Real-world effectiveness of Glasgow prognostic score and tumor biomarkers in predicting post-relapse survival in patients with recurrent cervical cancer after minimally invasive surgery

Junhui Guo (guojhhn96@yeah.net)
the second affiliated hospital of Henan University of Chinese Medicine
Yuanyuan Wang
the second affiliated hospital of henan university of Chinese Medicine
Xinxin Wang
the second affiliated hospital of henan university of Chinese Medicine
Shengli Zhou
Henan Provincial People's Hospital
Peimin Liu
the second affiliated hospital of henan university of chinese Medicine

Research

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Abstract

Background Cervical cancer ranks the third most common malignancy of women worldwide, and recurrence of cervical cancer treatment is the major concern. Carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), squamous cell carcinoma antigen (SCCA) and Glasgow Prognostic Score (GPS) were potential prognostic indicator for cervical cancer. However, none of these markers have been evaluated to predict post-relapse survival in recurrent cervical cancer after treatment based on real-world clinical data.

Aim To evaluate biomarkers CEA, CA125, SCCA and Glasgow Prognostic Score (GPS) in predicting post-relapse survival in recurrent cervical cancer after treatment based on real-world clinical data.

Results Among the 1607 patients, the majority of patients (75.5%) were non-smokers, and the majority of histologic type (68.3%) was squamous cell carcinoma. Except CEA, there were significant difference between different GPS groups in these markers. Areas under the curves (AUC) for GPS, CEA, CA125 and SCCA were 0.632, 0.617, 0.641 and 0.628, respectively. All clinicopathologic characteristics were significantly correlated with CA125. Higher levels of biomarkers and GPS had lower survival and GPS=2 and SCCA was an independent prognostic factor for survival (P=0.008 and P=0.010, respectively).

Conclusions In real-world settings, GPS and tumor biomarkers, especially SCCA to independently predict post-recurrence survival in patients with recurrent cervical cancer.

Background

Due to the widespread application of effective screening programs, the incidence of cervical cancer have decreased by 75% [1]. However, cervical cancer still ranks the third most common malignancy of women worldwide, and approximately 250,000 patients die each year [2, 3]. Among all factors, recurrence contributes a lot, and it has been reported that more than 50% of women with cervical cancer experience cancer recurrence [4]. Long-term survival can be achieved in few patients with a cancer relapse [5], and most patients will suffer further disease progression or death within a median time of 11–16 months [6–8].

Laparoscopic hysterectomy was introduced to decrease the morbidity of the operative procedure, and has been adopted as the standard approaches in gynecologic oncology [9, 10]. It has been proven that the laparoscopic approach is associated with fewer postoperative complications and recovery [11–13]. However, there have been concerns about the difficulties in achieving a sufficient resection margin by minimally invasive approaches. As a result, recurrence of cervical cancer after laparoscopic hysterectomy should be emphasized.

Serum tumor markers have long been used to predict prognosis and disease monitoring after primary treatment, of which carbohydrate antigen 125 (CA125) and squamous cell carcinoma antigen (SCCA) are two markers often used in cervical cancer. CA125 is membrane-bound glycoproteins expressed in some

epithelial cancers [14, 15]. Squamous cell carcinoma antigen (SCCA) can be overexpressed during the neoplastic transformation of the cervical squamous epithelium [16]. Apart from tumor markers, the inflammation-based Glasgow Prognostic Score (GPS) is a useful in predicting prognostic outcomes of cancer, which combines serum C-reactive protein (CRP) and albumin. Previous studies found that higher GPS at treatment time was independently associated with shorter survival of cervical cancer [17–19], suggesting that GPS is a potential prognostic indicator for cervical cancer. However, none of these markers have been evaluated to predict post-relapse survival in recurrent cervical cancer after minimally invasive surgery in real-world clinical data.

Here, we conducted a multicentered large-scale study to retrospectively compare the real-world effectiveness of these biomarkers in the survival of patients of cervical cancer.

Methods

Study cohort

The study was approved by the ethics committee of The Second Affiliated Hospital of Henan University of Chinese Medicine, China. As a retrospective study, informed consent was not required and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Between Jun 2005 and Oct 2015, a total of 6986 patients with cervical cancer from 5 hospitals in Henan, China(The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine: 2597; People's Hospital of Henan Province: 1743; The First Affiliated Hospital of Henan University of Traditional Chinese Medicine: 1039; The Third Affiliated Hospital of Henan University of Traditional Chinese Medicine: 904; People's Hospital of Zhengzhou: 703) were retrospectively screened and analyzed. All these patients were treated with minimally invasive surgery. Among them, 1607 patients (23.0%) experienced recurrence and were enrolled. All patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system. Patients' records were reviewed to collect data of serum albumin, CRP, CEA, CA125, SCCA and other clinical parameters available at the time of cancer recurrence. Finally, a total of 1435 patients were included in this analysis.

Clinical management and follow-up

Patients of FIGO IIa and before were managed with hysterectomy by means of minimally invasive approach. After surgery, patients were treated by adjuvant therapy if necessary according to FIGO guideline. Following initial surgery, patients underwent follow-up every 3 months. CT, MRI or positron emission tomography (PET)–CT was performed if clinically suggested or there was an elevation of tumor markers at each follow-up time. Cancer recurrence was diagnosed by biopsy or imaging examinations, and the time of recurrence was defined as the baseline point. Survival time after recurrence was documented for each patient. The endpoint of follow-up was defined as either death or survival after recurrence.

Measurement of serum parameters

All serum parameters were assessed at relapse time. Serum albumin and CRP levels were assayed with bromocresol green and immunoturbidimetric test respectively using Hitachi 7600 chemistry autoanalyzer. Serum CA125, CEA and SCCA levels were assessed with ARCHITECT reagent kits using ARCHITECT i2000SR.

Statistical analysis

SPSS version 22.0 statistical software (IBM, USA) were applied for all statistical analysis. Student T-test or Mann-Whitney test was applied to compare the differences between two groups. Receiver Operating Characteristics (ROC) Curves were depicted to evaluate the detecting efficiency of each marker, and DeLong test was applied to compare the different AUROC. For survival analysis, Kaplan-Meier analyses and log-rank test were used. Univariate and multivariate cox proportional hazard models were used to calculate hazard ratios and 95% confidence intervals. Two-tailed P value less than 0.05 was defined to be statistically significant.

Results

Patient characteristics

Table 1 shows the characteristics of patient categorized by GPS scores. Among the 1607 patients, the majority of patients (75.5%) were non-smokers, and 68.3% of them were squamous cell carcinoma. By recurrence, the majority of post-surgery patients were recurrent within pelvis (86.3%). Patients in different GPS groups have significantly different (P=0.045) median tumor-free intervals (TFI) after surgery, which decreased with GPS increasing. Except CEA, there were significant difference between GPS groups in these markers.

ROC curves for NLR, PLR and parametrial involvement and cutoff values determination

ROC curves of predictive significance of post-relapse survival values were shown in Fig. 1. Areas under the curves (AUC) for GPS, CEA, CA125 and SCCA were 0.632, 0.617, 0.641 and 0.628, respectively. DeLong test showed that there were no significant difference between every two of these four markers (P>0.05 for all). Youden indexes showed that the best cutoff values were 50 ng/ml for CEA, and 75 U/ml for CA125, and 8.5 ug/ml for SCCA.

Association between GPS, tumor biomarkers and clinicopathologic parameters

Patients were stratified into the high and low group according to the cutoff values above. The clinicopathologic characteristics were compared, as showed in Table 2. Overall, no significant relationships were noted between age, BMI, smoke with markers. However, a statistically significant correlation was observed between smoke, median TFI, primary tumor histology, site of recurrence and GPS (P<0.001, P=0.038, P<0.001, P<0.001, respectively); Significant correlations between BMI, median

TFI, primary tumor histology and CEA (P<0.001, P=0.012 and P<0.001, respectively); Significant correlations between smoke, primary tumor histology and SCCA (P=0.034 and P<0.001, respectively). All clinicopathologic characteristics were significantly correlated with CA125 (P<0.05 for all).

Survival analysis

Generally, the overall death within 50 months after cancer recurrence was detected in 508 (31.6%) patients, consisting of 419 (44.8%) patients in the GPS2 group, 58 (21.8%) patients in the GPS1 group, and 32 (7.9%) patients in GPS0 group. The median interval between recurrence and death was 21 months (range: 6–46 months) and 90% of death were identified within 2 years after recurrence. The estimated 1-, 2- and 3- year's survival rates for patients in the GPS0 group were 86.3%, 62.8%, and 58.2%, compared with 85.9%, 51.2%, and 30.4% for those in the GPS1 group, and 65.2%, 31.7%, and 18.4% for those in the GPS2 group, respectively. As shown in the figure 2, patients with a higher GPS scores had decreased survival (P < 0.001). Besides, different levels of tumor biomarkers could also predict the survival rates. Figure 2BCD showed that higher levels of all three biomarkers had lower survival.

Cox-regression analysis was used to further determine the prognostic value of these four markers. Other prognostic factors include age, smoke, BMI, TFI, histological type and site of recurrence. Prognostic factors that were significantly (Defined as P<0.1) associated with end points in the univariate analysis were adjusted in the multivariate analysis in a forward stepwise manner. As showed in Tables 3, univariate analysis revealed that there was a significant association between BMI (P=0.057), TFI (P=0.037), distant recurrence (P<0.001), GPS=1 (P<0.049) and GPS=2 (P=0.002), CEA≥ 50 ng/ml (P=0.096), CA125≥75 U/ml (P=0.046), SCCA≥8.5 ug/ml (P=0.004) with survival. In multivariable analysis, it was confirmed that GPS=2 and SCCA was an independent prognostic factor for survival (P=0.008 and P=0.010, respectively), as well as TFI (P=0.040) and distant recurrence (P=0.002). However, CEA and CA125 had no independent prognostic value for OS (P=0.115 and P=0.062, respectively).

Discussion

Few studies have addressed the post-recurrence survival in these patients. However, in clinical reality, estimation of post-recurrence survival is essential to individualize the treatment of cancer relapse. To our knowledge, this is first to investigate the usefulness of inflammatory and tumor markers as prognostic factors in patients with recurrent cervical cancer based on real-world clinical data. Our results confirmed the value of the GPS and SCCA for predicting post-recurrence survival in a large group of patients.

There has been no ideal tumor marker in current clinical practice, because most of tumor markers showed variable sensitivity and specificity in specific cancers. As for SCCA, increasing serum SCCA can precede the clinical diagnosis of relapse in 46%-92% of cases [19]. In a previous study by Esajas MD et al, serum higher level of SCCA did not contribute to better survival [20], but another study reported that treatment with radiotherapy or surgery resulted in better survival compared with chemotherapy in patients with serum SCCA < 14.0 ng/mL at relapse time [21]. However, our study showed that SCCA was a potent biomarker for predicting post-recurrence survival compared with CEA and CA125.

Borras et al. reported that the levels of CEA act as a prognostic indicator in cervical cancer [22]. However, our results showed that different levels of CEA have different survival after recurrence but the CEA had no independent prognostic value, suggesting that CEA was not a specific marker for cervical cancer. The clinical use of CA125 was similar with CEA, but we found an interesting results that smoking was inversely associated with CA125 concentrations, which is consistent with prior investigations in large populations [23].

Both inflammation and nutritional decline are characteristics of cachexia in cancer patients, and cachexia is indirectly responsible for the death of approximately 20% of all the cancer patients [24]. CRP and serum albumin were typical markers reflecting inflammation and nutritional. Previous studies showed that a higher GPS was predictive of shorter overall survival, independent of tumor stage and lymph node involvement [17]. Our results demonstrate a strong relationship between higher GPS at recurrence time and shorter survival in patients with recurrent cervical cancer. And besides, higher GPS was an independent risk factor for shorter post-relapse survival.

Real-world researches often enrolled an abundant number of participants with a relatively less limited inclusion criterion, so as to provide a satisfactory external validity [25]. Our study for the first time analyzed the efficacy of four markers in predicting post-recurrence survival based on real-world clinical data from 5 centers. As a result, larger number was the main strength of our study. However, there are some limitations that deserve to be mentioned. Within this study, data were retrospectively analyzed, leading to shortcomings, such as patient selection and incomplete data acquisition. In addition, due to the relatively long study period and complex methods of treatment after cancer recurrence, different types of treatment were not analyzed in this study.

Conclusion

The present study suggests that GPS and tumor biomarkers, especially SCCA could independently predict post-recurrence survival in patients with recurrent cervical cancer. In addition, distant relapse and shorter TFI after initial treatment were also associated with shorter post-recurrence survival. However, prospective and multi-centered study should be designed to validate this study.

Declarations

Acknowledgments

None.

Funding

None.

Availability of data and materials

The datasets and supporting materials generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JH Guo design the study, conducted the investigation and drafted the manuscript. YY Wang, XX Wang, SL Zhou and PM Liu collected and analyzed the data. All authors read and approved the final manuscript.

Notes

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of The Second Affiliated Hospital of Henan University of Chinese Medicine.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

HPV: human papilloma virus, SCCA: squamous cell carcinoma antigen, GPS: Glasgow Prognostic Score, ROC: Receiver Operating Characteristics, BMI: body mass index, TFI: tumor-free interval

Tables

Table 1 Clinical characteristics of patients with cervical cancer recurrence at recurrence time.

Characteristics	All	GPS			P
		0	1	2	
	1607	936(58.2%)	266(16.6%)	405(25.2%)	
recurrence	1607	53.7(41.8-61.8)	52.9(42.6-63.8)	51.8(48.9-60.9)	0.091
ıg					<0.001
ver	1214	752(61.9%)	154(12.7%)	308(25.4%)	
rrent or former	393	184(46.8%)	112(28.5%)	97(24.7%)	
$/m^2$	1607	24.1(20.8-29.8)	25.7(21.1-32.9)	23.7(19.6-28.3)	0.053
TFI from diagnosis, s	1607	18.5(11.3-35.8)	13.8(9.5-25.8)	11.1(7.3-25.4)	0.045
CRP, mg/L	1607	11.2(1.2-47.5)	27.8(9.8-67.8)	58.6(18.9-67.2)	0.003
albumin, g/L	1607	42.2(30.2-51.6)	34.2(25.5-40.5)	29.4(21.2-35.8)	0.001
markers					
A, ng/ml	1607	112.5(15.8-215.6)	213.2(59.4-315.9)	135.9(45.4-297.5)	0.067
125, ng/ml	1607	83.4(20.6-102.5)	289.1(101.2-384.2)	199.8(96.8-289.7)	0.053
CA, ug/l	1607	5.6(1.2-12.5)	7.6(2.4-19.8)	16.4(5.9-25.8)	0.038
tumor histology					<0.001
C	1318	807(61.2%)	207(15.7%)	304(23.1%)	
CC	289	129(44.6%)	59(20.5%)	101(34.9%)	
recurrence					<0.001
vis	1387	826(59.6%)	255(18.4%)	306(22.1%)	
tant	220	110(50.0%)	11(5.0%)	99(45.0%)	

BMI, body mass index; TFI, tumor-free interval; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; SCCA, squamous cell carcinoma antigen; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma.

Table 2 The relationship of GPS and tumor biomarkers with clinicopathological characteristics in cervical cancer patients.

tics	GPS			P	CEA, ng/ml		P	CA125, U/ml		P	SCCA, ug/ml		P
	0	1	2		<50	≥50		<75	≥75		<8.5	≥8.5	
				0.938			0.143			0.023			0.092
ars	462	128	199		295	494		292	497		443	346	
ars	474	138	206		335	483		348	470		372	346	
				<0.001			0.201			<0.001			0.034
or	752	154	308		825	387		732	482		915	299	
	184	112	97		281	112		292	101		275	118	
				0.082			<0.001			0.002			0.643
)	429	106	164		392	307		412	287		357	342	
0	507	160	241		628	280		605	303		452	456	
				0.038			0.012			0.002			0.064
	527	169	251		622	325		506	441		492	455	
	409	97	154		392	268		301	359		311	349	
nor				<0.001			<0.001			<0.001			<0.001
	807	207	304		895	423		565	753		786	532	
	129	59	101		108	181		96	793		135	154	
				<0.001			0.113			<0.001			0.401
	826	255	306		695	692		877	510		755	632	
	110	11	99		97	123		105	115		127	93	

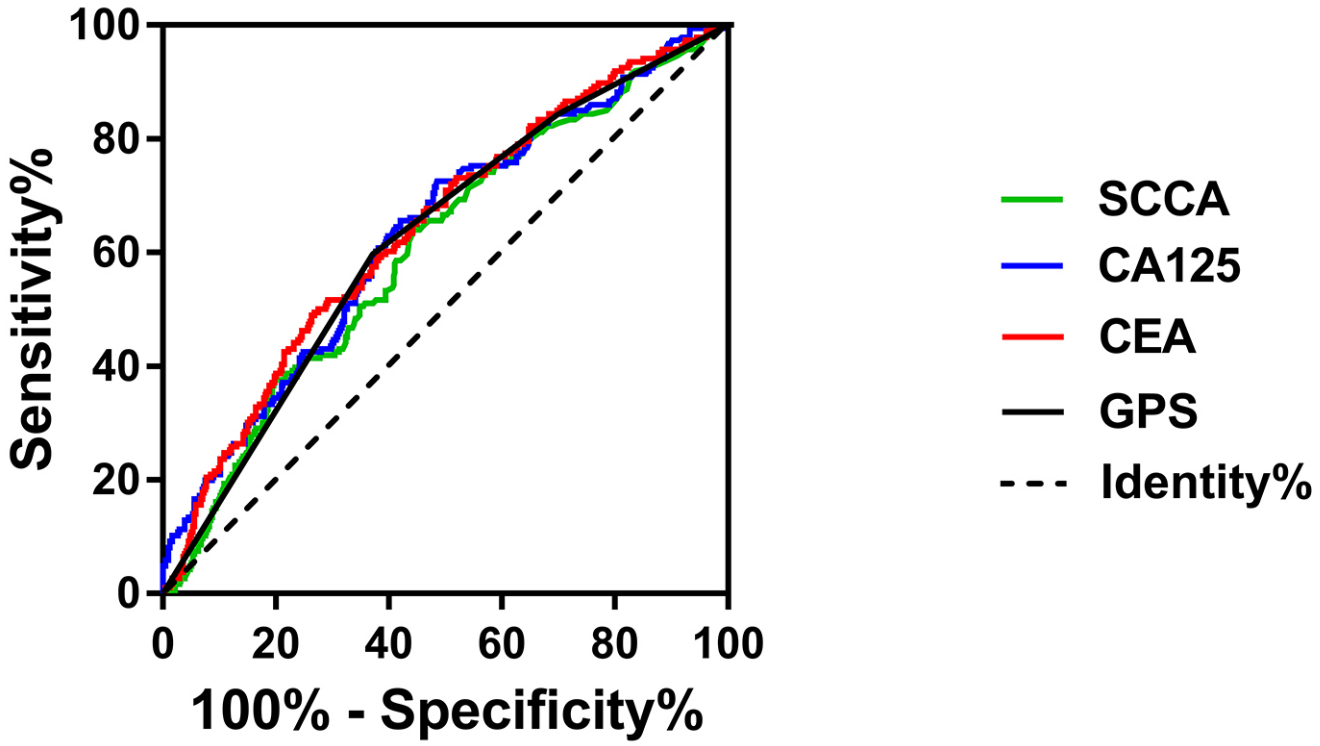
BMI, body mass index; TFI, tumor-free interval; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; SCCA, squamous cell carcinoma antigen; SCC, squamous cell carcinoma; NSCC, non-squamous cell carcinoma

Table 3 Univariate and multivariate cox proportional hazards regression analysis for post-recurrence survival.

	Univariate analysis		Multivariate analysis	
	P	*HR(95% CI)*	*P*	*HR(95% CI)*
Age, ≥50 yrs	0.780	0.92(0.42-2.35)		
Smoke	0.124	1.15(0.84-3.59)		
BMI, ≥24.0 kg/m^2	0.057	1.23(0.95-3.19)	0.067	1.26(0.93-3.25)
TFI, <12 months	0.037	1.47(1.02-2.29)	0.040	1.33(1.01-2.89)
GPS,				
1	0.049	1.12(1.01-1.98)	0.076	1.13(0.96-2.03)
2	0.002	2.03(1.89-3.16)	0.008	2.01(1.79-3.09)
Tumor markers				
CEA, ≥ 50 ng/ml	0.096	3.18(0.74-6.23)	0.115	3.22(0.76-5.98)
CA125, ≥ 75 U/ml	0.046	1.03(1.00-1.38)	0.062	1.02(0.98-1.26)
SCCA, ≥ 8.5 ug/ml	0.004	1.99(1.12-3.35)	0.010	1.89(1.09-3.27)
Histology, SCC	0.671	0.75(0.32-2.86)		
Site, distant	<0.001	2.24(1.46-3.58)	0.002	2.18(1.38-3.42)

HR, hazard ratio; BMI, body mass index; TFI, tumor-free interval; GPS, Glasgow prognostic score; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; SCCA, squamous cell carcinoma antigen; SCC, squamous cell carcinoma.

Figures



Group	AUROC	95% CI	P(DeLong test)				
GPS	0.632	0.595-0.674	0.314		0.754	0.826	
CEA	0.617	0.576-0.656		0.064			0.725
CA125	0.641	0.601-0.679	0.106				
SCCA	0.628	0.582-0.668					

Figure 1

ROC curves of GPS and tumor biomarkers in predicting post-recurrence survival. GPS, Glasgow prognostic score; CEA, carcinoembryonic antigen; CA125, carbohydrate antigen 125; SCCA, squamous cell carcinoma antigen

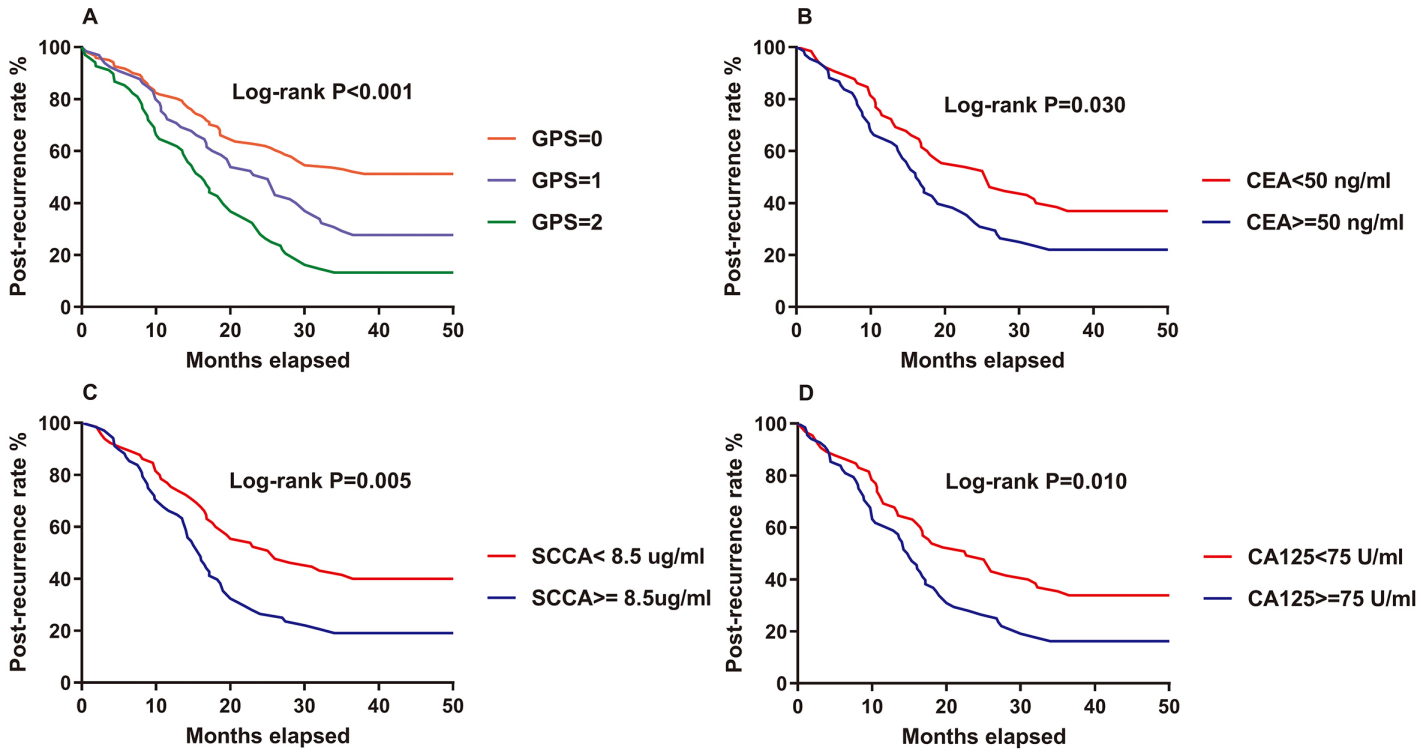


Figure 2

Post-recurrence survival categorized by different levels of GPS and tumor markers in recurrent cervical cancer participants. Participants were divided into different groups based on cut-off values calculated by ROC curves.