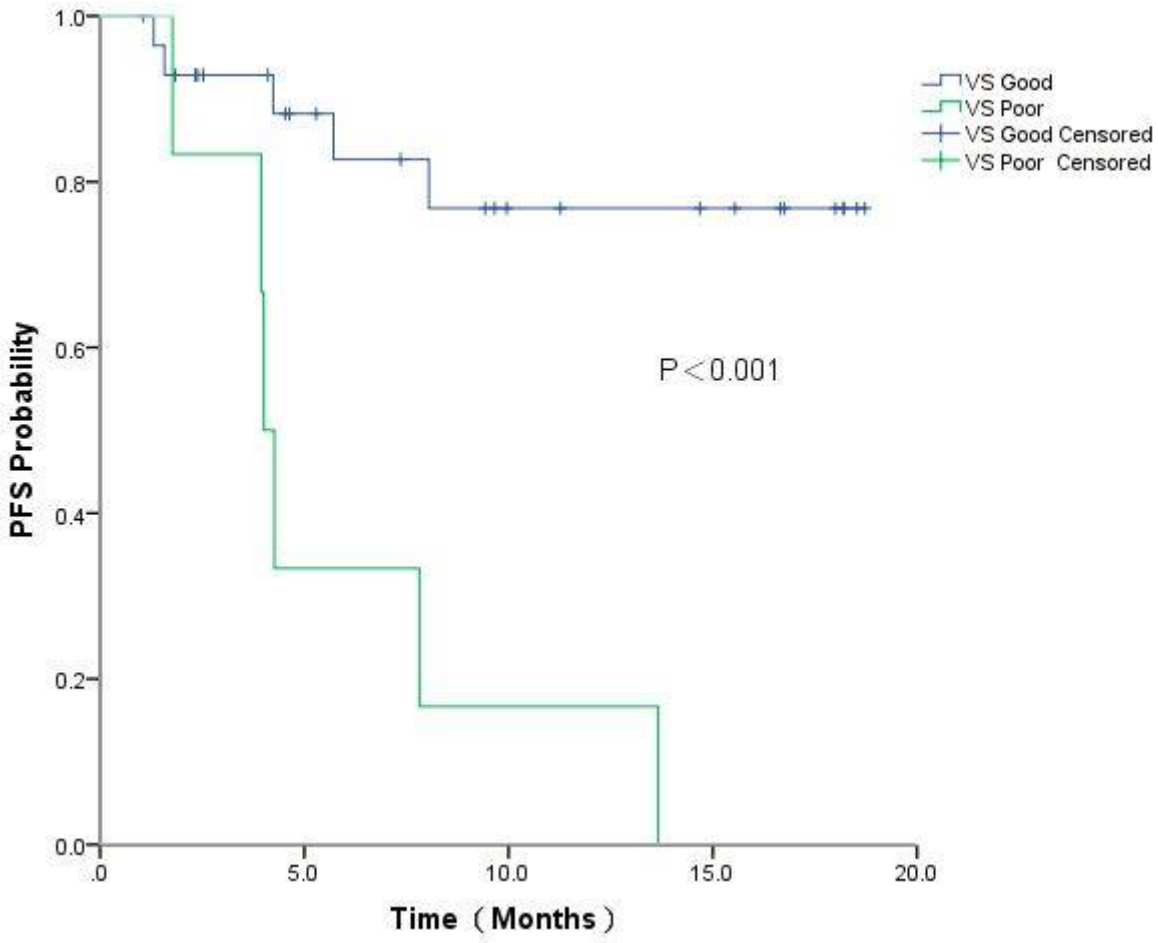

Figure 2

Progression-free Survival (PFS) by VS Classification for patients received chemotherapy alone

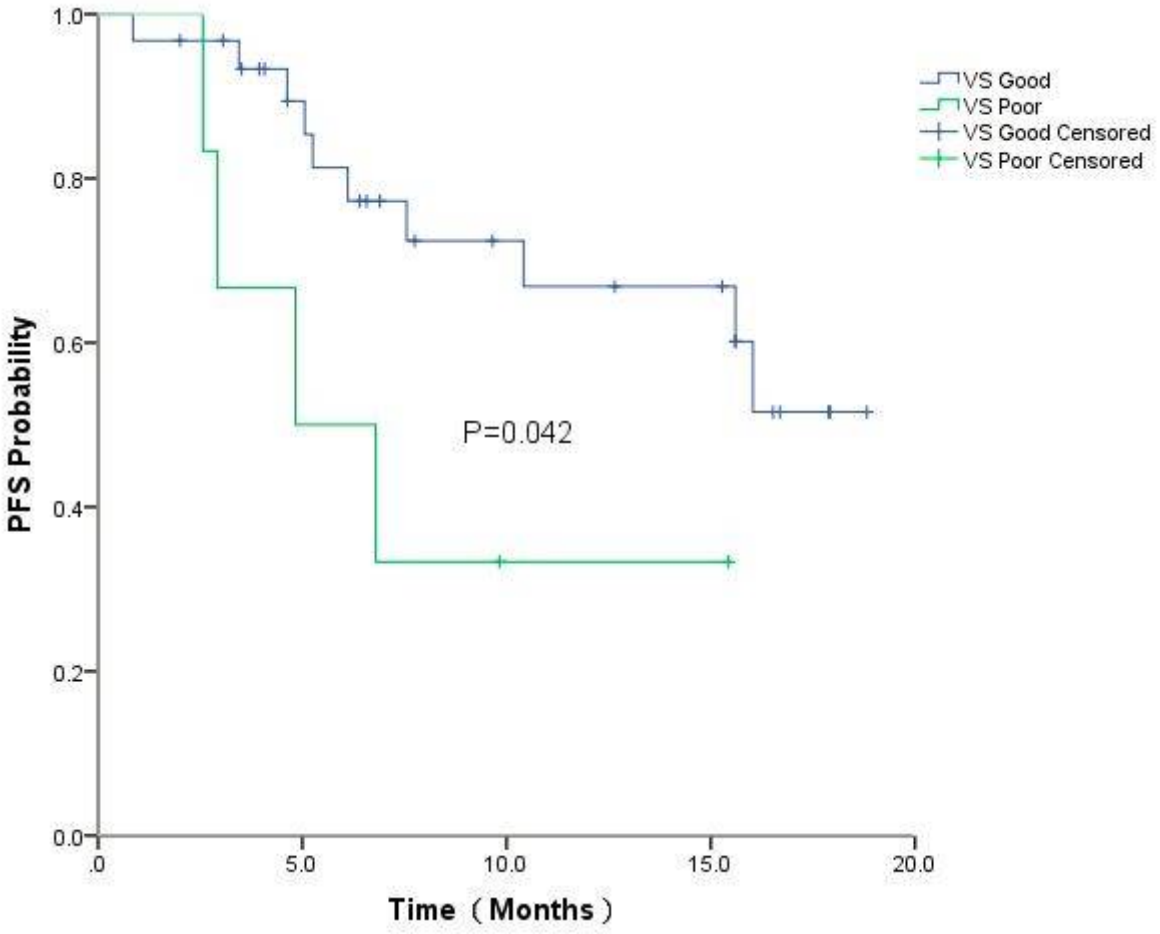

Figure 3

Progression-free Survival (PFS) by VS Classification for patients received chemotherapy and bevacizumab