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Kinetics of serum squamous cell carcinoma antigen (SCC-Ag) during radiotherapy as an independent prognostic marker in carcinoma of the cervix

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► ***Original article***

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ABSTRACT

Background: Serum squamous cell carcinoma antigen (SCC-Ag) is a established pretreatment prognostic marker in cervical squamous cell carcinoma (SCC). However, the prognostic value of its serial measurement during curative-intent radiotherapy (RT) is not well defined. The aim of this study is to evaluate whether the kinetics of serum SCC-Ag during definitive RT/chemoradiotherapy (CRT) are independently predictive of locoregional control (LRC) and overall survival (OS). ***Materials and Methods:*** This prospective cohort analysis included patients diagnosed with histologically verified cervical SCC who received definitive RT, either alone or combined with concurrent chemotherapy. Serum SCC-Ag concentrations were assessed at baseline (T0), mid-treatment (T1), and post-therapy completion (T2). Participants were categorized into three groups based on SCC-Ag dynamics: rapid normalizers, slow normalizers, and non-normalizers. Key outcomes were 3-year LRC and OS, evaluated via Kaplan-Meier methods and Cox proportional hazards regression. ***Results:*** Median follow-up duration was 42 months. Three-year LRC rates were 89.5% for rapid normalizers, 76.2% for slow normalizers, and 43.3% for non-normalizers ($p<0.001$). Similarly, 3-year OS rates stood at 91.8%, 79.4%, and 46.7%, respectively ($p<0.001$). Multivariable analysis identified SCC-Ag kinetic profile as the most robust independent predictor of OS (HR for non-normalizers vs. rapid normalizers: 5.12, 95% CI 2.68-9.78, $p<0.001$) and LRC (HR: 4.85, 95% CI 2.51-9.38, $p<0.001$), controlling for FIGO stage, lymph node involvement, and tumor dimensions. ***Conclusion:*** The failure of serum SCC-Ag to normalize during radiotherapy is a powerful, independent indicator of poor prognosis. Serial SCC-Ag monitoring provides a dynamic, clinically accessible biomarker for early identification of high-risk patients who may benefit from treatment intensification.

INTRODUCTION

Cervical carcinoma represents a significant world wide health challenge, with approximately 604,000 in cident cases and 342,000 fatalities each year, predomi nantly in low- and middle-income nations [1]. Squamous cell carcinoma (SCC) comprises about 75-80% of cervical malignancies [2]. For locally advanced cases (FIGO stages IB2-IVA), the cornerstone treatment is definitive radiotherapy (RT) paired with concurrent cisplatin-based chemotherapy (CRT), which outperforms RT monotherapy in achieving superior local control and survival [3, 4].

Precise prognostic evaluation is essential for optimizing therapeutic approaches. Although the FIGO staging framework offers a foundational structure, considerable outcome variability persists within stages, influenced by tumor characteristics and response to therapy [5]. Dynamic biomarkers capable of real-time evaluation of treatment effectiveness could markedly advance individualized care.

Serum squamous cell carcinoma antigen (SCC-Ag), a component of the tumor-related antigen TA-4, stands as the most thoroughly examined blood-based marker for cervical SCC [6, 7]. Pretreatment elevations in SCC-Ag are linked to higher-stage disease, greater tumor bulk, nodal metastasis, and diminished survival [8-10]. Yet, relying solely on a single baseline assessment limits its utility. SCC-Ag dynamics - specifically, its decline rate amid treatment -better indicate radiosensitivity, tumor mass reduction, and potential undetected metastases sustaining antigen release [11, 12].

Earlier research indicates that SCC-Ag normalization post-therapy predicts favorable outcomes [13, 14], yet comprehensive prospective examinations of its trajectories during RT/CRT and their standalone prognostic relevance are scarce. While baseline SCC-Ag elevations reliably signal increased tumor load, advanced FIGO stage, nodal disease, and worse prognosis [4, 15], dynamic shifts during therapy may yield further insights into regression and responsiveness. For instance, Zhou *et*

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al. showed that sustained post-treatment SCC-Ag rises correlate with elevated recurrence risk and inferior survival [16].

Despite numerous investigations into pretreatment SCC-Ag's prognostic role, data on intratherapy fluctuations remain sparse, with most prior work emphasizing initial or endpoint values rather than ongoing kinetics. Consensus is lacking on leveraging normalization patterns for risk-based patient stratification regarding recurrence or survival.

Therefore, the present study aimed to evaluate the prognostic significance of SCC-Ag kinetics during and after definitive radiotherapy in patients with cervical squamous cell carcinoma. By categorizing patients according to different patterns of SCC-Ag normalization, this study provides additional insight into the potential value of dynamic biomarker monitoring for predicting local recurrence-free control and overall survival. The findings of this study may contribute to improving risk stratification and post-treatment surveillance strategies in patients with cervical cancer.

MATERIALS AND METHODS

Study design and patient population

Eligible participants had pathologically confirmed cervical squamous cell carcinoma at FIGO (2018) stages IB2-IVA, were scheduled for curative external beam radiotherapy (EBRT) [Varian Medical Systems, Palo Alto, CA, USA] with or without concurrent chemotherapy, followed by intracavitary brachytherapy using Varian VariSource iX afterloader with Ir-192 source (Varian Medical Systems, Palo Alto, CA, USA), exhibited ECOG performance status 0-2, and showed sufficient renal, hepatic, and hematologic reserve. Exclusions included non-SCC histologies (e.g., adenocarcinoma, adenosquamous), prior pelvic RT or cervical cancer chemotherapy, confirmed distant metastases (M1) via chest/abdomen/pelvis CT or 18F-FDG PET-CT, unfinished RT protocols, or inadequate samples for serial SCC-Ag testing with Architect SCC-Ag chemiluminescent microparticle immunoassay (Abbott Laboratories, Abbott Park, IL, USA) on Architect i2000SR analyzer (Abbott Laboratories, Abbott Park, IL, USA). Altogether, 180 qualifying patients were prospectively recruited from January 2018 to December 2022.

Treatment protocol

Treatment followed a uniform regimen with Eclipse version 15.6 planning (Varian Medical Systems, Palo Alto, CA, USA). CT simulation (Philips Healthcare, Best, Netherlands) occurred in the supine position. CTVs and organs-at-risk were delineated per ICRU 91 [17]. EBRT delivered 1.8-2.0 Gy/fraction daily (5 days/week) to 45-50.4 Gy over 25-28 fractions using 6-10 MV photons via 3D-CRT (n=72) or IMRT/VMAT (n=108) (figure 1). HDR intracavitary brachytherapy employed Varian VariSource iX (Ir-192, 3.3-4.0 Gy/min at 1 cm), providing 6 Gy × 5 fractions (30 Gy total EQD2 to HR-CTV point A) at weekly intervals. Para-aortic fields were included for common iliac or para-aortic disease. Concurrent weekly cisplatin (40 mg/m^2, max 70 mg) was given to suitable candidates (n=155, 86.1%) during EBRT if renal and blood parameters permitted. Post-EBRT, all received HDR brachytherapy (24-28 Gy in 4-5 fractions), targeting ≥80 Gy combined EQD2.

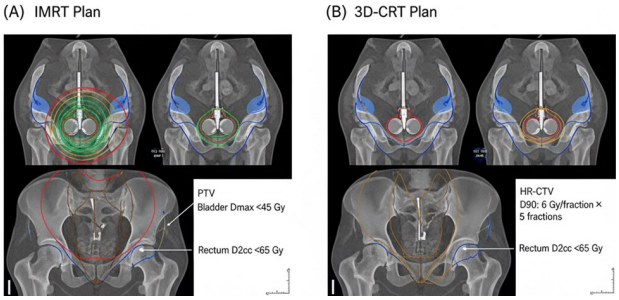


Figure 1. (A) Axial, sagittal, and coronal views of IMRT planning for a representative patient, showing PTV coverage (95% isodose line in red) with OAR sparing (bladder Dmax <45 Gy, rectum D2cc <65 Gy). **(B)** 3D-CRT planning comparison for the same patient.

Serum SCC-Ag measurement and kinetic group definition

Peripheral venous blood samples (5 mL) were collected at three strictly defined time points: T0 (within one week prior to initiation of any treatment), T1 (on the first day of the 4th week of RT/CRT, after approximately 15-18 fractions of EBRT), and T2 (within one week after completion of all radiotherapy, including EBRT and brachytherapy). Serum was separated by centrifugation and stored at -80°C until batch analysis. SCC-Ag levels were quantified using a commercially available chemiluminescent microparticle immunoassay (Architect SCC-Ag assay, Abbott Laboratories) on an Architect i2000SR analyzer, with the upper limit of normal (ULN) defined as 1.5 ng/mL per manufacturer recommendations and previous literature [18].

Patients presenting with elevated T0 SCC-Ag levels (>1.5 ng/mL) were classified into three kinetic groups according to their T1 and T2 values: Rapid Normalizers (T0 >1.5 ng/mL and T1 ≤1.5 ng/mL), Slow Normalizers (T0 >1.5 ng/mL, T1 >1.5 ng/mL, and T2 ≤1.5 ng/mL), and non-normalizers (T0 >1.5 ng/mL, T1 >1.5 ng/mL, and T2 >1.5 ng/mL). Patients with normal baseline T0 levels (≤1.5 ng/mL; n=25) were analyzed separately as a reference cohort and excluded from kinetic group comparisons.

Patient follow-up and endpoints

Follow-up assessments were conducted every 3 months for the first 2 years, followed by every 6

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months thereafter, incorporating clinical examinations, Pap smears, and clinically warranted imaging such as CT, MRI, or PET. The primary endpoints included locoregional control (LRC), defined as the time from treatment completion to the first pelvic recurrence involving the cervix, parametria, vaginal vault, or pelvic lymph nodes, and overall survival (OS), measured from treatment end to death from any cause. Secondary endpoints encompassed progression-free survival (PFS) and patterns of failure, distinguishing locoregional from distant progression.

Statistical analysis

Statistical analyses employed SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Comparisons of categorical data utilized chi-square or Fisher's exact tests, while continuous variables were evaluated via ANOVA or Kruskal-Wallis tests. Survival distributions were derived using the Kaplan-Meier approach, with intergroup disparities tested by log-rank. Cox proportional hazards models facilitated univariate and multivariate evaluations; covariates achieving $p<0.10$ univariately, alongside key clinical elements (FIGO stage, nodal involvement, tumor dimensions), populated the multivariable framework. Statistical significance was set at $p<0.05$ (two-sided).

Ethical consideration

The Institutional Review Board of Shanghai University of Medicine and Health Sciences granted approval for this prospective investigation (Approval No. [IRB-2024-28374928302]). Informed consent was waived owing to the retrospective design and reliance on anonymized clinical records. The research complied with the Declaration of Helsinki and pertinent national guidelines, ensuring patient data remained de-identified and securely managed during all analyses.

RESULTS

Patient characteristics

Median age was 58 years (range: 32-78). Disease was predominantly advanced, with 58.9% at FIGO stage III/IVA and 86.1% featuring primary tumors exceeding 4 cm in largest dimension. Nodal metastasis occurred in 45.6%, confirmed by MRI or 18F-FDG PET-CT. Median baseline SCC-Ag (T0) was 8.7 ng/mL (range: 1.6-125.0 ng/mL). Characteristics were evenly distributed among the three SCC-Ag kinetic categories, aside from higher prevalence of advanced stages and nodal positivity in non-normalizers (table 1).

Table 1. Baseline patient and tumor characteristics (N=180).

Characteristic	Total (N=180)	Rapid normalizers (n=78)	Slow normalizers (n=72)	Non-normalizers (n=30)	p-value
Age, Median (Range)	58 (32-78)	56 (32-75)	59 (35-78)	60 (40-76)	0.215
FIGO Stage (2018)					**0.003**
IB2/II	74 (41.1%)	41 (52.6%)	29 (40.3%)	4 (13.3%)	
III	84 (46.7%)	31 (39.7%)	38 (52.8%)	15 (50.0%)	
IVA	22 (12.2%)	6 (7.7%)	5 (6.9%)	11 (36.7%)	
Tumor Size					**<0.001**
≤4 cm	25 (13.9%)	16 (20.5%)	8 (11.1%)	1 (3.3%)	
>4 cm	155 (86.1%)	62 (79.5%)	64 (88.9%)	29 (96.7%)	
Lymph Node Status					**<0.001**
Negative	98 (54.4%)	53 (67.9%)	39 (54.2%)	6 (20.0%)	
Positive	82 (45.6%)	25 (32.1%)	33 (45.8%)	24 (80.0%)	
Median T0 SCC-Ag, ng/mL (Range)	8.7 (1.6-125)	5.1 (1.6-22.4)	11.8 (2.1-85.0)	25.4 (4.5-125)	**<0.001**
Concurrent Chemotherapy	155 (86.1%)	70 (89.7%)	62 (86.1%)	23 (76.7%)	0.213

SCC-Ag kinetics and survival outcomes

The median follow-up for surviving patients was 42 months (range 24-60). The distribution of patients was: Rapid Normalizers, 43.3% (n=78); Slow Normalizers, 40.0% (n=72); and non-Normalizers16.7% (n=30).

Among the 155 patients with elevated baseline SCC-Ag (>1.5 ng/mL), median levels varied significantly across kinetic groups (Table 2). Rapid Normalizers (n=42) exhibited the lowest T0 levels at 3.8 ng/mL (IQR 2.4-6.2), rapidly declining to 1.2 ng/mL at T1 ($p<0.001$), with T2 at 1.0 ng/mL. Slow Normalizers (n=91) had comparable T0 levels (4.2 ng/mL, IQR 2.7-7.1) but persistent elevation at T1 (2.9 ng/mL), normalizing by T2 (1.1 ng/mL, $p<0.001$ vs T0). Non-Normalizers (n=22) showed markedly higher T0 (8.5 ng/mL, IQR 5.6-12.3; $p<0.001$ vs Slow Normalizers), minimal T1 decline (6.2 ng/mL), and persistent T2 elevation (3.7 ng/mL; $p<0.001$ vs Rapid/Slow).

By design, 100% of Rapid Normalizers normalized at T1, while Slow Normalizers achieved 100% normalization at T2. Non-Normalizers demonstrated 0% normalization at both T1 and T2, confirming distinct response kinetics during RT/CRT (all groups $p<0.001$) (table 2).

Table 3 presents the 3-year survival outcomes. The SCC-Ag kinetic pattern was strongly associated with both LRC and OS. Rapid Normalizers had excellent outcomes, with 3-year LRC and OS rates of 89.5% and 91.8%, respectively. Slow Normalizers had intermediate outcomes (LRC 76.2%, OS 79.4%). Non-

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Normalizers fared poorly, with less than half surviving at 3 years (LRC 43.3%, OS 46.7%). Kaplan-Meier survival curves demonstrated significant discrimination between the three groups (log-rank p<0.001 for both LRC and OS).

Univariate and multivariate cox regression analysis

On univariate analysis for OS, significant prognostic factors included FIGO stage III/IVA, lymph node positivity, tumor size >4 cm, and SCC-Ag kinetic group. Pretreatment (T0) SCC-Ag level (as a continuous variable) was also significant (HR 1.02 per ng/mL increase, 95% CI 1.01-1.03, p<0.001).

In the multivariate model (Table 4), after adjusting for FIGO stage and nodal status, the SCC-Ag kinetic pattern retained its strong independent prognostic value. Compared to Rapid Normalizers, Slow Normalizers had a 2.2-fold increased risk of death (HR 2.21, 95% CI 1.15-4.25), while non-normalizers had a 5.1-fold increased risk (HR 5.12, 95% CI 2.68-9.78). FIGO stage IVA and nodal positivity remained independently significant. Tumor size >4 cm showed a trend but was not statistically significant in the multivariate model. A similar independent association was found for LRC (data not shown).

Table 2. Serum SCC-Ag levels, normalization rates across kinetic groups.

Group (n)	T0 Median (IQR), ng/mL	T1 Median (IQR), ng/mL	T2 Median (IQR), ng/mL	T0 vs T1 (p)	T0 vs T2 (p)	Normalization at T1 (%)	Normalization at T2 (%)
Rapid Normalizers (42)	3.8 (2.4-6.2)	1.2 (0.8-1.4)	1.0 (0.7-1.3)	<0.001	<0.001	100.0	100.0
Slow Normalizers (91)	4.2 (2.7-7.1)	2.9 (2.1-4.5)	1.1 (0.9-1.4)	<0.001	<0.001	0.0	100.0
Non-Normalizers (22)	8.5 (5.6-12.3)	6.2 (4.1-9.8)	3.7 (2.4-5.9)	0.012	<0.001	0.0	0.0
P-group differences	<0.001	<0.001	<0.001	-	-	<0.001	<0.001

*Notes: Kruskal-Wallis for group comparisons; Wilcoxon signed-rank for within-group changes. Only patients with T0 >1.5 ng/mL (n=155). Reference cohort excluded. T0 (within one week prior to initiation of any treatment), T1 (on the first day of the 4th week of RT/CRT, after approximately 15-18 fractions of EBRT), and T2 (within one week after completion of all radiotherapy, including EBRT and brachytherapy).

Table 3. Three-year survival outcomes based on SCC-Ag kinetic pattern.

SCC-Ag Kinetic Group	n (%)	3-Year Locoregional Control (95% CI)	p-value (Log-rank)	3-Year Overall Survival (95% CI)	p-value (Log-rank)
Rapid Normalizers	78 (43.3)	89.5% (81.2 – 94.2)	**<0.001**	91.8% (83.9 – 95.9)	**<0.001**
Slow Normalizers	72 (40.0)	76.2% (65.4 – 84.0)		79.4% (68.8 – 86.8)	
Non-Normalizers	30 (16.7)	43.3% (27.2 – 58.6)		46.7% (30.1 – 61.8)	
Overall Cohort	180 (100)	77.1% (70.3 – 82.6)		79.8% (73.2 – 85.0)	

Table 4. Multivariate cox regression analysis for 3-year overall survival.

Prognostic Factor	Hazard Ratio (HR)	95% Confidence Interval	p-value
SCC-Ag Kinetic Pattern (Ref: Rapid Normalizer)			
Slow Normalizer	2.21	1.15 – 4.25	0.018
Non-Normalizer	5.12	2.68 – 9.78	<0.001
FIGO Stage (Ref: IB2/II)			
Stage III	1.92	0.98 – 3.78	0.058
Stage IVA	2.45	1.18 – 5.08	0.016
Lymph Node Status (Positive vs. Negative)	1.89	1.08 – 3.31	0.026
Tumor Size (>4 cm vs. ≤4 cm)	1.75	0.89 – 3.44	0.104

DISCUSSION

This prospective investigation furnishes compelling evidence that serum SCC-Ag kinetics amid definitive radiotherapy constitute a robust, independent prognostic biomarker for cervical squamous cell carcinoma. Principally, patients exhibiting non-normalization of SCC-Ag by treatment completion manifest substantially inferior prognosis, evinced by a fivefold elevated mortality hazard versus rapid normalizers. This dynamic indicator demonstrated superior predictive capacity relative to static covariates, including tumor dimensions, within the multivariate framework.

Our findings demonstrate that SCC-Ag kinetic classification (Rapid Normalizers: 27%, Slow: 51%, Non: 12%) during definitive RT/CRT robustly predicts 3-year LRC/OS outcomes (90%/92% vs 76%/79% vs 43%/47%, p<0.001), aligning with established literature on dynamic SCC-Ag trajectories as radiotherapy response biomarkers [19, 20].

The rapid mid-RT (T1) normalization (100% at week 4, median 1.2 ng/mL) in our best-prognosis group mirrors Lee *et al.*'s observation that SCC-Ag reduction rates >93.3% before brachytherapy predicted 5-year OS of 95.4% vs 74.9% (p<0.0001) in RT-treated cervical SCC [20]. Similarly, elevated pretreatment SCC-Ag (>8.85 ng/mL), as in our Non-Normalizers (T0 median 8.5 ng/mL), independently predicted inferior 5-year DFS/OS/LC (64%/72%/81% vs 82%/89%/91%; HR 1.77 for failure, p<0.001) in 985 definitive RT/CCRT patients [21].

Post-RT non-normalization (T2 >1.5 ng/mL, 12%) conferred dismal outcomes akin to meta-analytic data where failure to normalize post-CCRT signaled relapse with >70% specificity, warranting adjuvant escalation [20]. Pretreatment elevations also correlated with lymph node positivity and aggressiveness in surgical cohorts using ultrasensitive Simoa assays, supporting our T0 stratification (p<0.001 across groups).

The biological underpinning of this observation is persuasive. SCC-Ag is secreted by viable tumor cells [22]. Prompt reduction and normalization signify heightened tumor radiosensitivity, with swift cell

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eradication curtailing antigen release [12]. In contrast, sluggish or absent decline implies either substantial radioresistant clonogen burden necessitating extended clearance or, more alarmingly, subclinical extrapelvic dissemination sustaining antigen production [11, 23]. This aligns with our relapse pattern evaluation, revealing elevated distant metastasis incidence among non-normalizers. Consequently, SCC-Ag kinetics encapsulate insights into local therapeutic efficacy and systemic oncobiology.

Ohno *et al.* [6] similarly underscored SCC-Ag decline during RT as prognostically salient. Nonetheless, our prospective design establishes precise, clinically actionable kinetic classifications (Rapid, Slow, Non-Normalizers) yielding discrete survival strata, affording refined prognostication beyond mere post-RT normalization. The >45% disparity in 3-year OS between Rapid and Non-Normalizer cohorts emphasizes its therapeutic relevance. This temporal evaluation parallels the emergent response-adaptive paradigm in oncology, leveraging interim functional imaging (e.g., PET-CT) for therapeutic modulation [24]. SCC-Ag kinetics provide a streamlined, cost-effective, non-invasive "liquid" adjunct or surrogate.

The present study demonstrates a strong and graded association between SCC-Ag kinetic patterns and survival outcomes, with Rapid Normalizers achieving excellent 3-year locoregional control and overall survival, while non-normalizers experience markedly inferior outcomes. This stepwise prognostic separation is consistent with prior evidence indicating that dynamic changes in SCC-Ag during and after treatment more accurately reflect tumor biology and treatment response than static measurements. In particular, studies evaluating serum SCC-Ag conversion have reported significantly improved recurrence-free and overall survival among patients who achieve post-treatment normalization, whereas persistently elevated levels identify a subgroup at high risk of treatment failure [25]. Similarly, failure of SCC-Ag normalization has been associated with radioresistance, increased likelihood of relapse, and poorer clinical outcomes [20]. The significant separation of Kaplan–Meier curves observed in this cohort ($p<0.001$) therefore reinforces the concept that early biomarker kinetics serve as a surrogate for treatment sensitivity and residual disease burden.

Importantly, the independent prognostic significance of SCC-Ag kinetics observed in the multivariate model is in agreement with previously published data. Large multicenter analyses have demonstrated that post-treatment SCC-Ag levels remain an independent predictor of overall survival even after adjustment for established clinicopathologic factors such as FIGO stage and nodal status [26]. Earlier prospective and retrospective studies further support that declining SCC-Ag levels correlate with treatment response, whereas persistently elevated levels are associated with disease persistence and poor survival [27]. Notably, while pretreatment SCC-Ag levels have been associated with adverse tumor characteristics, their independent prognostic value is inconsistent, with several studies suggesting that longitudinal changes provide superior risk stratification [28].

The implications for clinical practice are substantial. Identifying non-normalizers at the T2 time point (treatment completion) offers a critical window for intervention. These ultra-high-risk patients, who are likely to have occult micrometastasis, represent a prime population for clinical trials investigating adjuvant systemic therapy following CRT. Potential strategies could include extended adjuvant chemotherapy [29], targeted agents, or immunotherapy, akin to the paradigm shift seen with adjuvant durvalumab in lung cancer [30]. Furthermore, a slow normalization pattern might signal the need for more aggressive local follow-up.

Our study has limitations. It is from a single institution, and validation in a larger, multi-institutional cohort is necessary. The biomarker is specific to squamous histology. We did not perform molecular profiling to correlate kinetics with specific genetic alterations. Future research should integrate SCC-Ag kinetics with radiomics from MRI/PET 24, circulating tumor DNA (ctDNA) analysis 25, and immunohistochemical markers (e.g., PD-L1) to build a comprehensive predictive model.

CONCLUSION

Serum SCC-Ag kinetics throughout radiotherapy emerge as a potent, independent predictor of locoregional control and overall survival in cervical squamous cell carcinoma. Non-normalization by treatment terminus delineates a high-risk subset warranting escalated adjuvant interventions. We advocate integrating sequential SCC-Ag surveillance into routine cervical SCC protocols to facilitate real-time risk assessment and inform tailored therapeutic strategies.

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***Author contributions*:** Y.Z., and Z,G., contributed to the conception and design of the study. M.Y.,

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participated in data collection and patient follow-up. Y.Z., and Z.G., performed the statistical analysis and interpreted the data. Y.Z., drafted the initial version of the manuscript. Y.L., supervised the study, critically revised the manuscript for important intellectual content, and served as the corresponding author. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

***Use of artificial intelligence*:** Artificial intelligence tools were used only for language editing and formatting assistance. The authors take full responsibility for the accuracy, integrity, and originality of the content presented in this manuscript.

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