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RESEARCH PAPER

Serum conversion pattern of SCC-Ag levels between pre- and post-chemoradiotherapy predicts recurrence and metastasis in cervical cancer: a multi-institutional analysis

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Abstract

The value of squamous-cell carcinoma antigen (SCC-Ag) as a tumor marker for cervical cancer is controversial because it is not elevated (> 2 ng/mL) in a quarter of patients at diagnosis. Two hundred ninety one IB-IVA cervical squamous cell-carcinoma patients who underwent definitive chemoradiotherapy (CRT) were included in four tertiary institutions. Serum conversion pattern between pre- and post-treatment SCC-Ag levels was categorized into the following three arms: (1) Consistent Seronegative arm (both ≤ 2 ng/mL); (2) Negative Conversion arm (from > 2 ng/mL to ≤ 2 ng/mL); and (3) Consistent Seropositive arm (both > 2 ng/mL). Median follow-up time was 40.3 months. For Consistent Seronegative ($N = 67$), Negative Conversion ($N = 165$), and Consistent Seropositive ($N = 59$) arms, the 3-year recurrence-free survival (RFS) rates were 79.4%, 62.0%, and 48.4% ($P < 0.001$) and the 3-year overall survival (OS) rates were 86.3%, 80.6%, and 58.7% ($P = 0.001$), respectively. The serum conversion pattern of SCC-Ag between pre- and post-treatment was the most significant and potent prognostic factor of RFS ($P = 0.001$) and OS ($P = 0.007$) on the multivariate analysis. Simply checking whether SCC-Ag level is above or below 2 ng/mL before and after definitive CRT can provide clinicians with a simple rule-of-thumb for prediction of disease outcome in cervical cancer patients.

Keywords Cervix cancer · Recurrence · Survival · Metastasis · Squamous-cell carcinoma antigen

Abbreviations

SCC-Ag	Squamous-cell carcinoma antigen
CRT	Chemoradiotherapy
RFS	Recurrence-free survival
OS	Overall survival
CT	Computed tomography
MRI	Magnetic resonance imaging
LRFS	Locoregional recurrence-free survival
ICR	Intracavitary radiation

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Introduction

Approximately 14,000 women are diagnosed with cervical cancer in the United States each year and only two thirds of them remain alive at 5 years. At diagnosis, 45%, 35%, and 15% of them are staged localized, regional, and distant, respectively [1]. However, patients of the same stage do not always result in the same outcome. This makes oncologists worldwide persevere to treat with the best personalized approach for each patient. Tumor marker is a way to get a hint on the characteristics of a specific disease. It can be used not only for screening, diagnosis, and monitoring of disease but may also have prognostic or predictive roles. Tumor markers not only can predict the outcome of a disease itself without treatment but also can identify patients who will benefit from certain treatments.

For squamous-cell carcinoma of the cervix, squamous-cell carcinoma antigen (SCC-Ag) is the most actively explored candidate, which was originally purified from human cervical squamous-cell carcinoma specimens [2]. There are a few aspects to consider before applying the results of tumor marker research to clinical practice [3]. First, the analytic validity in case of SCC-Ag testing is well-established with accurate, reliable, and reproducible results. In addition, the clinical validity of SCC-Ag is supported by a wealth of studies reporting association between elevated SCC-Ag and outcomes such as recurrence-free survival or overall survival [4]. However, the clinical utility, or the reliability of SCC-Ag results used in making clinical decisions for patient management, is another problem. At least a quarter of cervical cancer patients have SCC-Ag levels within normal range at diagnosis [5, 6]. Moreover, the purportedly significant cut-off levels of SCC-Ag range widely in the literature, with pre-treatment cut-offs of 1.1–40 ng/mL and post-treatment cut-offs of 0.9–3.5 ng/mL. These wide range further complicate the clinical use of SCC-Ag in the real practice.

To overcome the dilemma of arbitrary cut-off levels owing to the inconsistency of patient cohorts and treatments among previous studies, we focused on the serum conversion pattern between baseline and post-treatment SCC-Ag in locally advanced cervical cancer treated with definitive chemoradiotherapy (CRT). To the best of our knowledge, this study is the first to apply the concept of serum conversion in SCC-Ag levels. We defined the different obtainable patterns of serum conversion and investigated the impact of serum conversion pattern of SCC-Ag on outcome by demonstrating its association with recurrence and survival in the multi-institutional data.

Methods and materials

Patients and work-up

This study was conducted in accordance with the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria [7]. Patients with biopsy-proven, stage IB2-IVA (by the American Joint Committee on Cancer staging system, 8th edition) squamous-cell carcinoma of the cervix who received definitive concurrent CRT between 2015 and 2019 in four tertiary university hospitals were analyzed. Inclusion criteria were as follows: (1) pathological confirmation of squamous-cell carcinoma, (2) primarily diagnosed as stage IB2-IVA uterine cervical cancer, (3) completed CRT of definitive aim, and (4) acquisition of SCC-Ag levels before initiation of radiotherapy as well as after completion of planned treatment. Patients with distant or extrapelvic disease (including para-aortic nodal metastases) at diagnosis were excluded.

Initial work-ups comprised patient history, pelvic examination, colposcopy, serum chemistry, and complete blood-cell count. Pre- and post-treatment SCC-Ag levels from serum samples were obtained. Serum SCC-Ag levels were measured using an immunoradiometric assay (Riakey SCC IRMA Tube, Shinjin Medics Inc., Goyang, Republic of Korea) with one-step non-competitive reaction. This kit detects both SCCA1 and SCCA2 isoforms of the SCC-Ag. The analytical sensitivity of this assay (calculated as 2 standard deviations above the zero standard) is 0.03 ng/mL. The upper limit of normal is 2.0 ng/mL.

Imaging study included chest computed tomography (CT), magnetic resonance imaging (MRI) of the pelvis, and positron emission tomography-CT. Staging was performed according to the American Joint Committee on Cancer staging system, 8th edition. The institutional review board (IRB) approved all procedures of this study (No. KC19RIMI0369).

Treatment and follow-up

All patients received pelvic external-beam radiotherapy based on CT simulation. Pelvic radiotherapy of 45–50.4 Gy (median, 46.8 Gy) was planned to cover target volumes including cervical gross tumor and internal, external, and presacral nodal areas contoured according to the Radiation Therapy Oncology Group guidelines [8]. Intracavitary radiation (ICR) was delivered to patients with patent cervical canals amenable to tandem insertion. High-dose rate ICR of median 30 Gy (range, 12–40 Gy) prescribed to point A in median 6 fractions (range, 3–8 fractions) was delivered following CRT. Boost to the

grossly involved lymph node was given up to median 59.4 Gy (range, 55.8–70.4 Gy). Concurrent 6 cycles of weekly cisplatin (30–40 mg/m^2) or intravenous cisplatin (75 mg/m^2/day) on day 1 and 5-fluorouracil (500 mg/m^2/day) on days 2–5 during the first and fifth week was administered with radiotherapy.

Post-treatment serum SCC-Ag levels were measured 1–2 months after completion of radiotherapy. Patients were followed up every 3 months for 2 years, every 6 months for the next 3 years, and every year thereafter. Follow-up studies after completion of CRT included clinical and pelvic examination, colposcopy, PAP smear, abdomino-pelvic CT, pelvic MRI, and biopsy if necessary.

Definition of serum conversion patterns of SCC-Ag

The normal SCC-Ag level was 0–2.0 ng/mL. Thus, serum SCC-Ag level > 2 ng/mL was defined as seropositive. A serum SCC-Ag level ≤ 2 ng/mL was defined as seronegative. Negative conversion was defined as pre-treatment SCC-Ag level > 2 ng/mL reduced to post-treatment SCC-Ag level ≤ 2 ng/mL. Positive conversion was defined as pre-treatment SCC-Ag level ≤ 2 ng/mL increased to post-treatment SCC-Ag level > 2 ng/mL.

Statistical analysis

Survival time was calculated from the date of initiation of radiotherapy. Overall survival (OS) was defined as the time interval from the first day of radiotherapy to the date of death from any cause. Recurrence-free survival (RFS) was defined as the time interval from the first day of radiotherapy to the date of any recurrence or death. Locoregional recurrence-free survival (LRFS) was defined as the time interval from the first day of radiotherapy to the date of first intrapelvic recurrence or death. Distant recurrence-free survival (DRFS) was defined as the time interval from the first day of radiotherapy to the date of extrapelvic recurrence or death. Recurrence and survival rates were estimated with the Kaplan–Meier method and compared using the log-rank test. Prognostic factors for recurrence and survival were evaluated with the Cox proportional hazards regression model in the multivariate analysis. Independent t-test was used to compare continuous variables and $\chi 2$ test was used to compare categorical variables. A P-value of < 0.05 was considered statistically significant. Statistical analyses were performed using the IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA) and the Microsoft Excel (Microsoft Corp., Redmond, WA, USA).

Results

A total of 291 patients who satisfied the inclusion criteria were analyzed. The median pre-treatment SCC-Ag level was 6.4 ng/mL (range, 0.1–130.5 ng/mL) at diagnosis. The median post-treatment SCC-Ag level was 1.1 ng/mL (range, 0.1–87.4 ng/mL). Pre-treatment SCC-Ag levels were obtained at diagnosis before initiation of CRT. Post-treatment SCC-Ag levels were acquired at a median of 5.5 weeks (range, 4–8 weeks) after completion of planned treatment.

The serum conversion pattern between pre- and post-treatment SCC-Ag levels of the patients included in this study was categorized into the following three arms: (1) the Consistent Seronegative arm including patients who had been seronegative before treatment and remained seronegative after treatment; (2) the Negative Conversion arm including patients who had been seropositive before treatment and became seronegative after treatment; and (3) the Consistent Seropositive arm including patients who had been seropositive before treatment and remained seropositive after treatment. There was no positive conversion observed in our cohort.

At baseline, 224 (77%) were seropositive. 165 patients underwent negative conversion, thus leaving 232 (79.7%) patients seronegative after treatment. There were 23% ($N = 67$), 56.7% ($N = 165$), and 20.3% ($N = 59$) patients included in the Consistent Seronegative, Negative Conversion, and Consistent Seropositive arms, respectively (Fig. 1). Two thirds of the patients (66.7%) were stage IIB (Table 1). Approximately two thirds (67.4%) had large tumors sized ≥ 4 cm. When the patient and treatment characteristics are compared among the three arms, the Consistent Seropositive arm tended to include larger tumors ($P = 0.002$) and higher stage ($P = 0.057$) than the Consistent Seronegative and Negative Conversion arms (Table 2).

Median follow-up time was 40.3 months (range, 5.8–70.8 months). At the time of analysis, there were total 61 recurrences, including 35 locoregional, 17 paraaortic, and 37 distant. The median SCC-Ag level at tumor recurrence was 3.3 ng/mL (range, 0.5–115 ng/mL). The 3-year LRFS ($P = 0.003$), DRFS ($P = 0.002$), RFS ($P < 0.001$), and OS ($P = 0.001$) rates were all significantly different among the three serum conversion arms (Fig. 2). The 3-year RFS rates were significantly higher in the order of Consistent Seronegative ($N = 67$), Negative Conversion ($N = 165$), and Consistent Seropositive ($N = 59$) arms (79.4%, 62.0%, and 48.4%; $P < 0.001$). The 3-year OS rates were significantly higher in the order of Consistent Seronegative ($N = 67$), Negative Conversion ($N = 165$), and Consistent Seropositive ($N = 59$) arms (86.3%, 80.6%, and 58.7%; $P = 0.001$).

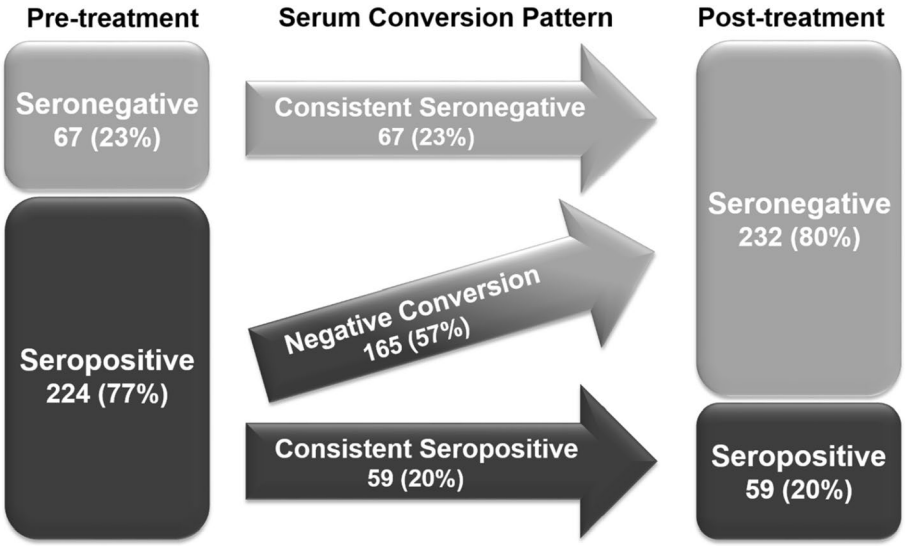

Fig. 1 Definition of three arms according to the serum conversion pattern of squamous-cell cancer antigen (SCC-Ag) between pre-treatment and post-treatment levels

Table 1 Patient and treatment characteristics ($N=291$)

	Total $N=291$ (%)	Consistent Seronegative $N=67$ (%)	Negative Conversion $N=165$ (%)	Consistent Seropositive $N=59$ (%)	*P*
Age, year					0.160
≤60	165 (56.7)	39 (13.4)	99 (34.0)	27 (9.3)	
>60	126 (43.3)	28 (9.6)	66 (22.7)	32 (11)	
Stage					0.057
IB	30 (10.3)	14 (4.8)	11 (3.8)	5 (1.7)	
IIA	18 (6.2)	5 (1.7)	11 (3.8)	2 (0.7)	
IIB	194 (66.7)	42 (14.4)	115 (39.5)	37 (12.7)	
IIIA	9 (3.1)	2 (0.7)	6 (2.1)	1 (0.3)	
IIIB	23 (7.9)	2 (0.7)	13 (4.5)	8 (2.7)	
IVA	17 (5.8)	2 (0.7)	9 (3.1)	6 (2.1)	
Tumor size, cm					
<4	95 (32.6)	33 (11.3)	50 (17.2)	12 (4.1)	0.002
≥4	196 (67.4)	34 (11.7)	115 (39.5)	47 (16.2)	
Pelvic nodal involvement					0.070
Yes	153 (52.6)	27 (9.3)	92 (31.6)	34 (11.7)	
No	138 (47.4)	40 (13.7)	73 (25.1)	25 (8.6)	
Concurrent chemotherapeutic regimen					0.420
Weekly Cisplatin	230 (79.0)	51 (17.5)	133 (45.7)	46 (15.8)	
Monthly Cisplatin and Fluorouracil	61 (21.0)	16 (5.5)	32 (10.9)	13 (4.6)	

For all patients, the 3-year LRRFS, DRFS, and RFS rates were 71.8%, 72.6%, and 68.8%, respectively. Fifty-nine patients had expired at the time of analysis and the 3-year OS rate was 78.1%.

Factors associated with RFS were serum conversion pattern of SCC-Ag ($P<0.001$) and tumor size ($P=0.006$) on the multivariate analysis. Serum conversion pattern of SCC-Ag was most significantly related to RFS, with the Negative conversion arm (hazard ratio [HR] of 1.74 and 95% confidence interval [CI] 1.13–3.28) and the Consistent Seropositive arm (HR of 3.74 and 95% CI 1.83–7.63), as compared to the Consistent Seronegative arm. Likewise, factors associated with OS were serum conversion pattern of SCC-Ag and tumor size in both the univariate and multivariate analyses. Serum conversion pattern of SCC-Ag had the strongest association with OS ($P=0.007$), of which the Consistent Seropositive arm had a HR of 3.43 (95% CI 1.46–8.08) compared to the Consistent Seronegative arm.

Table 2 Factors associated with recurrence-free survival and overall survival

	Recurrence-free survival				Overallsurvival			
	Univariate		Multivariate		Univariate		Multivariate	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, year								
≤60	1.00 (reference)	0.058	1.00 (reference)	0.078	1.00 (reference)	0.595	1.00 (reference)	0.580
>60	0.66 (0.43–1.01)		0.67 (0.42–1.05)		0.87 (0.51–1.47)		0.85 (0.48–1.50)	
Stage	1.00 (reference)	0.065	1.00 (reference)	0.365	1.00 (reference)	0.203	1.00 (reference)	0.683
I	1.35 (0.62–.95)		1.21 (0.55–2.68)		0.85 (0.38–1.90)		0.80 (0.35–1.85)	
II	2.29 (0.92–5.68)		1.66 (0.66–4.20)		1.37 (0.51–3.68)		1.02 (0.67–2.84)	
III	3.18 (1.11–9.10)		2.16 (1.17–3.66)		2.09 (0.66–6.62)		1.39 (0.42–4.57)	
IVA								
Tumor size, cm								
<4	1.00 (reference)	0.001	1.00 (reference)	0.006	1.00 (reference)	0.001	1.00 (reference)	0.012
≥4	3.60 (1.71–7.57)		2.17 (1.24–3.79)		2.88 (1.41–5.86)		2.53 (1.19–5.39)	
Pelvic nodal involvement								
No	1.00 (reference)	0.137	1.00 (reference)	0.906	1.00 (reference)	0.643	1.00 (reference)	0.177
Yes	1.38 (0.90–2.10)		1.03 (0.66–1.61)		0.89 (0.53–1.48)		0.68 (0.39–1.19)	
Concurrent chemotherapy	1.00 (reference)	0.827	1.00 (reference)	0.799	1.00 (reference)	0.94	1.00 (reference)	0.95
Weekly cisplatin	1.05 (0.70–1.65)		0.94 (0.58–1.53)		0.98 (0.55–1.75)		1.02 (0.53–1.96)	
Cisplatin + Fluorouracil								
Serum conversion pattern of	1.00 (reference)	<0.001	1.00 (reference)	<0.001	1.00 (reference)	0.002	1.00 (reference)	0.007
SCC-Ag	2.00 (1.07–3.73)		1.74 (1.13–3.28)		1.81 (0.83–3.91)		1.47 (1.07–3.21)	
Consistent seronegative	4.02 (2.00–8.08)		3.74 (1.83–7.63)		4.31 (1.84–10.06)		3.43 (1.46–8.08)	
Negative conversion								
Consistent seropositive								

*CI*Confidence interval,*SCC-Ag* Squamous-cell carcinoma antigen

Discussion

The factor most significantly associated with RFS and OS in our data was serum conversion pattern of SCC-Ag. Survival rates decreased in the order of Consistent Seronegative, Negative Conversion, and Consistent Seropositive arms. Although tumor size was also related to outcome, the association was independent of SCC-Ag level. Previous studies assessing the value of SCC-Ag in cervical cancer often include heterogeneous population of patients who had been treated with either surgery or RT with or without chemotherapy [9, 10]. However, removing the tumor by surgery and keep having the tumor after delivery of chemoradiation need to be approached separately in terms of SCC-Ag because it is secreted from the tumor cells. Recent studies with radiotherapy including CRT cohorts reported statistically significant association between pre-treatment SCC-Ag and DFS or OS. However, several studies failed to demonstrate a significant correlation between pre-treatment SCC-Ag and OS in cervical cancer after radiotherapy [11–15]. Post-treatment SCC-Ag has not been studied as extensively as pre-treatment SCC-Ag and yet some reported that post-CRT SCC-Ag, not pre-CRT SCC-Ag was related to RFS and OS [16–20]. Although these studies suggest that SCC-Ag may play a role in predicting outcome, the wide cut-off levels and a constant proportion of patients with normal levels at diagnosis hinder direct clinical application of published results.

SCC-Ag is a tumor antigen which is produced during the squamous formation of epithelial tissue. It is increased when the neoplastic transformation occurs in the cervical squamous epithelium [21]. SCC-Ag is comprised of two isoforms, the neutral SCCA1 (*SERPINB3*) and the acidic SCCA2 (*SERPINB4*), both of which belong to the ovalbumin family of serine protease inhibitors [22, 23]. Over 90% of the residues are identical in SCCA1 and SCCA2, which results in identical secondary structures [24]. Murakami et al. reported that both SCCA1 and SCCA2 protect tumor cells from radiation-induced apoptotic cell death [25]. Based on the observation that SCCA1 functioned as a prosurvival factor by neutralizing lysosomal proteases released during cell stress, Markovina et al. tested the role of SCCA1 in response to radiation in cervical tumor cell lines [15]. They first showed that serum SCC-Ag levels correlated with intra-tumoral SCC-Ag by immunohistochemistry. Then they demonstrated that knockout of *SERPINB3* decreased cell survival after radiation in cervical tumor cell lines. When

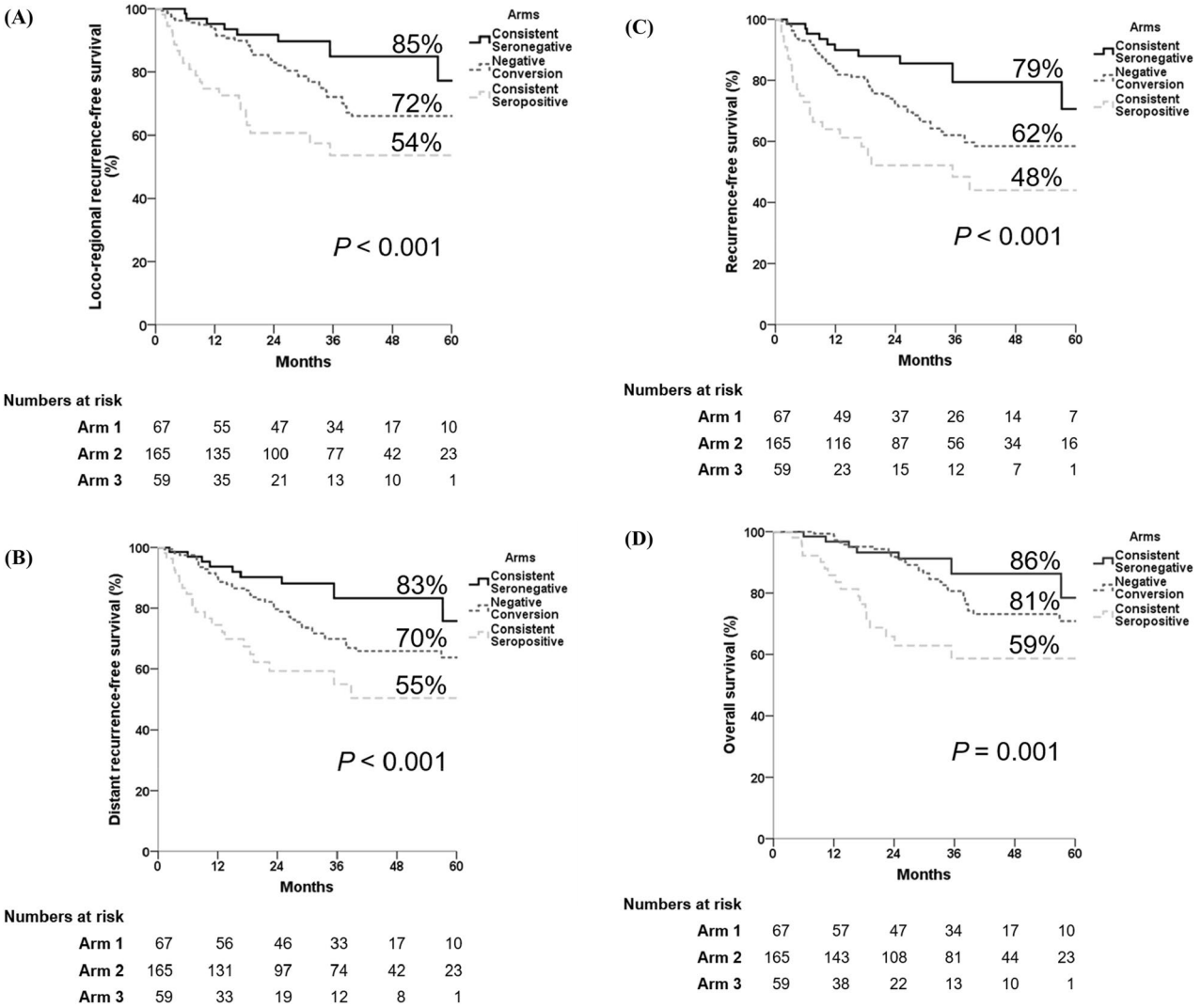

Fig. 2 Loco-regional recurrence-free survival (**A**), distant recurrence-free survival (**B**), recurrence-free survival (**C**), and overall survival (**D**) according to the serum conversion pattern of squamous-cell cancer antigen (SCC-Ag) between pre-treatment and post-treatment levels

the SCCA1-expressing vector was transfected in to the cell lines, increased radio-resistance was observed.

Because SCC-Ag promotes resistance to radiation in tumor cells, the serum conversion pattern of SCC-Ag before and after radiation is biologically more apt to predict tumor outcome in contrast with SCC-Ag levels measured at single time points, either at before or after treatment. By integrating whether pre-treatment SCC-Ag was elevated with whether post-treatment SCC-Ag was normalized, the serum conversion pattern may reflect not only the treatment-naïve disease nature but also the response to radiotherapy.

Locoregional recurrence occurs in up to a quarter of cervical cancer patients and over 10% experience distant recurrence after definitive CRT as demonstrated in randomized trials of cisplatin-based CRT [26–29]. We consider that the biology underlying these constant proportion of patients nonresponsive to therapy can be better represented by this novel categorization with serum conversion pattern of SCC-Ag which provides a risk stratification such as consistent seropositive as high risk, consistent seronegative as low risk, and negative conversion as intermediate risk for poor outcome. To the best of our knowledge, this is the first study to report serum conversion in the context of SCC-Ag. Adopting the concept of serum conversion and distinct categorization according to its pattern underscores the originality of this study.

The main limitation of this study is that despite continuous decrement of SCC-Ag up to 3 months after treatment the majority of post-treatment samplings were aggregated between 5 to 6 weeks post-treatment in our data, which is why we were unable to analyze in depth the optimal timing for post-treatment serum sampling. There had been previous

attempts to assess the value of serially sampled SCC-Ag. Again, patients included in those studies are heterogeneous and most underwent radical surgery [30]. Analysis of serial SCC-Ag in the true sense, obtained from diagnosis through definitive CRT and during follow-up is lacking in locally advanced cervical cancer treated with definitive CRT, which leaves it an area of further investigation that we plan to initiate shortly. Also, caution is advised when interpreting the serum conversion of SCC-Ag because cases with aggressive biologic features independent of SCC-Ag cannot be completely ruled out even in the consistent seronegative subgroup [31, 32].

In conclusion, serum conversion pattern of SCC-Ag pre- and post-chemoradiotherapy was significantly associated with recurrence and survival in locally advanced cervical cancer. Our data suggest that simply checking whether the level of SCC-Ag is above or below 2 ng/mL before and after treatment can provide clinicians with a convenient tool for prediction of tumor outcome.

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Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the Institutional Review Board (No. KC19RIMI0369).

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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