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Prognostic value of pretreatment carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix

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Additional Declarations:

Tables 1 and 2 are available in the Supplementary Files section.

Original article

Prognostic value of pretreatment carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix

Short title: Carcinoembryonic antigen in SCC of uterine cervix

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ABSTRACT

Background: This study aimed to evaluate the prognostic significance of pretreatment serum carcinoembryonic antigen (CEA) as a continuous biomarker in patients with squamous cell carcinoma (SCC) of the uterine cervix.

Methods: We conducted a retrospective cohort study of 873 patients with histologically confirmed cervical SCC treated between 2013 and 2022. Pretreatment serum CEA and SCC antigen (SCC-Ag) levels were measured and log2-transformed for continuous-variable analyses. The primary endpoint was overall survival (OS); the secondary endpoint was progression-free survival (PFS). Cox proportional hazards models were constructed. Interactions between CEA and FIGO stage were also evaluated.

Results: Among 873 patients, the median pretreatment CEA level was 2.1 ng/mL (interquartile range, 1.3–4.1). During follow-up, 106 deaths and 184 PFS events occurred. In multivariable analyses, each doubling of pretreatment CEA was independently associated with poorer OS (hazard ratio [HR] 1.15; 95% confidence interval [CI], 1.02–1.29) and PFS (HR 1.13; 95% CI, 1.02–1.24). In contrast, continuous SCC-Ag levels were not independently associated with OS or PFS. No significant interaction between CEA and FIGO stage was observed for OS (P for interaction=0.45) or PFS (P for interaction=0.73).

Conclusions: Higher pretreatment serum CEA levels were independently associated with poorer OS and PFS in patients with cervical SCC. The prognostic association of pretreatment CEA did not significantly differ across FIGO stages. Incorporating pretreatment CEA levels into baseline assessment may complement FIGO staging and enhance prognostic stratification.

Keywords: carcinoembryonic antigen, overall survival, prognostic marker, progression-free survival, squamous cell carcinoma antigen, uterine cervix

INTRODUCTION

The prognosis of cervical cancer is primarily determined by clinicopathological factors such as lymph node metastasis (LNM), parametrial invasion (PI), and distant metastasis, which are closely associated with clinical stage as defined by the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system [1–6]. However, survival outcomes vary substantially among patients within the same stage. Identifying prognostic biomarkers that provide information beyond clinical stage may help refine baseline risk stratification and improve individualized treatment planning.

Among serum tumor markers, squamous cell carcinoma antigen (SCC-Ag) is the most established in cervical cancer. Elevated pretreatment SCC-Ag levels are associated with adverse features, including advanced stage, large tumor size (>4 cm), PI, and LNM [7–9]. However, its independent prognostic role remains inconclusive across studies [9–15]. Carcinoembryonic antigen (CEA), a tumor-associated glycoprotein, represents a promising candidate. From a biological standpoint, immunohistochemical studies suggest that CEA expression varies across histologic subtypes [16,17]. Clinically, serum CEA levels are elevated in approximately 24%–38% of patients with cervical cancer [18–21] and are associated with larger tumor size (>4 cm), PI, and pelvic LNM [8,11,22]. However, the correlation between CEA and clinical stage has been inconsistent [8,11].

Previous studies have several limitations: most included mixed histologic subtypes [11], enrolled only a minority of patients with FIGO III–IV disease [12,15], and were primarily restricted to radiotherapy or concurrent chemoradiotherapy settings [12,15]. Consequently, the independent prognostic significance of pretreatment CEA in a broad population encompassing different disease stages and treatment modalities remains unclear. Thus, this study aimed to evaluate the prognostic significance of pretreatment serum CEA as a continuous biomarker in patients with squamous cell carcinoma (SCC) of the uterine cervix. We hypothesized that pretreatment serum CEA is independently associated with prognosis in cervical SCC. SCC-Ag was analyzed as an exploratory comparator. Clarifying the prognostic significance of pretreatment CEA may contribute to more refined baseline risk stratification in cervical SCC.

PATIENTS AND METHODS

Ethics

This study was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (approval no. 2023-GB-079; SRB No. 1775). The requirement for written informed consent was waived owing to the retrospective design, and an opt-out approach was used. This study

was conducted in accordance with the Declaration of Helsinki.

Patient Selection

We retrospectively reviewed patients with cervical cancer who initiated primary treatment at our institution between January 2013 and December 2022. Patients with histologically confirmed invasive SCC of the uterine cervix were eligible for inclusion. Patients with unavailable pretreatment serum CEA or SCC-Ag measurements, unknown survival outcomes, or concurrent malignancies were excluded. Disease stage was retrospectively reassessed according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system using clinical and radiological findings and postoperative pathological findings when available.

Variables and Definitions

The primary explanatory variable was the pretreatment serum CEA level. Pretreatment serum SCC-Ag was evaluated as an exploratory comparator. Both markers were log2-transformed and analyzed as continuous variables, such that the corresponding hazard ratios (HRs) represent the relative change in hazard associated with each doubling of the marker level.

Other clinical variables included age, body mass index (BMI), smoking history, FIGO 2018 stage, and initial treatment. Smoking history was categorized as ever smoking (current or former smokers) or never smoking. FIGO stage was categorized into four groups (I, II, III, and IV). Initial treatment was classified into three groups: surgery-based treatment (surgery or neoadjuvant chemotherapy followed by surgery), radiation-based treatment (concurrent chemoradiotherapy or radiotherapy alone), and systemic/palliative treatment (chemotherapy or best supportive care).

For secondary analyses, CEA and SCC-Ag were dichotomized using prespecified cutoff values of 5.0 ng/mL for CEA [12,15] and 1.5 ng/mL for SCC-Ag [22–24], based on previous reports and institutional upper reference limits.

Endpoints

The primary endpoint was overall survival (OS), and the secondary endpoint was progression-free survival (PFS). OS was defined as the time from the initiation of primary treatment to death from any cause. Patients who were alive at the last follow-up were censored at that time. PFS was defined as the time from the initiation of initial treatment to the first occurrence of radiologically or pathologically confirmed recurrence or progression,

or death from any cause, whichever occurred first. Patients without a PFS event were censored at the date of the last confirmation of progression-free status.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics. Continuous variables were presented as medians with interquartile ranges (IQRs), and categorical variables as numbers and percentages. Differences in pretreatment CEA and SCC-Ag levels across FIGO stages were assessed using the Kruskal–Wallis test. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test.

Cox proportional hazards models were used to estimate HRs and 95% confidence intervals (CIs) for OS and PFS. In the primary multivariable analyses, CEA and SCC-Ag were modeled as log2-transformed continuous variables. Models were adjusted for age, smoking history, FIGO stage (I, II, III, and IV), log2-transformed SCC-Ag, and initial treatment. Binary analyses using prespecified cutoff values for CEA and SCC-Ag were performed as secondary analyses.

Time-dependent receiver operating characteristic (ROC) analyses were performed to evaluate the discriminative performance of pretreatment CEA for OS and PFS at 2 and 3 years. Optimal cutoff values were identified using the Youden index. These analyses were considered exploratory.

To assess whether the prognostic association of CEA differed according to FIGO stage, an interaction term between log2-transformed CEA and FIGO stage was incorporated into the Cox model. The overall interaction was evaluated by a likelihood ratio test comparing models with and without the interaction terms. Stage-specific HRs for CEA were estimated from the interaction model.

All tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using EZR (Easy R; Jichi Medical University Saitama Medical Center, Saitama, Japan), a graphical user interface for R (version 1.68).

RESULTS

Of 1,789 patients with cervical cancer who initiated primary treatment at our institution between 2013 and 2022, 1,084 had invasive SCC. After excluding patients with unavailable pretreatment serum CEA or SCC-Ag levels or with unknown survival outcomes or concurrent malignancies, 873 patients were included in the final analysis (Fig. 1). The median age and BMI were 49 years and 21.4 kg/m², respectively. FIGO stages I, II, III, and IV were observed in 349 (40.0%), 120 (13.8%), 326 (37.3%), and 78 (8.9%) patients, respectively. The median pretreatment

serum CEA level was 2.1 ng/mL (interquartile range [IQR], 1.3–4.1); the median SCC-Ag level was 3.4 ng/mL (IQR, 1.3–10.7). The median observation period was 53.4 (IQR, 31.8–66.4) months. During follow-up, 106 (12.1%) deaths and 184 (21.1%) PFS events occurred (Table 1). Pretreatment serum CEA levels differed significantly across FIGO stages ($p<0.001$), with median levels of 1.50, 2.40, 2.70, and 4.75 ng/mL in stages I, II, III, and IV, respectively (Online Resources 1 and 2).

Kaplan–Meier analyses using the prespecified CEA cutoff of 5.0 ng/mL showed poorer OS and PFS in patients with elevated CEA levels (Fig. 2 and Online Resource 3; both log-rank $p<0.001$).

Cox proportional hazards analyses for OS and PFS are shown in Table 2. In multivariable Cox proportional hazards analyses, higher pretreatment serum CEA levels were independently associated with poorer OS and PFS. Each doubling of pretreatment CEA was associated with a 15% higher hazard of death (HR 1.15, 95% CI 1.02–1.29, $p=0.021$) and 13% higher hazard of progression or death (HR 1.13, 95% CI 1.02–1.24, $p=0.015$). In contrast, pretreatment SCC-Ag levels were not independently associated with OS (HR 1.03, 95% CI 0.94–1.14, $p=0.53$) or PFS (HR 1.06, 95% CI 0.98–1.15, $p=0.16$) (Table 2).

There was no evidence that the prognostic association of pretreatment CEA differed according to FIGO stage. Likelihood ratio tests showed no significant interaction between continuous CEA levels and FIGO stage for either OS (p for interaction=0.45) or PFS (p for interaction=0.73). Stage-specific estimates of associations between CEA and survival outcomes are shown in Fig. 3.

In secondary analyses using the prespecified cutoff of 5.0 ng/mL, 175 patients (20.1%) had elevated pretreatment CEA levels (Online Resource 1). In multivariable analyses, CEA ≥5.0 ng/mL was independently associated with poorer OS (HR 1.55, 95% CI 1.03–2.31, p=0.034) and PFS (HR 1.51, 95% CI 1.10–2.07, p=0.011; Online Resource 4). Kaplan–Meier curves stratified by this cutoff are shown in Fig. 2. Exploratory time-dependent ROC analyses at 2 and 3 years are presented in Online Resource 5.

DISCUSSION

In this study, high pretreatment serum CEA levels were independently associated with poorer OS and PFS in patients with cervical SCC, even after adjustment for FIGO stage and other clinical factors. In contrast, SCC-Ag was not independently associated with survival outcomes in the multivariable analyses. Although pretreatment CEA levels differed significantly across FIGO stages, no significant interaction between CEA and FIGO stage was observed. These findings suggest that pretreatment serum CEA levels provide prognostic information complementary to anatomical staging.

Previous studies have reported inconsistent association between serum CEA levels and disease stage, despite associations with tumor size, pelvic lymph-node metastasis, and parametrial invasion [8,11,25]. These discrepancies may partly reflect differences in staging systems. Early studies predominantly used the FIGO 2009 classification, which did not incorporate lymph-node status into stage assignment. In contrast, the FIGO 2018 classification incorporates nodal involvement and allows the use of imaging and pathological findings to assess disease extent. In the present study, disease stage was retrospectively reassessed according to the FIGO 2018 classification, which may have contributed to the observed association between CEA levels and disease stage. Nevertheless, CEA remained independently associated with survival after adjustment for FIGO stage and other clinical factors. Furthermore, no statistically significant interaction between continuous CEA levels and FIGO stage was identified.

To our knowledge, few studies have systematically evaluated the prognostic value of CEA. Although one study performed multivariable analyses, that study was constrained by mixed histologic subtypes and limited statistical rigor [11]. Even studies restricted to SCC had limited generalizability due to restriction to concurrent chemoradiotherapy and the small number of advanced-stage cases [12,15]. Most other studies relied on univariate analyses or heterogeneous populations and did not adequately assess the independent prognostic value of CEA [7,8,25,26]. Differences according to histologic subtype have also been reported [16,17,27–31], further contributing to the heterogeneity of previous findings.

The biological mechanisms underlying the association between circulating CEA levels and survival in cervical cancer remain unclear. CEA, encoded by the CEA-related cell adhesion molecule 5 (CEACAM5) gene, is a cell-surface glycoprotein involved in intercellular adhesion [32,33]. Experimental studies in colorectal cancer have demonstrated that membrane-associated CEA can inhibit anoikis and promote experimental metastasis [34]. In cervical SCC, CEA-related antigen expression has been observed in intravascular tumor cells and vessel walls, suggesting a possible role in tumor–vascular interactions [35]. Although tumor CEACAM5 expression has been associated with poorer survival in cervical cancer [36], its prognostic significance in cervical SCC remains to be fully established. The findings of the current study suggest that elevated circulating CEA levels reflect not only tumor burden but also biological characteristics associated with tumor aggressiveness. However, the relationship between circulating CEA levels and tumor CEACAM5 expression was not assessed in the present study, and this interpretation remains hypothesis-generating.

This study had several methodological strengths. First, we evaluated a relatively large cohort of 873 patients encompassing FIGO stages I-IV and various initial treatment modalities. Second, restriction to SCC reduced

heterogeneity related to histological subtype. Third, CEA was primarily analyzed as a continuous variable, avoiding reliance on a single dichotomization threshold. Finally, multivariable analyses accounted for relevant clinical factors, including FIGO stage, smoking history, SCC-Ag, and initial treatment, and the potential interaction between CEA and FIGO stage was formally evaluated.

Some limitations should be acknowledged. First, the retrospective, single-institution design may limit the generalizability of our findings. In addition, pretreatment serum CEA measurements were performed at the discretion of the treating physicians, and patients without available measurements were excluded. This may have introduced selection bias if the decision to measure CEA was associated with patient or disease characteristics. Second, although initial treatment was included in multivariable models, residual confounding related to treatment selection, disease characteristics, and other unmeasured factors cannot be excluded. Third, FIGO stage was retrospectively reassessed using available clinical, radiological, and pathological information. Because postoperative pathological findings were available primarily for surgically treated patients, the information available for staging may have differed according to treatment modality. Fourth, tumor CEACAM5 expression was not evaluated, preventing the direct investigation of the biological relationship between circulating CEA and tumor characteristics. Finally, the incremental prognostic performance of CEA when added to established clinical factors was not directly evaluated, and external validation is needed.

Together, our findings support pretreatment serum CEA as a potential complementary prognostic marker in cervical SCC. Although CEA should not be used in isolation to guide treatment decisions, its assessment alongside FIGO stage and other established clinical factors may contribute to individualized risk assessment. Further studies are warranted to validate these findings and determine whether incorporating CEA into existing prognostic models improves risk stratification.

CONCLUSION

Higher pretreatment serum CEA levels were independently associated with poorer OS and PFS in patients with cervical SCC. No significant interaction between CEA and FIGO stage was observed. These findings suggest that pretreatment serum CEA complements established clinical factors in prognostic assessment; however, further external validation is required.

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Statements and Declarations

Funding

No funding was received for conducting this study.

Competing interests

The authors declare that they have no competing interests relevant to the content of this article.

Ethics approval

This study was approved by the Institutional Review Board of the Cancer Institute Hospital of the Japanese Foundation for Cancer Research (approval no. 2023-GB-079; SRB No. 1775). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent to participate

The requirement for written informed consent was waived by the Institutional Review Board because of the retrospective study design. Information about the study was made publicly available, and patients were provided an opportunity to opt out of participation.

Consent to publish

Not applicable.

Data availability

The data that support the findings of this study are not publicly available due to patient privacy considerations but are available from the corresponding author upon reasonable request, subject to institutional approval.

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FIGURE CAPTIONS

Fig. 1 Patient selection flowchart.

The final study cohort included 873 patients.

Fig. 2 Kaplan–Meier curves for overall survival and progression-free survival according to pretreatment serum CEA levels (<5.0 vs ≥5.0 ng/mL).

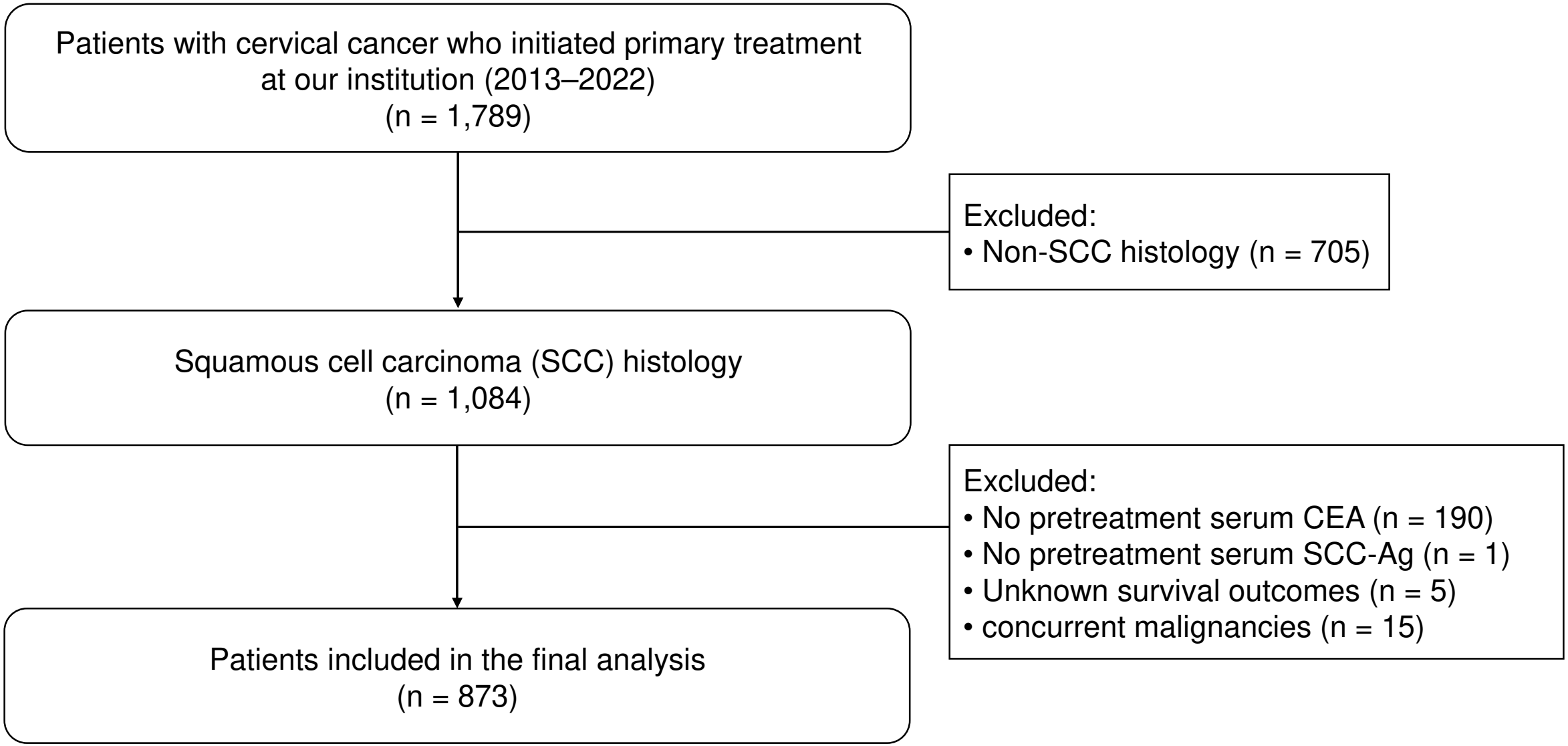
Overall survival is shown in (a) and progression-free survival in (b). Tick marks indicate censored observations. Numbers at risk are shown below each panel. Differences between groups were assessed using the log-rank test (both $p<0.001$).

CEA, carcinoembryonic antigen; OS, overall survival; PFS, progression-free survival

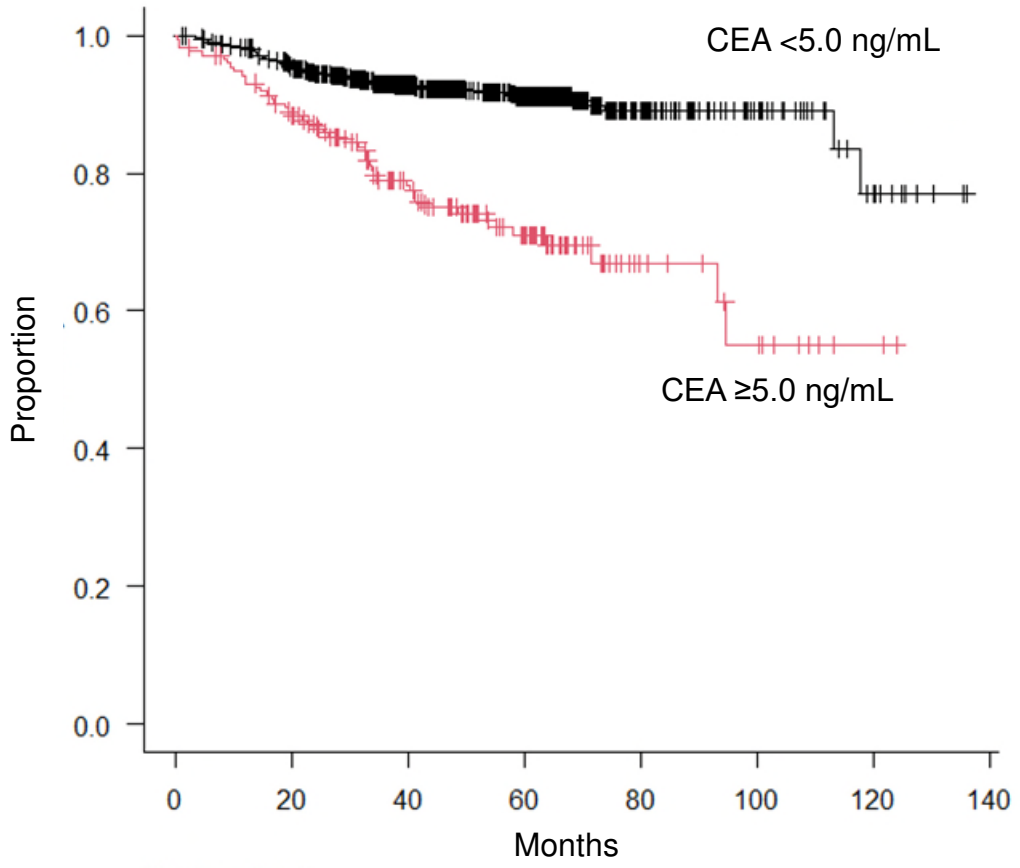
Fig. 3 Associations of pretreatment serum CEA levels with overall and progression-free survival according to FIGO stage.

Hazard ratios and 95% confidence intervals for overall survival (upper panel) and progression-free survival (lower panel) are shown for each doubling of pretreatment serum CEA levels according to FIGO stage. Squares indicate hazard ratios, and horizontal lines indicate 95% confidence intervals. *P* values for interaction were obtained using likelihood ratio tests comparing Cox models with and without an interaction term between log2-transformed CEA and FIGO stage.

CEA, carcinoembryonic antigen; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OS, overall survival; PFS, progression-free survival


Patients with cervical cancer who initiated primary treatment at our institution (2013–2022) (n = 1,789)
Excluded:
• Non-SCC histology (n = 705)
Squamous cell carcinoma (SCC) histology (n = 1,084)
Excluded:
• No pretreatment serum CEA (n = 190)
• No pretreatment serum SCC-Ag (n = 1)
• Unknown survival outcomes (n = 5)
• concurrent malignancies (n = 15)
Patients included in the final analysis (n = 873)

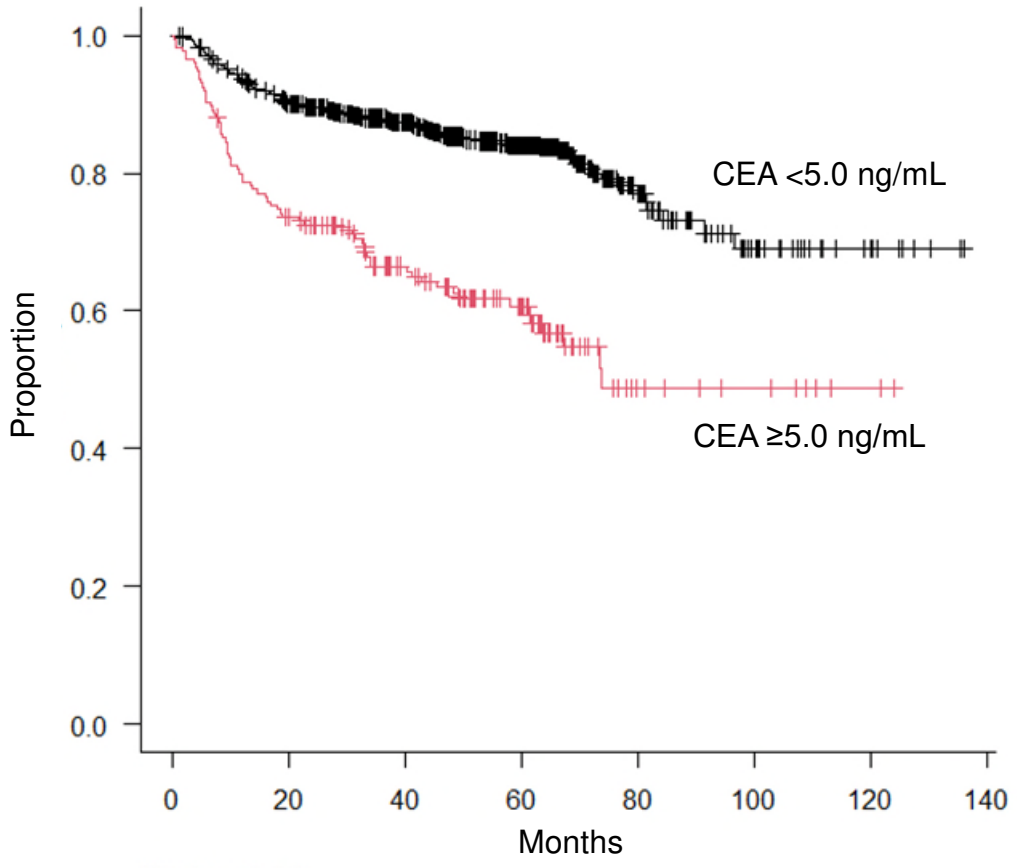
(a)



Number at risk

CEA <5.0	698	638	460	301	82	33	11	0
CEA ≥5.0	175	149	100	62	15	9	2	0

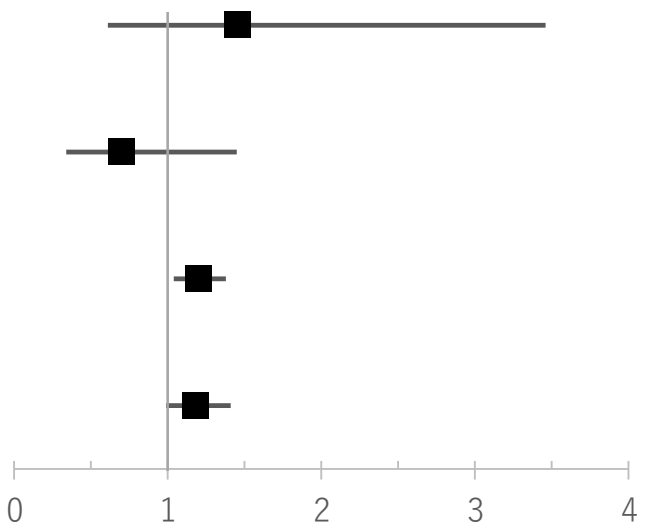
(b)



Number at risk

CEA <5.0	698	604	444	287	68	26	10	0
CEA ≥5.0	175	127	88	55	11	7	2	0

			HR for CEA per doubling [95% CI]	p value
OS	FIGO stage	I	1.46 [0.61-3.46]	0.45
		II	0.70 [0.34-1.45]	
		III	1.20 [1.04-1.38]	
		IV	1.18 [0.99-1.41]	
PFS	FIGO stage	I	1.22 [0.81-1.84]	0.73
		II	0.94 [0.63-1.40]	
		III	1.18 [1.05-1.33]	
		IV	1.14 [0.97-1.33]	



Supplementary Files

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- Table.docx
- onlineresourcesubmit.pdf