

Peripheral Blood Markers Predict Prognosis and Treatment-Related Adverse Events of Stage IB–IVA Cervical Squamous Cell Carcinoma Treated with Chemoradiotherapy Combined with Hyperthermia

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Abstract

This retrospective cohort study evaluated the clinical efficacy and safety of radical concurrent chemoradiotherapy (CCRT) combined with deep microwave hyperthermia in 193 patients with stage IB–IVA cervical squamous cell carcinoma (CSCC). With a median follow-up of 40.6 months, the 3-year overall survival (OS) and progression-free survival (PFS) rates were 81.34% and 81.27%, respectively. Multivariate analysis identified International Federation of Gynecology and Obstetrics (FIGO) stage and serum squamous cell carcinoma antigen (SCC-Ag) levels as independent poor prognostic factors for both OS and PFS. Treatment-related adverse events (TRAEs), predominantly myelosuppression, occurred in 54.9% of patients. Notably, the lymphocyte-to-monocyte ratio (LMR) served as an independent protective factor against TRAEs (odds ratio = 0.405, $P = 0.003$); patients with $\text{LMR} \leq 4$ faced a significantly higher toxicity risk. Pretreatment SCC-Ag and LMR are reliable biomarkers for prognosis and safety profiling, supporting personalized risk-stratified management in clinical practice.

Introduction

Cervical cancer remains a major malignancy threatening women's health, particularly in developing countries, where approximately 85% of the estimated 600,000 new global cases annually occur[1]. Despite advancements in diagnostic techniques and the widespread adoption of human papillomavirus (HPV) vaccination, which have contributed to a gradual decline in incidence[2],[3], the prognosis for patients with locally advanced cervical cancer (LACC) remains suboptimal. Over 50% of patients in developing countries present with locally advanced or metastatic disease at diagnosis, facing a modest 5-year relative survival rate of 50–60%[4]. Current guidelines, including those from the National Comprehensive Cancer Network (NCCN), establish radical concurrent chemoradiotherapy (CCRT) as the standard of care for stage IB2-IVA disease[5]. However, CCRT exhibits significant limitations in high-risk populations characterized by bulky tumors, extensive parametrial invasion, or multiple lymph node metastases, often resulting in residual lesions, pelvic recurrence, and distant metastasis[6],[7]. Consequently, there is an urgent need to explore novel therapeutic strategies to improve long-term outcomes.

Hyperthermia (HT) has emerged as a promising adjunctive modality in multidisciplinary cancer treatment[8]. By elevating tumor tissue temperatures to cytotoxic levels, HT directly induces apoptosis and necrosis. Moreover, it enhances tumor microenvironment perfusion, increases oxygen tension, augments chemotherapeutic drug concentration, and reverses radioresistance, thereby synergizing with radiotherapy and chemotherapy[8],[9]. Crucially, HT exerts minimal damage to normal tissues, making it an attractive option for mitigating treatment-related toxicities[10]. Nevertheless, the clinical application of HT in gynecological oncology remains underexplored [8]. While the synergistic effects of HT combined with chemoradiotherapy have been validated in esophageal, rectal, and ovarian cancers[11],[12], robust clinical evidence regarding its efficacy and safety in cervical cancer is lacking. Previous studies have suffered from small sample sizes and heterogeneous methodologies, lacking unified standards for clinical application and efficacy assessment[13]. Additionally, reliable biomarkers capable of predicting

treatment response or toxicity in patients undergoing CCRT + HT are scarce[14]. To address these gaps, we conducted a retrospective cohort study to systematically evaluate the clinical value of CCRT combined with deep hyperthermia. We aimed to identify clinical and biological factors influencing survival and safety by analyzing historical patient data, ultimately providing a basis for precise prognostic assessment and individualized therapeutic strategies.

Results

Baseline characteristics

The baseline characteristics of the 193 identified patients are summarized in Table 1. The median age was 59 years (range: 32–75). According to FIGO 2018 staging, 7 (3.63%) patients were stage IB, 80 (41.45%) stage II, 96 (49.74%) stage III, and 10 (5.18%) stage IVA. Tumor diameter was > 4 cm in 102 patients (52.85%). Lymph node involvement was present in 82 patients (42.49%). TRAEs occurred in 109 patients (56.48%).

Table 1
Baseline Clinical Characteristics of Patients
with Stage IB–IVA Cervical Cancer.

Feature	N (%)
Age	
≤ 60	113 (58.55)
>60	80 (41.45)
Comorbidities	
Yes	70 (36.27)
No	123 (63.73)
FIGO stage	
IB	7 (3.63)
II	80 (41.45)
III	96 (49.74)
IVA	10 (5.18)
TRAEs	
Yes	109 (56.48)
No	84 (43.52)
Lymph node involvement	
Yes	82 (42.49)
No	111 (57.51)

Baseline laboratory parameters

Based on established literature [22], cutoff values were defined as follows: SCC-Ag, 4 ng/mL; neutrophil-to-lymphocyte ratio (NLR), 5; platelet-to-lymphocyte ratio (PLR), 185; lymphocyte-to-monocyte ratio (LMR), 4; and prognostic nutritional index (PNI), 45. Using these thresholds, patients were stratified accordingly (Table 2). Reference ranges for other tumor markers were: carcinoembryonic antigen (CEA) (0–5 ng/mL) and cancer antigen 125 (CA125) (0–35.0 U/mL).

Table 2
Baseline Peripheral Blood
Markers in Patients with
Stage IB–IVA Cervical
Cancer.

Variable	N (%)
Diameter	
≤ 4 cm	91 (47.15)
>4 cm	102 (52.85)
CEA	
≤ 5 ng/mL	145 (75.13)
>5 ng/mL	48 (24.87)
CA125	
≤ 35 U/mL	163 (84.46)
>35 U/mL	30 (15.54)
SCC-Ag	
≤ 4 ng/mL	76 (39.38)
>4 ng/mL	117 (60.62)
NLR	
≤ 5	155 (80.31)
>5	38 (19.69)
PLR	
≤ 185	102 (52.85)
>185	91 (47.15)
LMR	
≤ 4	97 (50.26)
>4	96 (49.74)
PNI	
≤ 45	61 (31.61)
>45	132 (68.39)

Survival analysis: overall survival (OS)

The median OS was 40.6 months (range: 4.9–71.5 months). The estimated 1-, 2-, and 3-year OS rates were 95.34% (95% CI: 92.36%–98.31%), 86.46% (95% CI: 81.62%–91.30%), and 81.34% (95% CI: 75.63%–87.06%), respectively. Univariate Cox regression identified FIGO stage (hazard ratio [HR] = 2.296, 95% CI: 1.159–4.551, $P = 0.017$), tumor diameter (HR = 2.036, 95% CI: 1.050–3.948, $P = 0.035$), lymph node involvement (HR = 2.084, 95% CI: 1.105–3.930, $P = 0.023$), SCC-Ag level (HR = 2.479, 95% CI: 1.218–5.045, $P = 0.012$), PLR (HR = 2.122, 95% CI: 1.112–4.051, $P = 0.023$), and NLR (HR = 2.241, 95% CI: 1.133–4.435, $P = 0.020$) as unfavorable prognostic factors (Fig. 2, 3). Conversely, comorbidities, TRAEs, CEA, CA125, PNI, and LMR showed no significant association with OS. Multivariate analysis using backward stepwise selection retained FIGO stage and SCC-Ag as independent predictors of poor OS. Specifically, advanced FIGO stage (HR = 2.132, 95% CI: 1.070–4.250, $P = 0.031$) and elevated SCC-Ag (HR = 2.234, 95% CI: 1.086–4.598, $P = 0.029$) were independently associated with increased mortality risk. The impact of PLR approached but did not reach statistical significance (HR = 1.765, 95% CI: 0.915–3.406, $P = 0.090$) (Table 3).

Table 3
Univariate Cox Regression Analysis of Factors Associated with OS.

Variable	HR (95% CI)	P value
FIGO stage	2.296 (1.159–4.551)	0.017
Comorbidities	1.136 (0.606–2.207)	0.659
Diameter (> 4cm)	2.036 (1.050–3.948)	0.035
LN metastasis	2.084 (1.105–3.930)	0.023
TRAEs	0.851 (0.453–1.597)	0.615
SCC-Ag (> 4 ng/mL)	2.479 (1.218–5.045)	0.012
CEA (> 5 ng/mL)	1.420 (0.719–2.805)	0.313
CA125 (> 35 U/mL)	1.149 (0.507–2.606)	0.739
PNI (≤ 45)	0.911 (0.461–1.801)	0.788
LMR (≤ 4)	0.932 (0.497–1.749)	0.827
PLR (> 185)	2.122 (1.112–4.051)	0.023
NLR (> 5)	2.241 (1.133–4.435)	0.020

Survival analysis: progression-free survival (PFS)

The median PFS was 40.1 months (range: 4.5–71.5 months). The 1-, 2-, and 3-year PFS rates were 93.26% (95% CI: 89.62%-96.91%), 83.78% (95% CI: 78.09%-89.47%), and 81.27% (95% CI: 75.07%-87.47%), respectively. Univariate analysis revealed that FIGO stage, lymph node involvement, SCC-Ag, NLR, and PLR were significant risk factors for disease progression (all $P \leq 0.05$) (Fig. 4, 5). Multivariate analysis confirmed that FIGO stage (HR = 2.002, 95% CI: 1.004–3.996, $P = 0.049$) and SCC-Ag level (HR = 2.144, 95% CI: 1.049–4.380, $P = 0.036$) were independent predictors of PFS. Similar to OS, the effect of PLR was marginal (HR 1.770, 95% CI: 0.918–3.410, $P = 0.088$) (Table 4).

Table 4 Multivariate Cox Regression Analysis of Factors Associated with OS.				
Variable	HR	95% CI Lower	95% CI Upper	P value
FIGO stage	2.132	1.070	4.250	0.031
SCC-Ag (> 4 ng/mL)	2.234	1.086	4.598	0.029
PLR (> 185)	1.765	0.915	3.406	0.090

Treatment-related adverse events (TRAEs)

TRAEs were observed in 106 patients (54.9%). The most prevalent toxicity was myelosuppression (91 cases), followed by urinary symptoms (23 cases), diarrhea (11 cases), and dermatological reactions (5 cases). Myelosuppression severity was graded as follows: Grade I (55 cases), Grade II (24 cases), Grade III (9 cases), and Grade IV (1 case).

Univariate logistic regression identified comorbidities, CA125, PNI, and LMR as potential correlates of TRAEs ($P < 0.1$) (Table 5). In the multivariate model, LMR emerged as the sole independent protective factor against TRAEs (odds ratio [OR] = 0.405, 95% CI: 0.223–0.735, $P = 0.003$). Notably, patients with $LMR \leq 4$ faced a significantly elevated risk of toxicity. Pre-existing comorbidities exhibited a trend toward protective effect, though this did not reach statistical significance (OR = 0.541, 95% CI: 0.292–1.003, $P = 0.051$) (Table 6).

Table 5 Multivariate Cox Regression Analysis of Factors Associated with PFS.				
Variable	HR	95% CI Lower	95% CI Upper	P value
FIGO stage	2.002	1.004	3.996	0.049
SCC-Ag (> 4 ng/mL)	2.144	1.049	4.380	0.036
PLR (> 185)	1.770	0.918	3.410	0.088

Table 6
Univariate Logistic Regression Analysis of Predictors for TRAEs.

Variable	No TRAEs (N = 87)	TRAEs (N = 106)	OR (95% CI)	P value
FIGO stage (III-IV)	45	61	1.265 (0.715–2.238)	0.419
Diameter (> 4 cm)	46	56	1.002 (0.568–1.778)	0.995
Comorbidities (Yes)	30	40	0.464 (0.255–0.843)	0.012
LN metastasis (Yes)	34	48	1.290 (0.725–2.295)	0.386
SCC-Ag (> 4 ng/mL)	49	60	1.012 (0.571–1.792)	0.969
CEA (> 5 ng/mL)	21	27	1.074 (0.557–2.073)	0.831
CA125 (> 35 U/mL)	9	21	2.141 (0.925–4.956)	0.075
PNI (≤ 45)	20	41	0.473 (0.251–0.892)	0.021
LMR (≤ 4)	32	65	0.367 (0.204–0.659)	0.001
PLR (> 185)	39	52	1.185 (0.671–2.093)	0.558
NLR (> 5)	14	24	1.526 (0.735–3.169)	0.257

Discussion

The synergistic antitumor effects of hyperthermia combined with chemoradiotherapy are mechanistically underpinned by several key processes: radiosensitization via inhibition of DNA repair[15], enhanced intratumoral cisplatin accumulation due to improved microcirculation[16], promotion of apoptosis through heat shock protein dysregulation[15], and reversal of multidrug resistance[15]. While these mechanisms are well-established in preclinical models, their clinical translation in cervical squamous cell carcinoma requires further validation[17]. Our retrospective study focused on clinically accessible peripheral blood biomarkers to facilitate risk stratification. We demonstrated that pretreatment FIGO stage and SCC-Ag levels are robust independent prognosticators, whereas LMR serves as a potential predictor of TRAEs[18].

SCC-Ag is a well-established tumor-associated antigen for squamous cell carcinomas[19]. Given that squamous cell carcinoma accounts for 70–80% of cervical cancer cases in China, SCC-Ag monitoring is clinically relevant[20]. However, current guidelines do not uniformly recommend SCC-Ag for routine prognostic assessment. Historically, a cutoff of 1.5–2.5 ng/mL has been used for diagnostic purposes, yet its utility in predicting survival remains controversial[21]. Aligning with recent evidence[22], we adopted a cutoff of 4 ng/mL. Our survival analysis revealed significantly superior PFS and OS in the SCC-Ag ≤ 4 ng/mL group. Multivariate analysis confirmed elevated SCC-Ag as an independent risk factor for both recurrence and mortality. Despite its utility, SCC-Ag has limitations, including suboptimal specificity (elevated in benign conditions)[23], lack of standardized cutoffs across laboratories[24], and poor

sensitivity for non-squamous histologies[25]. Future multicenter studies should standardize assay protocols and explore combined models incorporating SCC-Ag, PNI, imaging parameters, and other biomarkers to enhance predictive accuracy.

Regarding safety, our study highlights the significance of the lymphocyte-to-monocyte ratio (LMR) in predicting TRAEs. LMR reflects the balance between anti-tumor immunity (lymphocytes) and immunosuppressive inflammation (monocytes)[26]. We found that patients with $LMR \leq 4$ had a substantially higher risk of developing adverse events, particularly myelosuppression. This aligns with the understanding that lymphopenia impairs the ability to repair cytotoxic damage induced by CCRT, while monocytosis may indicate a pro-inflammatory state detrimental to treatment tolerance[26],[27]. Therefore, routine assessment of pretreatment LMR could guide supportive care strategies, such as prophylactic growth factors or aggressive management of comorbidities, to ensure treatment continuity[28]. The observed trend suggesting a protective effect of comorbidities warrants cautious interpretation, potentially reflecting confounding by indication or variations in baseline health status, and necessitates validation in larger cohorts.

Limitations: As a retrospective, single-center study, inherent selection bias and unmeasured confounding factors may exist despite rigorous statistical adjustments. Although our findings highlight the predictive value of LMR and SCC-Ag, external validation through large-scale prospective trials is warranted to confirm these results before clinical implementation.

Methods

Patient selection and baseline data

This retrospective cohort study reviewed the medical records of patients with histologically confirmed stage IB–IVA cervical squamous cell carcinoma at the Affiliated Hospital of Chengde Medical University between April 2020 and July 2024. Inclusion criteria were: (1) pathologically confirmed squamous cell carcinoma; (2) complete clinical and pathological records; (3) FIGO 2018 stage IB–IVA; (4) completion of at least four cycles of concurrent chemotherapy; and (5) completion of at least eight sessions of hyperthermia. Exclusion criteria included: (1) history of other malignancies; (2) prior antitumor therapy; (3) insufficient treatment cycles (< 4 chemotherapy or < 8 hyperthermia sessions); and (4) incomplete clinical data. Ultimately, 193 patients were included in the final analysis (Fig. 1). Given the retrospective nature of the study, the requirement for written informed consent was waived. The study protocol adhered to the NCCN guidelines and the Chinese Cervical Cancer Diagnosis and Treatment Guidelines.

Treatment protocols

Hyperthermia was administered using a deep microwave hyperthermia system (HY-7000, Frequency: 40.68 MHz). Temperature probes were placed in the vaginal fornix and rectum to monitor target temperatures, maintained at 40.5–43.0°C for at least 45 minutes per session (total duration 60 minutes), twice weekly with intervals ≥ 72 hours. Radiotherapy was delivered via intensity-modulated radiation

therapy (IMRT) to a total dose of 50.4 Gy. Concurrent chemotherapy consisted of weekly cisplatin. The primary endpoints were 3-year OS and PFS; the secondary endpoint was the incidence of TRAEs.

Outcome measures

Demographic characteristics, tumor diameter, hematological indices, and survival data were extracted from electronic medical records. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression or death from any cause. Overall survival (OS) was defined as the time from initial treatment to death from any cause; patients alive at the last follow-up were censored. Hematological ratios were calculated as follows: NLR = neutrophil count/lymphocyte count; PLR = platelet count/lymphocyte count; LMR = lymphocyte count/monocyte count. The prognostic nutritional index (PNI) was calculated as: serum albumin (g/L) + 5 × total lymphocyte count (×10⁹/L).

Follow-up

Patients were monitored via outpatient visits and telephone interviews. The final follow-up date was March 31, 2026, with a median follow-up duration of 40.6 months. At the study's conclusion, 39 deaths and 18 losses to follow-up were recorded, yielding a follow-up rate of 86.16%.

Statistical analysis

Statistical analyses were performed using SPSS version 27.0. Survival curves were generated using the Kaplan-Meier method, and intergroup differences were assessed via the log-rank test. Variables with P < 0.1 in univariate Cox regression, along with clinically relevant confounders (age, maximum tumor diameter), were entered into a multivariate Cox proportional hazards model using backward likelihood ratio selection. The proportional hazards assumption was verified using Schoenfeld residuals (P > 0.05 for all covariates). For TRAEs, variables with P < 0.1 in univariate logistic regression were included in the multivariate model. A two-sided P ≤ 0.05 was considered statistically significant.

Table 7
Multivariate Logistic Regression Analysis of Predictors for TRAEs in 193 Patients.

Variable	OR (95% CI)	P value
LMR (≤ 4)	0.405 (0.223–0.735)	0.003
Comorbidities (Yes)	0.541 (0.292–1.003)	0.051
Data Availability Statement		
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.		

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

The present study was approved by the Medical Ethics Committee of Affiliated Hospital of Chengde Medical University (Approval No. CYFYLL2023552). Given the retrospective nature of the study and the use of anonymized data, the requirement for written informed consent was waived by the Ethics Committee. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Author Contribution

J.Y.Y. and L. Bai conceived and designed the overall research framework. F.Y. Shi, Z. Wang and X. Liu collected the experimental and clinical data. J.Y.Y. and S.S. Liu performed statistical analysis, dataset sorting and data visualization. J.Y.Y. drafted the original manuscript of the study. L. Bai and S.S. Liu critically revised the manuscript, reviewed, and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

Flowchart of patient selection

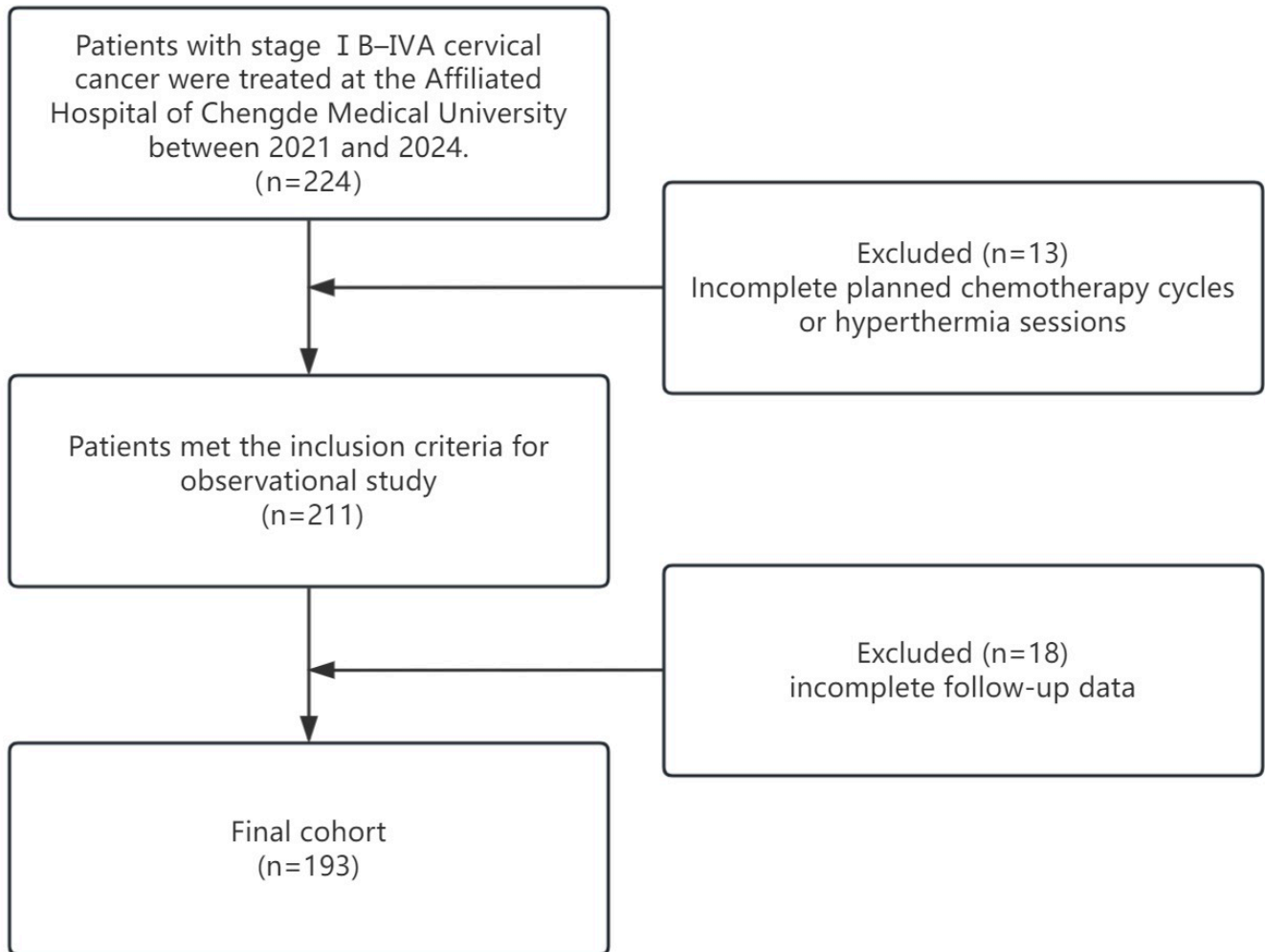


Figure 1

Flowchart of patient selection.

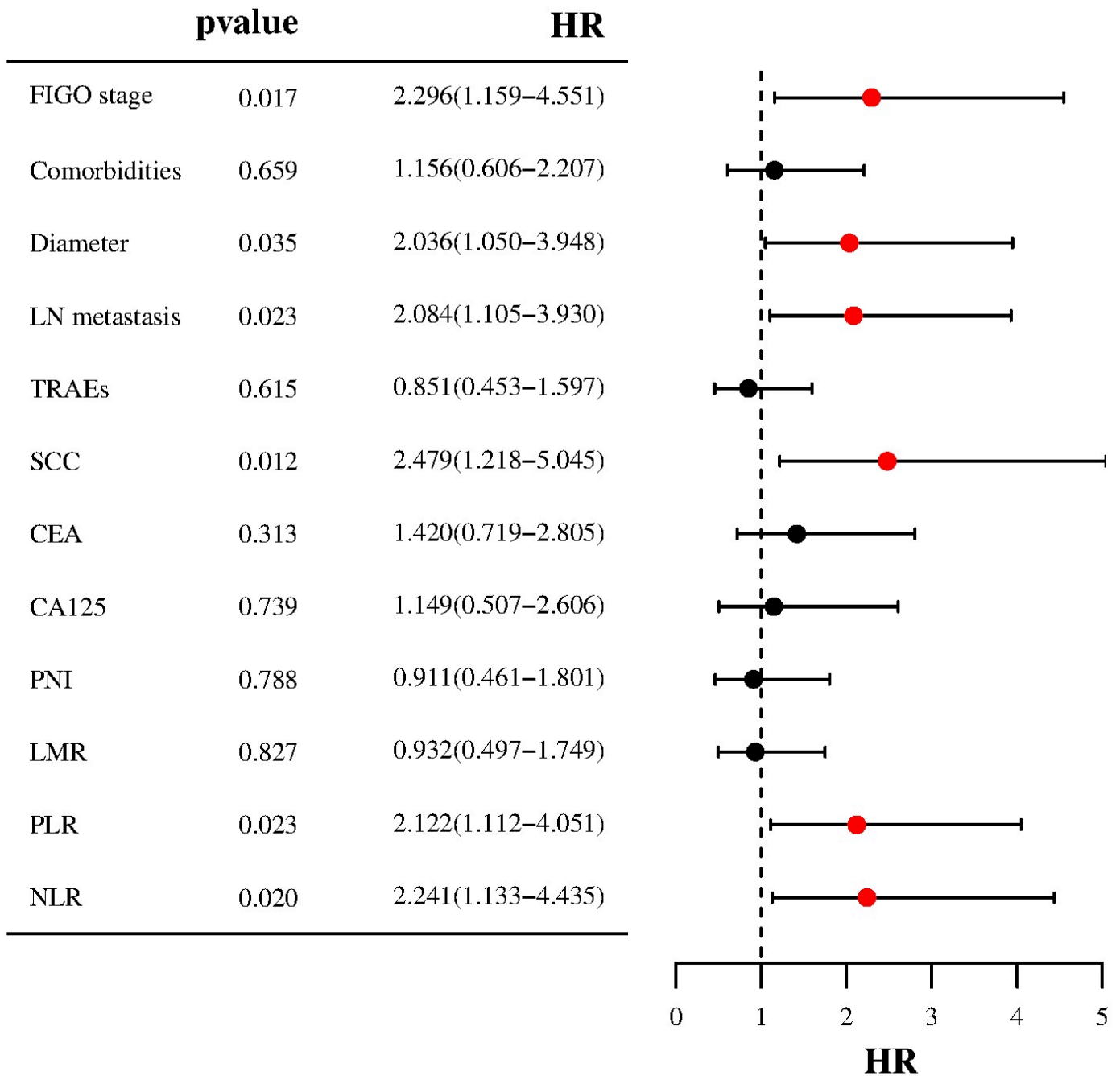


Figure 2

Univariate Cox regression of OS predictors in 193 stage IB–IVA cervical carcinoma treated with CCRT+hyperthermia.

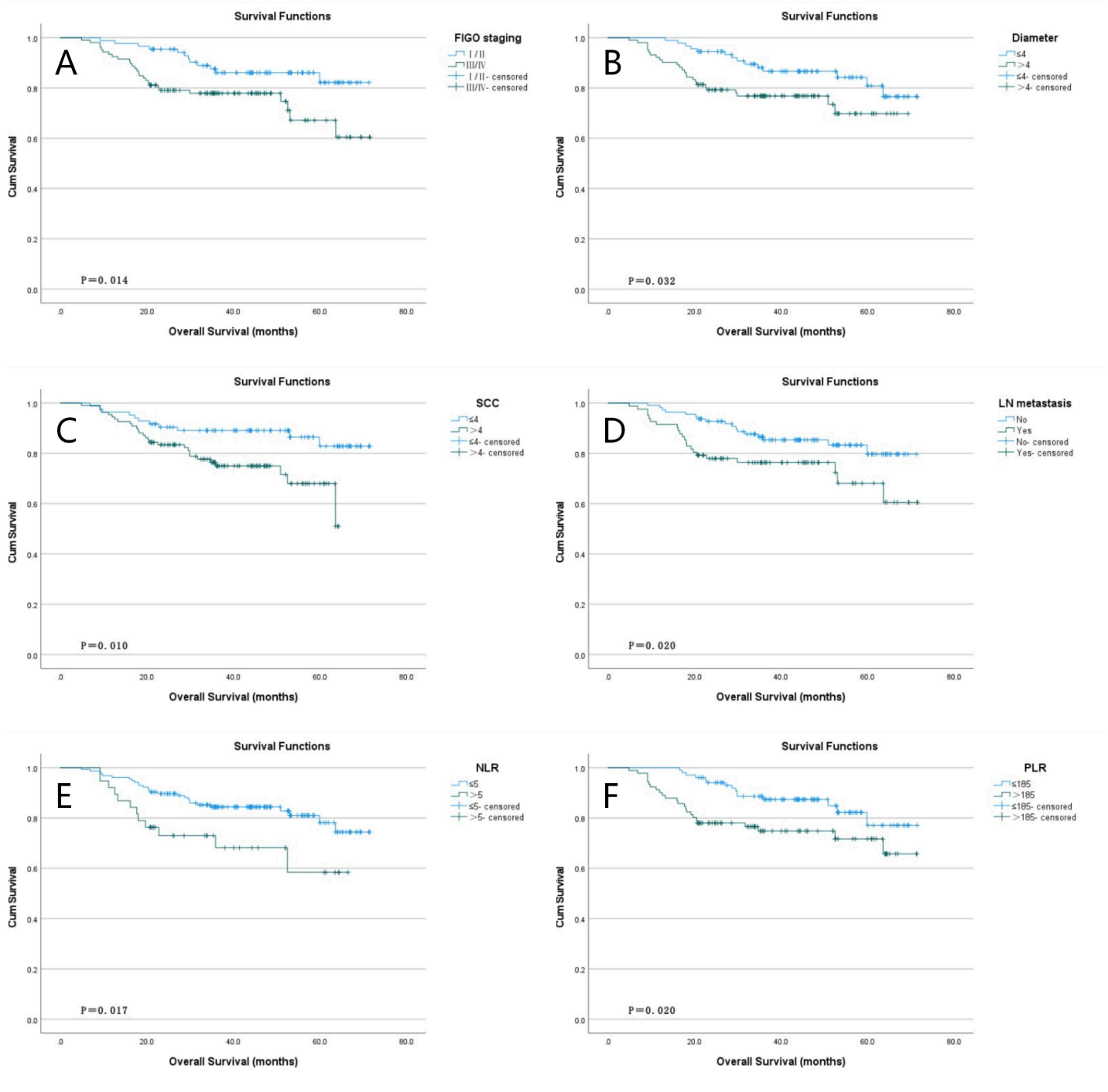


Figure 3

Kaplan-Meier OS curves of 193 stage IB–IVA cervical cancer patients receiving CCRT plus hyperthermia (A-F).

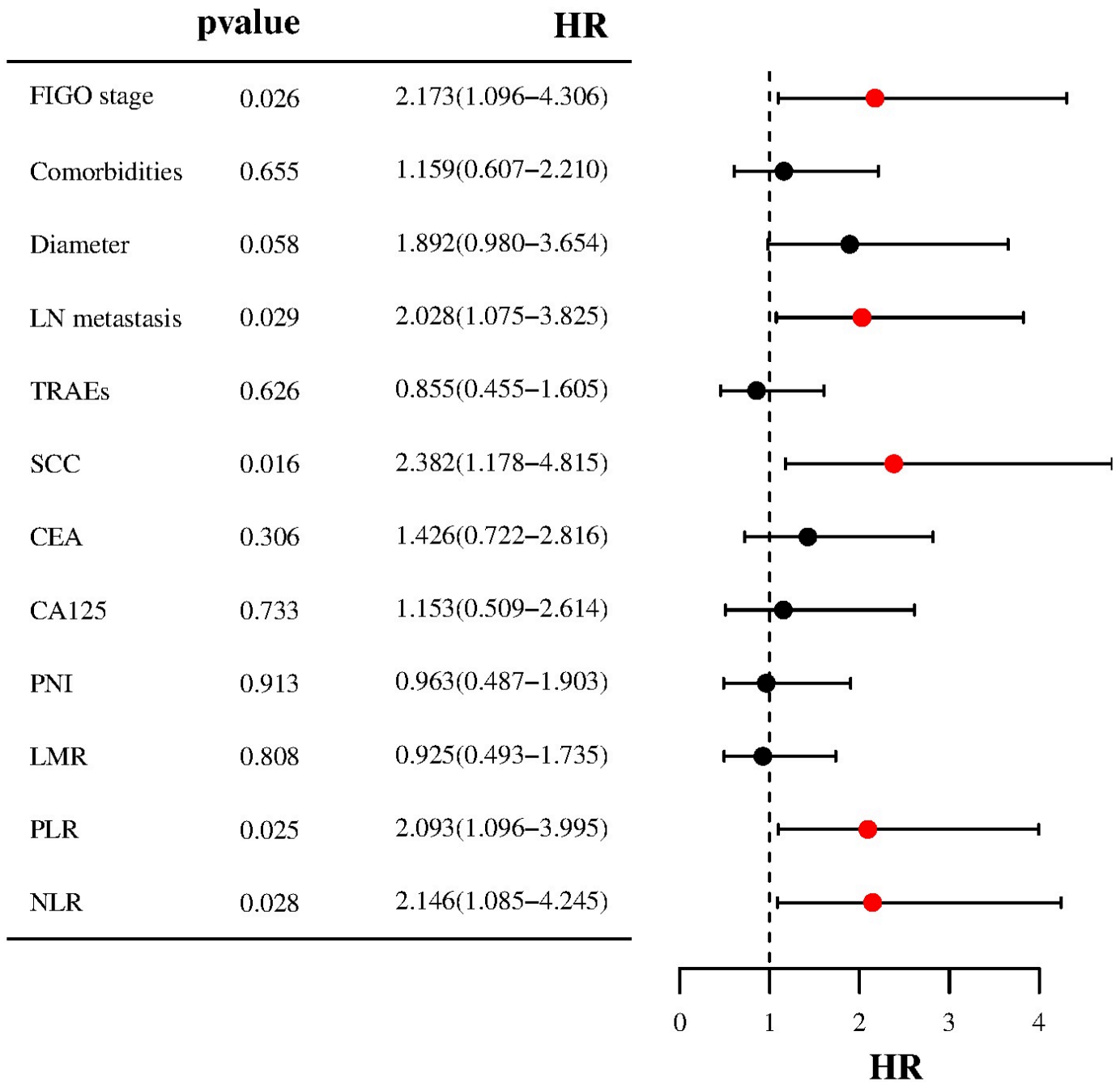


Figure 4

Univariate Cox regression of PFS predictors in 193 stage IB–IVA cervical carcinoma treated with CCRT+hyperthermia.

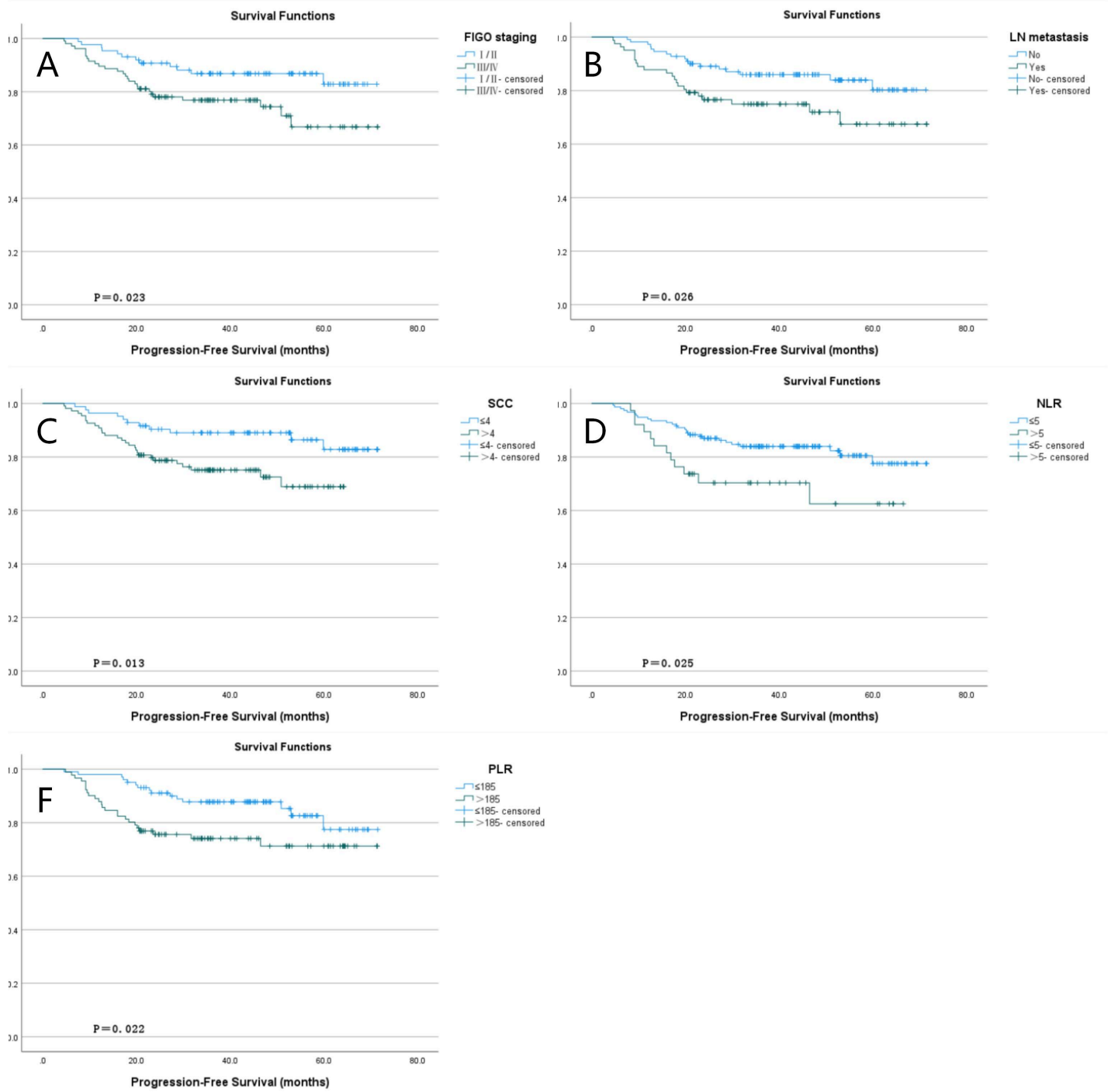


Figure 5

Kaplan-Meier PFS curves of 193 stage IB–IVA cervical cancer patients receiving CCRT plus hyperthermia (A-F).