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Pretreatment Squamous Cell Carcinoma Antigen (SCC-Ag) as a Predictive Factor for the Use of Consolidation Chemotherapy in Cervical Cancer Patients After Postoperative Extended-Field Concurrent Chemoradiotherapy

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Abstract

Objective: The goal of this study was to confirm the clinical value of pretreatment serum squamous cell carcinoma antigen (SCC-Ag) in the administration of consolidation chemotherapy in patients with cervical cancers undergoing postoperative extended-field radiotherapy (EFRT) and concurrent chemotherapy (CCRT). **Methods:** Between 2007 and 2018, a total of 113 patients were treated with postoperative extended-field intensity-modulated radiotherapy (EF-IMRT) and CCRT. There were 63 patients receiving extended-field concurrent chemoradiotherapy (EF-CCRT) and consolidation chemotherapy, while another 50 patients underwent EF-CCRT alone. For the planning target volume, the prescribed dose was 45 to 50.4Gy/25 to 28 fractions. The consolidation chemotherapy regimen contained docetaxel and cisplatin. **Results:** For the patients with high pretreatment SCC-Ag, the addition of consolidation chemotherapy significantly improved their treatment outcomes and they had better 5-year overall survival (OS) (81.02% vs 63.44%, $P = .018$) and disease-free survival (DFS) (76.95% vs 61.12%, $P = .007$) than those without it. Meanwhile, the patients with consolidation chemotherapy had a lower rate of distant metastasis (8.8% vs 34.8%, $P = .001$). For the patients with low pretreatment SCC-Ag, there was no difference in prognosis between patients receiving consolidation chemotherapy and those not receiving consolidation. In multivariate analysis, consolidation chemotherapy was found to be a factor significantly associated with DFS ($P = .035$, 95% confidence interval (CI): 0.304-0.977) and distant metastasis ($P = .009$, 95% CI: 0.125-0.841). **Conclusion:** The patients who received consolidation chemotherapy showed significantly better DFS. Furthermore, pretreatment serum SCC-Ag > 6.5 ng/mL may be a predictive factor for the use of consolidation chemotherapy in cervical cancer patients treated with postoperative EF-CCRT.

Keywords

cervical cancer, squamous cell carcinoma antigen, extended-field radiotherapy, concurrent chemotherapy, consolidation chemotherapy

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Abbreviations

CCRT, concurrent chemotherapy; CI, confidence interval; CIN, common iliac node; CT, computed tomography; CTV, clinical target volume; DFS, disease-free survival; DM, distant metastasis; DSI, deep stromal invasion; EF-IMRT, extended-field intensity-modulated radiotherapy; EFRT, extended-field radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Hb, hemoglobin; HDR, high-dose rate; HT, helical tomotherapy; LC, local control; LRF, locoregional failure; LVSI, lymph-vascular space invasion; MRI, magnetic resonance imaging; OS, overall survival; PALN, para-aortic lymph node; PTV, planned target volume; SCC-Ag, squamous cell carcinoma antigen.

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Introduction

In China, early-stage cervical cancer is usually treated by radical hysterectomy. Postoperative patients with adverse "high-risk" surgicopathologic factors, such as parametrial involvement, positive surgical margins, and lymph node metastasis, should receive postoperative concurrent chemoradiotherapy (CCRT).[1] If a common iliac node (CIN) and/or a para-aortic lymph node (PALN) metastasis is identified, extended-field radiotherapy (EFRT) with concurrent chemotherapy (CCRT), including treatment of the para-aortic region and pelvic lymph node region, has been suggested.[2] Many studies have found that postoperative EFRT with CCRT provides a satisfactory locoregional control rate, but distant metastases constitute the major patterns of failure.[3-6] Matsuo et al. have shown that postoperative patients with positive pelvic nodes or PALNs who underwent adjuvant chemotherapy had a lower incidence of distant metastases than patients who received only CCRT.[7] However, the problem is that it is unknown who should receive consolidation chemotherapy in addition to postoperative extended-field concurrent chemoradiotherapy (EF-CCRT). Moreover, previous studies have not reached a consensus on this topic, which has resulted in either too much or too little treatment for some patients who were treated with postoperative EF-CCRT.

Squamous cell carcinoma antigen (SCC-Ag), which is a tumor-related antigen, has been confirmed as a sensitive and positive predictive tumor marker in invasive squamous cell cervical cancer.[8,9] Previous studies have shown that 74% to 88% of patients had elevations of SCC-Ag with carcinoma of the cervix, whereas 70% to 86% of patients manifested elevated SCC-Ag with recurrence.[10,11] Choi KH et al. found that the level of pretreatment SCC-Ag could predict tumor recurrence after definitive chemoradiotherapy.[12] However, the question of whether pretreatment SCC-Ag as a predictive marker can be used to identify patients who can benefit from consolidation chemotherapy in patients who have undergone postoperative EF-CCRT is still unknown.

The aim of our study was to identify the clinical value of SCC-Ag in the administration of consolidation chemotherapy in patients with cervical cancers undergoing postoperative EF-CCRT.

Methods

Patients

This study was approved by the Qilu Hospital of Shandong University Ethics Committee (approval No. KYLL-576). Between 2007 and 2018, 113 patients with International Federation of Gynecology and Obstetrics (FIGO) stages IB, IIA and IIB cervical cancer who were treated with postoperative EFRT and CCRT were retrospectively reviewed at our institution. Consolidation chemotherapy was added depending on the physician's preference. For example, in the case of postoperative pathology showing lymph-vascular space invasion (LVSI) and positive PALN or CIN, consolidation chemotherapy was added. The following selection criteria were used: patients who underwent radical hysterectomy, pelvic lymph node dissection, and PALN sampling; patients who had surgicopathologically confirmed invasive squamous cell cancer with positive CIN and/or PALN; patients who were given postoperative extended-field intensity-modulated radiotherapy (EF-IMRT) and concurrent cisplatin-based chemotherapy; and patients who had no previous treatments for cervical cancer. All of the included patients underwent the following procedures: a medical history and a physical examination; contrast-enhanced thoracic computed tomography (CT); contrast-enhanced abdominal and pelvic magnetic resonance imaging (MRI); complete blood count; assessments of liver and renal functions; and measurements of pretreatment SCC-Ag. The median level of SCC-Ag was used as a cutoff level to distinguish between the two groups.[13] The normal reference range of SCC-Ag is <2.0 ng/mL in our institution. The median level of SCC-Ag was 6.5 ng/mL in this study. When SCC-Ag ≥6.5 ng/mL, the patients were categorized into the high SCC-Ag level group. In contrast, when SCC-Ag <6.5 ng/mL, the patients were categorized into the low SCC-Ag level group. All medical information was anonymous. The Ethical Committee thought written informed consent was necessary prior to radical operation, and at that time, the patients gave consent for their medical information to be anonymously used.

Treatment

The details of sufficiently delineated targets have been previously described.[6] External beam radiation therapy was

delivered with conventional intensity-modulated radiotherapy (IMRT) or helical tomotherapy (HT). We conducted weekly cone beam CT procedures for patients with conventional IMRT and daily on-board megavoltage CT procedures for patients who were treated with HT before treatment. The clinical target volume (CTV) covered the PALN regions and pelvic lymph node regions. The superior CTV border was usually at T12 or L1, and the inferior border was at the lower margin of the obturator. To shape the planned target volume (PTV), we assigned margins of 0.8 to 1 cm to the CTV for the conventional IMRT, and 0.5 to 0.8 cm for the HT. The radiation therapy prescribed dose was 45 to 50.4 Gy/25 to 28 fractions. High-dose rate (HDR) intracavitary brachytherapy was given to the patients with preoperative large tumors (diameters of >4 cm) or positive surgical margins or if the tumor was adjacent (<5 mm) to the surgical margin of the vagina. We did not treat the patients with parametrial invasion with intracavitary brachytherapy. The prescription dose was 20 Gy/4 fractions and was delivered to a depth of 5 mm below the vaginal mucosa.

The regimen of CCRT was cisplatin (40 mg/m^2) and was given to all of the patients on a weekly basis. Consolidation chemotherapy contained 75 mg/m^2 docetaxel plus 75 mg/m^2 cisplatin and was given to some of the patients every 3 weeks. The median No. of cycles of consolidation chemotherapy was 2 (1-3 cycles).

Follow-up

The first follow-up examination was conducted 1 month after the initial treatment. Afterward, a follow-up examination was conducted every 3 months in the first 2 years, every 6 months from the third to fifth years, and annually after 5 years. The conventional follow-up evaluation included gynecological examinations, SCC-Ag measurements, abdomen and pelvic enhanced MRI, and chest enhanced CT. If some patients were suspicious for recurrence, positron emission tomography-CT and biopsy were performed. We defined disease-free survival (DFS) and overall survival (OS) from the time of diagnosis to the time of distant metastasis, local recurrence, or the last follow-up and to the date of death or the last follow-up, respectively.

Statistical Analysis

The statistical analyses of the data were conducted with SPSS software, version 19.0. We analyzed the categorical variables with the chi-square test or Fisher's exact test and the continuous variables were analyzed with the Mann–Whitney U test. A Cox proportional hazards regression test was used to conduct multivariate analyses of DFS, local control (LC), and distant metastasis. $P < .05$ was considered to be statistically significant. The DFS and OS rates were determined by the Kaplan–Meier method.

Results

Patient Characteristics

Among the 113 patients eligible for the study, 63 patients (55.8%) received EF-CCRT and consolidation chemotherapy, whereas another 50 patients underwent only EF-CCRT. The basic clinical features of the patients were shown in Table 1. The median follow-up was 57.8 months (range: 3.9-132.4 months). The median level of SCC-Ag was 6.5 ng/mL (range: 0.9-654 ng/mL). There were no differences in FIGO stage, hemoglobin (Hb) level, histological grade, pretreatment tumor size, LVSI, deep stromal invasion (DSI), and lymph node metastasis between the two groups. Patients who received

Table 1. The Basic Clinical Features of All Patients.

Factors	EF-CCRT + Consolidation Chemotherapy (n = 63)	EF-CCRT (n = 50)	*P* value ($P < .05$)
Age (years)			
Median	59	62	.049
SCC-Ag			.244
≥6.5 ng/mL	34	23	
<6.5 ng/mL	29	27	
FIGO stage			.689
IB	27	23	
IIA	23	17	
IIB	13	10	
Hemoglobin			.723
≥110 g/L	51	47	
<110 g/L	12	13	
Histological grade			.945
G1	12	10	
G2	34	29	
G3	17	11	
Primary tumor size			.576
≥4 cm	21	19	
<4 cm	42	31	
DSI			.898
Yes	52	42	
No	11	8	
LVSI			1.000
Yes	25	21	
No	38	29	
Lymph nodes metastasis			.554
CIN(+)	42	36	
PAN(+)	14	10	
CIN(+) and PAN(+)	7	4	
HDR brachytherapy			1.4
Yes	22	24	
No	41	26	

Abbreviations: SCC-Ag, squamous cell carcinoma antigen; FIGO, International Federation of Gynecology and Obstetrics; DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; CIN, common iliac node; PAN, para-aortic node; EF-CCRT, extended-field concurrent chemoradiotherapy; HDR, high-dose rate.

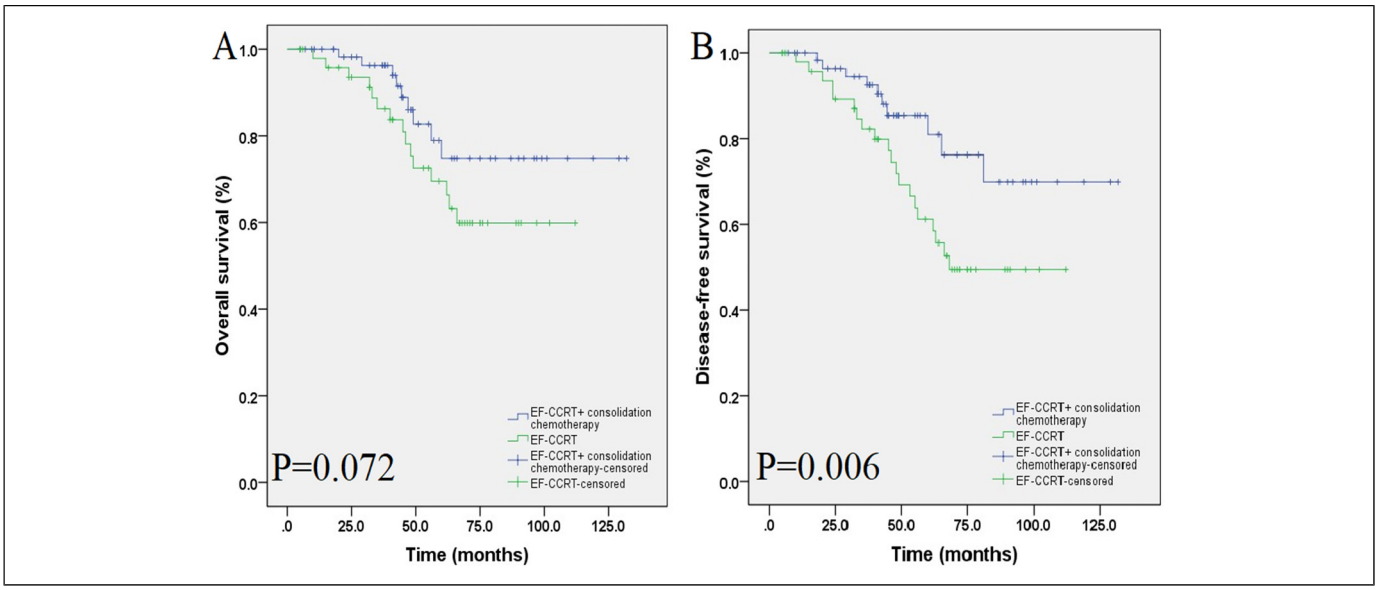

Figure 1. A and B Overall survival ($P = .072$) and disease-free survival ($P = .006$) for the entire group of patients.

consolidation chemotherapy tended to be younger than those who did not receive consolidation chemotherapy ($P = .049$).

Survival Analysis for All Patients

The 5-year OS rates for patients with and without consolidation chemotherapy were 80.31% and 70.92%, respectively. There was no statistically significant difference in the OS rate between the two groups of patients ($P = .072$) (Figure 1A). The 5-year DFS rates for the two groups were 76.39% and 65.08%, respectively. The patients receiving consolidation chemotherapy had a better DFS ($P = .006$) (Figure 1B). Among all of the patients, 24 patients (21.2%) died at the end of the follow-up period. A total of 39 patients (34.5%) had a tumor recurrence, including 10 patients (8.8%) with local relapse (in-field failure), 23 patients (20.4%) with distant metastases (out-field failure), and 6 patients (5.3%) with concurrent local relapse and distant metastases. The most common site of distant metastasis was the lung (9 patients) or the cervical lymph nodes (7 patients).

Effect of Squamous Cell Carcinoma Antigen Levels on the Survival

In the group with high SCC-Ag levels, 16 patients died (6 patients died of cervical cancer. Ten patients died due to other reasons: 3 patients died of heart failure, 1 patient died of acute myocardial infarction, 2 patients died of chronic obstructive pulmonary disease, 1 patient died of pulmonary embolism, 1 patient died of interstitial lung disease, and 2 patients died of intracranial hemorrhage), and 22 patients developed a recurrence. Six patients suffered from a local recurrence, and 11 patients had distant metastases. In addition, 5 patients were diagnosed with both local recurrence and distant metastases. For the high SCC-Ag levels, the study showed that patients with consolidation chemotherapy obtained better 5-year OS (81.02% vs 63.44%, $P = .018$) and DFS (76.95% vs 61.12%, $P = .007$) than those without consolidation chemotherapy (Figure 2A and B, Table 2A). Although the difference was not obvious in regard to local recurrence, the addition of consolidation chemotherapy significantly reduced the chances of distant metastases (8.8% vs 34.8%, $P = .001$) (Table 3A). We also performed a multivariate analysis of patients with elevated levels of SCC-Ag (Table 4). The results revealed that older ages (≥60 years) and a low Hb level (<110 g/L) were associated with worse DFS ($P = .001$, 95% CI: 1.401-2.989; $P = .027$, 95% CI: 0.089-3.246, respectively). Tumors ≥4 cm indicated worse DFS ($P = .019$, 95% CI: 1.119-6.568) and LC ($P = .002$, 95% CI: 1.366-6.902) than tumors < 4 cm. The decision of whether to receive consolidation chemotherapy was a factor that was significantly associated with DFS ($P = .035$, 95% CI: 0.304-0.977) and distant metastasis ($P = .009$, 95% CI: 0.125-0.841), indicating that patients receiving consolidation chemotherapy experienced lower rates of distant metastases than patients without consolidation chemotherapy.

In the group with low SCC-Ag levels, 8 patients died (4 patients died of cervical cancer. Four patients died due to other reasons: 1 patient died of intracranial hemorrhage, 1 patient died of renal insufficiency, and 2 patients died of heart failure). Seventeen patients experienced a recurrence, including 2 patients with local recurrence, 13 patients with distant metastases, and 2 patients with both local recurrence and distant metastases. There was no difference in the 5-year OS (81.01% vs 78.69%, $P = .961$) and DFS (76.73% vs 71.08%, $P = .117$) between patients with consolidation chemotherapy and those patients who did not receive consolidation chemotherapy (Figure 2C and D, Table 2B). The type of tumor recurrence was also not significantly different between the two groups (Table 3B).

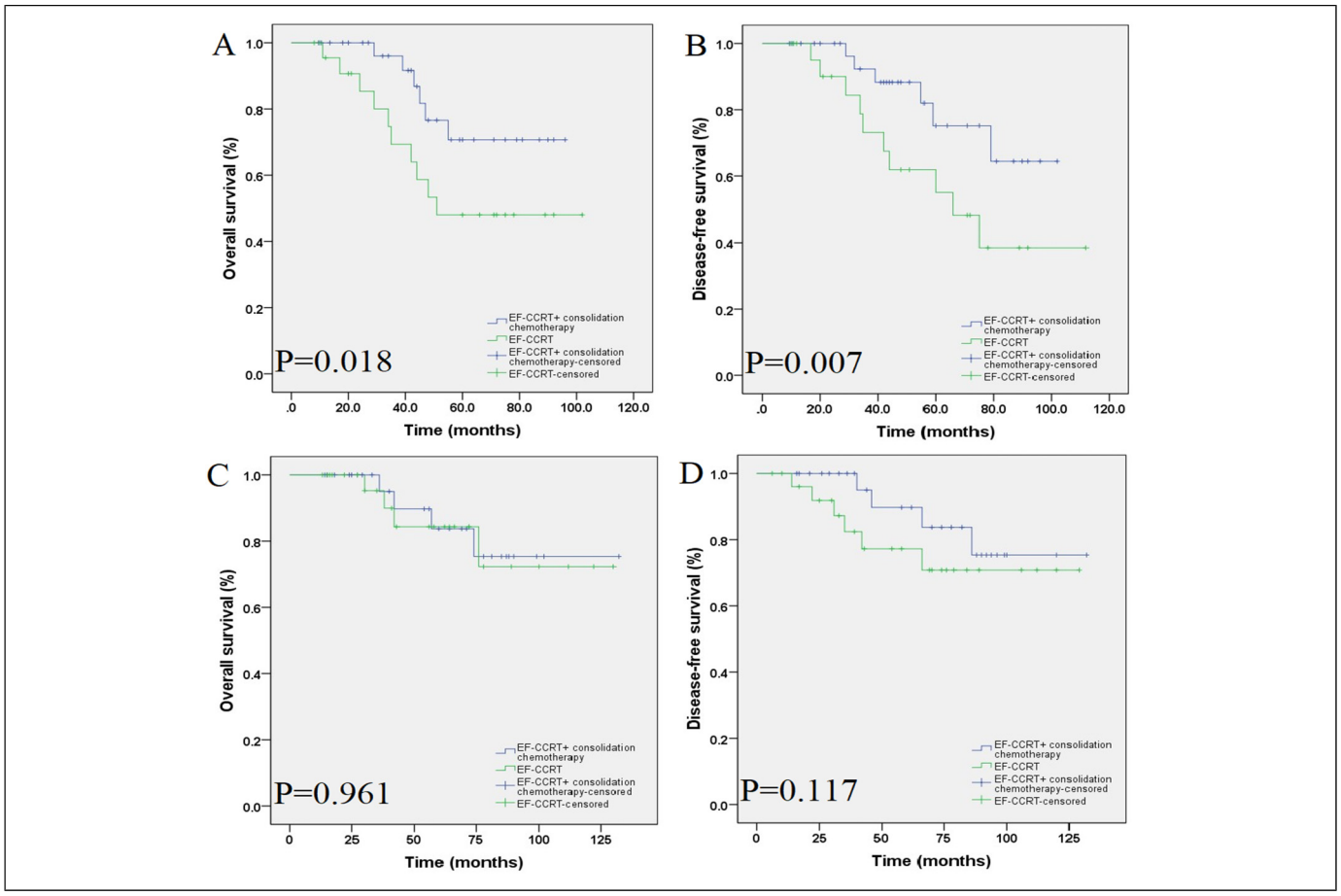

Figure 2. A and B Overall survival ($P = .018$) and disease-free survival ($P = .007$) for the patients with elevated levels of squamous cell carcinoma antigen (SCC-Ag). C and D Overall survival ($P = .961$) and disease-free survival ($P = .117$) for the patients with low levels of SCC-Ag.

Discussion

The level of SCC-Ag as a tumor marker had been found to correlate with recurrence or progression and survival in cervical squamous carcinoma.[11,14] Duk et al. demonstrated that the pretreatment level of SCC-Ag was independently predictive of DFS in stages IB-IIA postoperative squamous cervical carcinoma.[15] Another previous study analyzed 304 squamous cell carcinoma patients receiving CCRT and found that patients with elevated levels of SCC-Ag had a poor OS and high rates of regional recurrence and distant metastases.[12] In addition, the pretreatment level of SCC-Ag had been proven to be an independent prognostic factor of distant recurrence.[16] Previous studies had shown that the early detection of tumor recurrence can improve survival.[17,18] In our study, we demonstrated that for patients undergoing EF-CCRT, those patients with consolidation chemotherapy exhibited better DFS than those patients without consolidation chemotherapy (although there was no statistically significant difference in OS). We found that consolidation chemotherapy in the high SCC-Ag level group (≥6.5 ng/mL) was associated with obviously improved DFS and OS compared with those patients who did not receive consolidation chemotherapy. However, for the

Table 2A. Survival of Patients With Elevated Levels of SCC-Ag.

	EF-CCRT + Consolidation Chemotherapy (n = 34)		EF-CCRT (n = 23)		
Group	3-year	5-year	3-year	5-year	*P* value ($P < .05$)
OS	85.81	81.02	77.46	63.44	.018
DFS	81.38	76.95	69.39	61.12	.007

Table 3A. Tumor Recurrence Form of Patients With Elevated Levels of SCC-Ag.

	EF-CCRT + Consolidation Chemotherapy (n = 34)		EF-CCRT (n = 23)		
Group	3-year	5-year	3-year	5-year	*P* value ($P < .05$)
LRF	2(5.9%)	4(11.8%)	3(13%)	4(17.4%)	.071
DM	2(5.9%)	3(8.8%)	5(21.7%)	8(34.8%)	.001

Table 2B. Survival of Patients With Low Levels of SCC-Ag.

Group	EF-CCRT + Consolidation Chemotherapy (n = 29)		EF-CCRT (n = 27)		*P* value ($P < .05$)
	3-year	5-year	3-year	5-year	
OS	90.37	81.01	85.73	78.69	.961
DFS	86.58	76.63	75.01	71.08	.117

Abbreviations: DFS, disease-free survival; EF-CCRT, extended-field concurrent chemotherapy; OS, overall survival; SCC-Ag, squamous cell carcinoma antigen.

Table 3B. Tumor Recurrence Form of Patients With Low Levels of SCC-Ag.

Group	EF-CCRT + Consolidation Chemotherapy (n = 29)		EF-CCRT (n = 27)		*P* value ($P < .05$)
	3-year	5-year	3-year	5-year	
LRF	1(3.4%)	2(6.9%)	1(3.7%)	2(7.4%)	.598
DM	1(3.4%)	4(13.8%)	5(18.5%)	6(22.2%)	.713

Abbreviations: DM, distant metastasis; LRF, locoregional failure; EF-CCRT, extended-field concurrent chemotherapy; SCC-Ag, squamous cell carcinoma antigen.

low SCC-Ag level group (<6.5 ng/mL), consolidation chemotherapy seemed to have a weak effect on survival. Furthermore, according to the multifactor analysis, our study demonstrated that consolidation chemotherapy was an independent prognostic factor for DFS, LC, and distant metastasis in patients with elevated pretreatment SCC-Ag levels.

For the first time, we demonstrated that the clinical value of pretreatment SCC-Ag levels for patients experiencing EF-CCRT was a predictive factor for the use of consolidation chemotherapy. A previous study demonstrated that pretreatment SCC-Ag levels could predict treatment failure or survival in cervical cancer patients following definitive CCRT.[12] A high level of pretreatment SCC-Ag was associated with more local-regional recurrence, distant metastasis, and para-aortic recurrence.[12,19] Adjuvant therapies, such as neoadjuvant chemotherapy or consolidation chemotherapy, should be considered for patients with high SCC-Ag levels.[20,21] To date, there is no consensus on the cutoff value of SCC-Ag.[22-25] In the present study, we found that patients with Hb <110 g/L and an elevated SCC-Ag level had worse oncologic outcomes, similar to the results of a previous study.[26] However, the underlying mechanism of how a lower pretreatment Hb level affects treatment outcomes remains unknown. One hypothesis suggested that tumor-related anemia was a sign of tumor aggressiveness and that poor tumor sensitivity to radiotherapy was due to a decreased oxygen supply.[26]

For patients receiving postoperative EF-CCRT, distant recurrence was the main form of treatment failure. This may be the possible explanation for why postoperative EF-CCRT can achieve obvious locoregional control alone but fails to improve OS.[3,6] The continuation of chemotherapy to treat occult systemic disease may decrease the rate of distant metastasis; thus, the addition of consolidation chemotherapy to their treatment may be legitimate for cervical cancer patients after postoperative EF-CCRT. A previous study revealed that the benefit of consolidation chemotherapy on survival and DFS was clear for early-stage cervical cancer with high-risk factors.[27] In another study, Siriwan T et al. showed that adjuvant chemotherapy after CCRT significantly decreased systemic recurrences but not OS or locoregional failure in locally advanced cervical cancer.[28] Furthermore, Manders DB et al. reported that adjuvant systemic chemotherapy was effective in patients with cervical cancer metastatic to PALN.[29] However, few studies have directly investigated factors indicating when consolidation chemotherapy is necessary for cervical cancer patients undergoing postoperative EF-CCRT. In this

Table 4. Multivariate Analysis of Factors Influencing DFS, LC, DM, and OS for Patients With Elevated Levels of SCC-Ag.

Factors	DFS HR (95%CI)	*P*	LC HR (95%CI)	*P*	DM HR (95%CI)	*P*	OS HR (95%CI)	*P*
Age (years) (≥60 vs <60)	2.121 (1.401-2.989)	.001	1.472 (1.006-1.925)	.091	2.627 (0.824-4.569)	.083	1.019 (0.671-1.716)	.075
Hemoglobin (< 110 g/L vs ≥110 g/L)	2.301 (0.089-3.246)	.027	1.449 (0.627-3.447)	.345	1.440 (0.901-2.893)	.068	1.548 (1.045-2.508)	.083
Tumor size (≥4 cm vs < 4 cm)	2.236 (1.119-6.568)	.019	2.399 (1.366-6.902)	.002	1.512 (0.651-3.44)	.219	1.359 (0.787-2.572)	.348
DSI (Yes vs no)	1.947 (0.875-3.911)	.061	2.716 (1.552-7.415)	.045	1.301 (0.501-2.982)	.379	2.028 (0.979-4.233)	.186
LVSI (No vs yes)	.591 (0.421-1.411)	.272	0.708 (0.311-1.624)	.342	0.711 (0.351-1.677)	.361	0.976 (0.812-2.021)	.536
Consolidation chemotherapy (Yes vs no)	0.511 (0.304-0.977)	.035	0.628 (0.294-1.511)	.241	0.372 (0.125-0.841)	.009	0.861 (0.457-1.974)	.097

Abbreviations: HR, hazard ratio; CI, confidence interval; DSI, deep stromal invasion; LVSI, lymph-vascular space invasion; CIN, common iliac node; PAN, para-aortic node; DFS, disease-free survival; LC, local control; DM distant metastasis; OS, overall survival.

study, we showed that SCC-Ag was an effective indicator for guiding the use of consolidation chemotherapy. More specifically, when the pretreatment SCC-Ag level was high, consolidation therapy should be performed because of improved survival. However, when the level was low, consolidation chemotherapy failed to improve oncologic outcomes. After a multifactor analysis, we found that consolidation chemotherapy was significantly associated with distant metastasis, thus suggesting that patients who received consolidation chemotherapy had a lower risk of s distant recurrence. Additionally, pretreatment tumor size was also an independent predictive factor of DFS and LC, which was consistent with other studies.[30,31]

Our study inevitably had the disadvantages associated with a retrospective study. Selection bias was unavoidable. Although we found that there were no significant differences in the clinical variables between patients with high and low levels of SCC-Ag, the patients who received consolidation chemotherapy tended to be younger than those who did not receive consolidation chemotherapy. Second, the sample size was comparatively small in the present study. One of the reasons for this may be that we only selected patients with invasive squamous cell cancer with positive CIN and/or PALN and did not include patients with other pathological types. Moreover, we selected the median pretreatment level of SCC-Ag as the basis for grouping patients, and this study was a single-center experience.

In conclusion, for patients undergoing postoperative EF-CCRT, pretreatment SCC-Ag might be a predictive factor for the use of consolidation chemotherapy, especially when the pretreatment SCC-Ag level was elevated by more than 6.5 ng/mL. We hope to conduct prospective randomized controlled studies to validate these results.

Authors' Note

Conception and design of the research: CF; acquisition of data: HW and YZ; analysis and interpretation of data: GZ, LM, and HW; statistical analysis: GZ, LM, and YZ; drafting the manuscript: GZ; and revision of manuscript for important intellectual content: CF. All authors read and approved the final manuscript. The study was approved by the Qilu Hospital of Shandong University Ethics Committee (approval No. KYLL-576). All patients provided written informed consent prior to enrollment in the study.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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