RESEARCH

Prognostic value of tumor measurement parameters and SCC-Ag changes in patients with locally-advanced cervical cancer

Wenjuan Chen[*†] , Siyi Xiu[†], Xingyun Xie, Huiming Guo, Yuanji Xu, Penggang Bai and Xiaoyi Xia

Abstract

Objective: To investigate the prognostic relevance of specific measurement parameters such as tumor diameter, tumor volume, tumor volume reduction rate (TVRR), and changes in the squamous cell carcinoma antigen (SCC-Ag) level in patients with locally-advanced cervical cancer (LACC) undergoing concurrent radiotherapy and chemotherapy.

Methods: This was a retrospective study of 203 patients with stage IIA–IVA cervical squamous cell carcinoma who were newly diagnosed at our hospital between January 2011 and March 2015. Clinical data and pre-and post-treatment imaging information were collected and each parameter was calculated using 3DSlicer software. The pre/post-treatment tumor diameter ($TD_{pre/post}$), tumor volume ($TV_{pre/post}$), SCC-Ag ($SCC_{pre/post}$), and TVRR, SCC-Ag reduction rate (SCCRR) were analyzed and their prognostic relevance evaluated.

Results: The median follow-up was 69 months. The 5-year overall survival (OS) and disease progression-free survival (PFS) rates were 69.5% and 64.5%, respectively. On univariate analysis, $TD_{pre/post}$, $TV_{pre/post}$, TVRR, $SCC_{pre/post}$ and SCCRR showed significant association with OS and PFS ($P < 0.05$). On multivariate analysis, TD_{pre} [Hazard ratio (HR) $= 0.373$, $P = 0.028$], TD_{post} ($HR = 0.376$, $P = 0.003$) and SCC_{post} ($HR = 0.374$, $P = 0.001$) were independent predictors of OS. TVRR ($HR = 2.998$, $P < 0.001$), SCC_{pre} ($HR = 0.563$, $P = 0.041$), and SCC_{post} ($HR = 0.253$, $P < 0.001$) were independent predictors of PFS. Tumor measurement parameters showed a positive correlation with SCC-Ag ($P < 0.05$).

Conclusion: $TD_{pre/post}$, $TV_{pre/post}$, TVRR, $SCC_{pre/post}$, and SCCRR were prognostic factors in LACC. $TD_{pre/post}$ and SCC_{post} showed the most significant prognostic value. TVRR and $SCC_{pre/post}$ were closely related to disease progression. Further studies should investigate the correlation between measurement parameters of tumor and SCC-Ag.

Keywords: Cervical cancer, Tumor diameter, Tumor volume, Tumor volume reduction rate, Squamous cell carcinoma antigen (SCC-Ag)

Background

Cervical cancer (CC) is the fourth most common malignant tumor in women. An estimated 530,000 new cases of CC and 270,000 deaths attributed to CC are reported each year across the world [1]. More than two-thirds of patients with CC have the locally-advanced disease at the time of diagnosis [2]. Concurrent chemoradiation is still the standard treatment for locally-advanced cervical cancer (LACC) [3]. The combination of external beam radiotherapy (EBRT) and brachytherapy (BRT) represents the mainstay in the primary treatment of patients with cervical cancer. While in elderly patients who refuse brachytherapy or are not amenable to brachytherapy, intensity modulated radiation therapy with simultaneous

*Correspondence: chenwj92@126.com
†Wenjuan Chen and Siyi Xiu have contributed equally to this work
Department of Radiation Oncology, Fujian Medical University Cancer Hospital, Fujian Cancer Hospital, No. 420 Fuma Road, Fuzhou 350000, Fujian, China

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 2 of 10

integrated boost (SIB) to macroscopic disease can be proposed, as an alternative to brachytherapy [4]. Studies have demonstrated the prognostic value of clinical stage, pathological type, lymph node metastasis, depth of tumor invasion, tumor size, and tumor differentiation in patients with CC [5–7]. Tumor volume has always been a key determinant of the prognosis of CC [8, 9]. Squamous cell carcinoma antigen (SCC-Ag) is a protein (molecular weight: 48000d) which is often increased in patients with cervical squamous cell carcinoma [10]. Studies have shown that the change in SCC-Ag level is not only related to the tumor size, but also one of the important diagnostic and prognostic markers of CC [11–13].

The reported 5-year overall survival (OS) rate of patients with the International Federation of Gynecology and Obstetrics (FIGO) stage II, stage III, and stage IV CC are 65–69%, 40–43%, and 15–20%, respectively [14]. In recent years, several studies have investigated the prognostic value of several factors (such as tumor size, volume, lymph node status) and changes in SCC-Ag in predicting the treatment outcomes of patients with CC. SCC-Ag was shown to be a marker for early diagnosis and post-treatment disease recurrence [15, 16].

Previous studies have investigated the value of tumor diameter, volume, and SCC-Ag in predicting the therapeutic response of CC during radiotherapy [17]. However, there is no clear consensus on the optimal cut-off value for parameters such as tumor diameter, volume, and tumor volume reduction rate (TVRR).

Moreover, most previous studies have not analyzed the relationships among the pre-treatment, post-treatment tumor diameter (TD_{pre}, TD_{post}), and pre-treatment tumor volume (TV_{pre}). Furthermore, the prognostic relevance of post-treatment tumor volume (TV_{post}) and TVRR is not well characterized in patients with CC. Few studies have addressed the prognostic relevance of SCC-Ag-related parameters such as pre-treatment SCC-Ag (SCC_{pre}), post-treatment SCC-Ag (SCC_{post}), and SCC-Ag reduction rate (SCCRR) during RT for CC. Further in-depth exploration of the prognostic value of tumor measurement parameters and SCC-Ag level in patients with CC is a key imperative.

Materials and methods
Study population
We retrospectively reviewed data pertaining to 203 patients with locally-advanced cervical squamous cell carcinoma who were newly diagnosed at our center between January 2011 and March 2015. Patients were staged using the 2009 version of FIGO staging system. All patients had complete medical history and MRI images, and were treated with concurrent chemoradiotherapy and individualized high-dose rate intracavitary brachytherapy.

Acquisition of tumor measurement parameters
The 3D Slicer software [18] is a scalable medical image processing and visualization application platform. Pretrearment MR means the Magnetic resonance imaging prior to chemotherapy and radiationtherapy. Post-treatment MR was underwent nearly the end of the EBRT. Pre- and post-treatment MR imaging data of 203 patients were imported into DICOM format and processed by the 3D Slicer software. Two radiologists delineated and outlined the primary tumor target area and residual tumor target area during radiotherapy. TD_{pre} and TD_{post} were measured by the related software modules, and then the TV_{pre}, TV_{post}, and TVRR were calculated by 3D Slicer.

$TVRR = (TV_{pre} - TV_{post})/TV_{pre} \times 100\%$ (the difference between TV_{pre} and TV_{post} divided by the percentage of TV_{pre}).

Treatment strategy
All patients received CCRT. Radiotherapy consisted of intensity-modulated radiotherapy (IMRT) or conventional 4-field box conformal radiotherapy technique (CRT). The external whole-pelvis irradiation was performed with a dose of 1.8–2.0 Gy per fraction 5 times per week up to a total external dose of 45.0–50.0 Gy. For positive pelvic lymph nodes, the radiotherapy dose was boosted to 10–16 Gy. This was followed by a high-dose rate intracavitary radiation with a fractional dose of 7.0 Gy (weekly) to a total dose of 28.0 Gy in four weeks. The preferred regimen in the guideline of National Comprehensive Cancer Network is cisplatin [3]. While many patients can not tolerant cisplatin because it is highly emetic and nephrotoxic. So chemotherapy was applied during radiotherapy, using nedaplatin monotherapy every three weeks at a dose of 80 mg/m^2 or nedaplatin in combination with paclitaxel 135 mg/m^2.

Statistical analysis
The changes in each parameter (independent and dependent groups) were compared using t test. Kaplan–Meier method was used for survival analysis. Log-rank test and Cox proportional hazard regression model were applied to analyze the prognostic factors among parameters related to TD, TV, and SCC-Ag level. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off values using the Youden index. P values < 0.05 were considered indicative of statistical significance. All statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, Illinois).

Results

Characteristics of the study population

The median age of patients in our cohort (n = 203) was 52 years (range, 32–76). The median interval between the pre-treatment and post-treatment MR was 45 days (range 35–71).The basic information and clinical characteristics of the study population are summarized in Table 1. The dicotimization value of age, TD_{pre}, TV_{pre}, TD_{post}, TV_{post}, TVRR, SCC_{pre} and SCC_{post} are based on the analysis of the ROC curves.It should be noticed that 80 patients (39.4%) underwent conventional radiation therapy due to poor economic conditions. The median duration of follow-up was 69 months (range 3–116). Among the 203 patients, 11 patients had local or regional recurrence; 28 patients had distant metastasis; and 3 patients had local/regional recurrence and distant metastasis at the same time. Among the 65 patients who died, 27 died of local regional recurrence or distant metastasis; 24 patients died of complications; and 14 patients died of unknown causes. The 5-year OS and PFS in our cohort were 69.5% and 64.5%, respectively (Fig. 1).

Analysis of tumor measurement parameters and SCC-Ag value

The median TD_{pre} and TD_{post} in our cohort were 4.5 cm (range, 1.7–9.7) and 2.1 cm (0.7–7.7), respectively; the median TV_{pre} and TV_{post} were 45.08 cm^3 (range, 4.80–328.71) and 6.52 cm^3 (0.41–140.45); the median TVRR was 0.84% (range, 0–0.98); the median SCC_{pre} and SCC_{post} were 4.7 µg/L (range, 0.5–70.0) and 0.9 µg/L (range, 0.2–47.8), respectively; and the median SCCRR was 1.0 (0–1.0) × 100%. Among the 203 patients included, pre-treatment SCC values of 57 patients were within the normal range (normal reference range: < 2 µg/L). In order to reduce statistical errors, the SCC values of these 57 patients were processed as missing values.

ROC curve analysis

On ROC curve analysis, the optimal cut-off value of TD_{pre} and TD_{post} (based on the Youden index) was 4.4 cm and 2.4 cm, respectively. The optimal cut-off value of TV_{pre} and TV_{post} was 45.71 cm^3 and 10.45 cm^3, respectively. The optimal cut-off value of TVRR was 80.1%. The optimal cut-off value for SCC_{pre} and SCC_{post} was 11.4 µg/L and 1.9 µg/L, respectively. The optimal cut-off value for age was 54 years (Fig. 2).

Survival analysis

Analysis of OS

TDpre, TDpost, TVpre, TVpost, TVRR, SCCpre, SCCpost, SCCRR, FIGO staging, lymph node

Table 1 Patient and tumor characteristics

Characteristics	n	%
Age (years)		
< 54	108	53.2
≥ 54	95	46.8
FIGO stage		
IIa	14	6.9
IIb	105	51.7
IIIa	8	3.9
IIIb	75	36.9
IVa	1	0.5
Infection		
Yes	15	7.4
No	188	92.6
Anemia		
Yes	80	39.4
No	123	60.6
Lymph node metastasis		
Yes	57	28.1
No	146	71.9
TD_{pre}* (cm)		
≤ 4.4	88	43.3
> 4.4	115	56.7
TV_{pre}* (cm^3)		
≤ 45.71	105	51.7
> 45.71	98	48.3
TD_{post}* (cm)		
≤ 2.4	127	62.6
> 2.4	76	37.4
TV_{post}* (cm^3)		
≤ 10.45	137	67.5
> 10.45	66	32.5
TVRR* (%)		
< 80.1	78	38.4
≥ 80.1	125	61.6
Radiotherapy		
IMRT	123	60.6
CRT	80	39.4
Total dose of radiotherapy (Gy)		
≤ 84	107	52.7
> 84	96	47.3
Number of chemotherapy cycles		
< 4	65	32.0
≥ 4	138	68.0
SCC_{pre} (µg/L)		
≤ 11.4	145	71.4
> 11.4	58	28.6
SCC_{post} (µg/L)		
≤ 1.9	180	88.7
> 1.9	23	11.3
SCCRR (%)		
= 100	122	60.1
< 100	24	11.8

*Radiological characteristics

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 4 of 10

metastasis, and chemotherapy cycles all showed a significant association with OS ($P < 0.05$). The 5-year OS rate in the $TD_{pre} \leq 4.4$ cm group was significantly greater than that in the $TD_{pre} > 4.4$ cm group (84.1% vs 58.3%, $P < 0.001$). The 5-year OS rate in the $TV_{pre} \leq 45.71$ cm^3 group was significantly greater than that in the $TV_{pre} > 45.71$ cm^3 group (81.9% vs 56.1%, $P < 0.001$). The 5-year OS rate in the $TD_{post} \leq 2.4$ cm group and $TD_{post} > 2.4$ cm group was 82.5% and 44.7%, respectively ($P < 0.001$). The 5-year OS rate in the $TV_{post} \leq 10.45$ cm^3 group and $TV_{post} > 10.45$ cm^3 group was 82.5% and 42.4%, respectively ($P < 0.001$). The 5-year OS in the $TVRR \geq 80.1\%$ group was also significantly greater than that in the $TVRR < 80.1\%$ group (84.0% vs 46.2%, $P < 0.001$). The 5-year OS rate in the $SCC_{pre} \leq 11.4$ μg/L group and $SCC_{pre} > 11.4$ μg/L group was 75.2% and 55.2%, respectively ($P = 0.001$). The 5-year OS rate in the $SCC_{post} \leq 1.9$ μg/L group and $SCCpost > 1.9$ μg/L was 75.3% and 34.5%, respectively ($P < 0.001$). The 5-year OS rates in the group with SCCRR of 100% and SCCRR < 100% were 75.4% and 33.3%, respectively ($P < 0.001$) (Table 2).

On multivariate analysis, TD_{pre}, TD_{post}, and SCC_{post} were identified as independent predictors of OS. The OS of patients with $TD_{pre} \leq 4.4$ cm was significantly better than that of patients with > 4.4 cm [Hazard ratio (HR) = 0.373, 95% confidence interval (CI): 0.155–0.898, $P = 0.028$]; the OS of patients with $TD_{post} \leq 2.4$ cm was better than that of patients with > 2.4 cm (HR = 0.376, 95% CI 0.198–0.715, $P = 0.003$). The OS of patients with $SCC_{post} \leq 1.9$ μg/L was better than that of patients > 1.9 μg/L (HR = 0.374, 95% CI 0.207–0.677, $P = 0.001$) (Table 3).

Analysis of PFS
On univariate analysis, SCC-Ag, FIGO staging, and chemotherapy cycles were all prognostic factors for

PFS. $TD_{pre} \leq 4.4$ cm group showed a significantly better 5-year PFS rate than $TD_{pre} > 4.4$ cm group (80.7% vs 52.2%, $P < 0.001$). $TV_{pre} \leq 45.71$ cm^3 group had better 5-year PFS than $TV_{pre} > 45.71$cm^3 group (78.1% vs 50.0%, $P < 0.001$). The 5-year PFS of $TD_{post} \leq 2.4$ cm group and $TD_{post} > 2.4$ cm group were 79.5% and 39.5%, respectively ($P < 0.001$). The 5-year PFS of $TV_{post} \leq 10.45$ cm^3 group and $TV_{post} > 10.45$ cm^3 group was 78.1% and 36.4%, respectively ($P < 0.001$). The 5-year PFS of $TVRR \geq 80.1\%$ group and $TVRR < 80.1\%$ group was 79.2% and 41.0%, respectively ($P < 0.001$). The 5-year PFS of $SCC_{pre} \leq 11.4$ μg/L group and $SCC_{pre} > 11.4$ μg/L group was 73.1% and 43.1%, respectively ($P < 0.001$). The 5-year PFS of $SCC_{post} \leq 1.9$ μg/L group and $SCC_{post} > 1.9$ μg/L group was 70.6% and 17.4%, respectively ($P < 0.001$). The 5-year PFS in the SCCRR 100% group and SCCRR < 100% group was 69.7% and 20.8%, respectively ($P < 0.001$) (Table 2).

On Cox regression multivariate analysis, TVRR, SCC_{pre}, and SCC_{post} were identified as independent predictors of PFS. Patients with $TVRR \geq 80.1\%$ showed obvious PFS benefit (HR = 2.998, 95% CI 1.739–5.171, $P < 0.001$). The PFS of patients with $SCC_{pre} \leq 11.4$ μg/L was significantly better than that of patients with $SCC_{pre} \leq 11.4$ μg/L (HR = 0.563, 95% CI 0.325–0.977, $P = 0.041$). The PFS of patients with $SCC_{post} \leq 1.9$ μg/L was also better than that of patients with $SCC_{post} > 1.9$ μg/L (HR = 0.253, 95% CI 0.143–0.447, $P < 0.001$) (Table 3).

Correlation analysis between tumor parameters
We used a linear regression equation to further assess the correlation between tumor measurement parameters and SCC-Ag. TD_{pre} and SCC_{pre} showed the strongest correlation (Pearson = 0.37, $P < 0.001$). In addition, there was a certain correlation between TD_{post} and SCC_{post}, between TV_{pre} and SCC_{pre}, between TV_{post} and SCC_{post}, and between TVRR and SCCRR (Fig. 3).
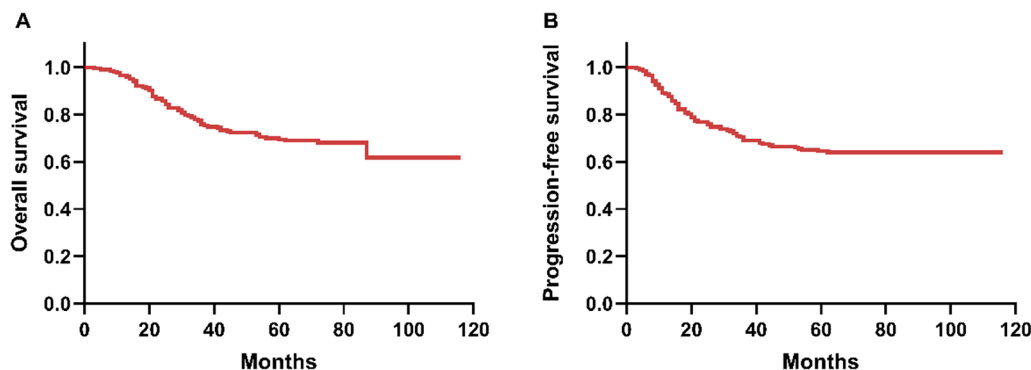

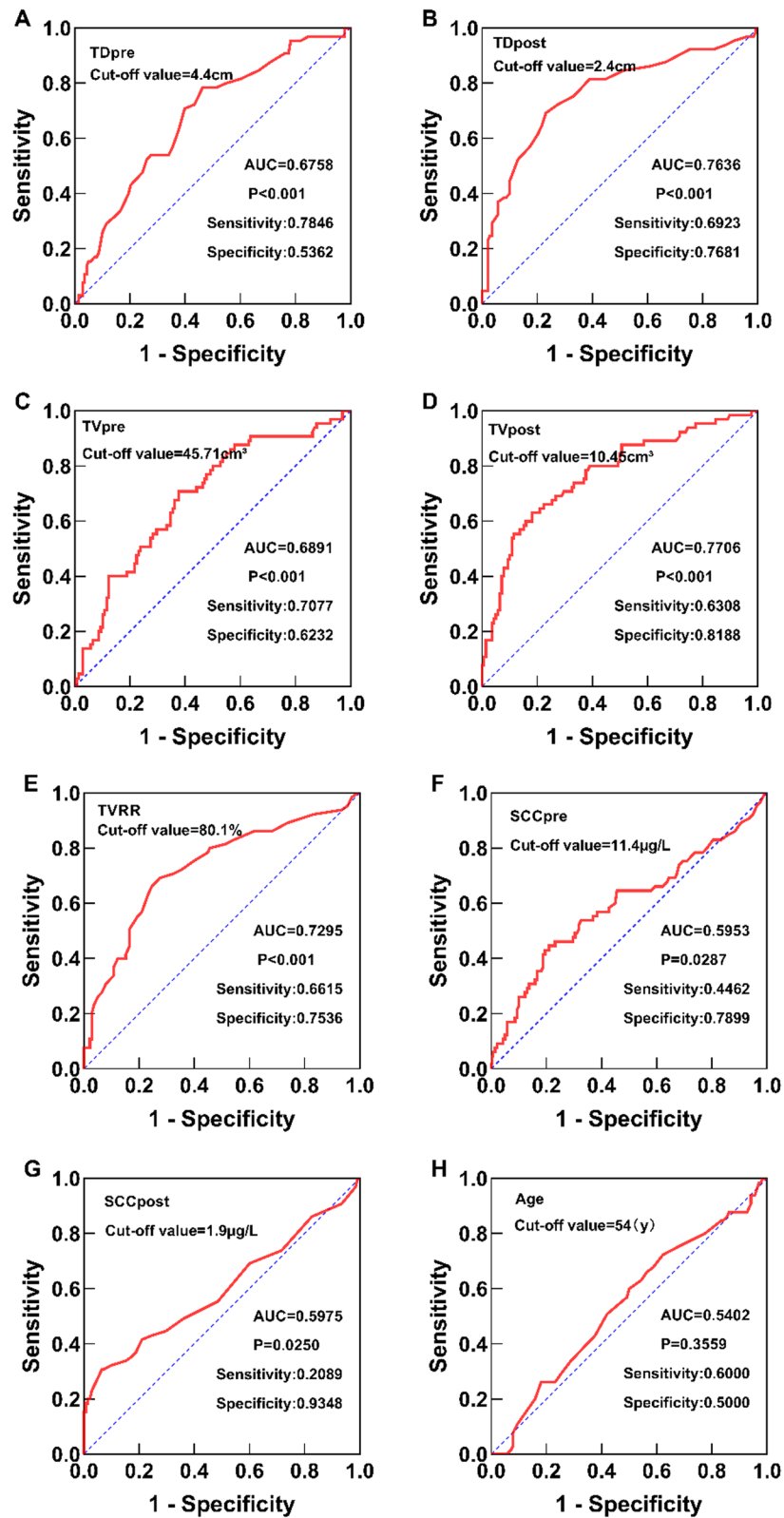**Fig. 1** Survival analysis. **a** Overall survival (OS) and **b** progression-free survival (PFS)

Fig. 2 Results of receiver operating characteristic (ROC) curve analysis: **a** TD$_{pre}$; **b** TD$_{post}$; **c** TV$_{pre}$; **d** TV$_{post}$; **e** TVRR; **f** SCC$_{pre}$; **g** SCC$_{post}$; **h** age

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 6 of 10

Table 2 Univariate analysis of OS and PFS

Variable	Univariate analysis			
	5-y OS (%)	P	5-y PFS (%)	P
Age (years)				
< 54	65.7	0.201	59.3	0.118
≥ 54	73.7		70.5	
FIGO stage				
≤ IIb	78.2	0.001	73.1	0.002
> IIb	57.1		52.4	
Infection				
Yes	33.3	< 0.001	33.3	0.001
No	72.3		67.0	
Anemia				
Yes	56.2	< 0.001	50.0	< 0.001
No	78.0		74.0	
Lymph node metastasis				
Yes	56.1	0.012	47.4	< 0.001
No	74.7		71.2	
TD_{pre}* (cm)				
≤ 4.4	84.1	< 0.001	80.7	< 0.001
> 4.4	58.3		52.2	
TV_{pre}* (cm^3)				
≤ 45.71	81.9	< 0.001	78.1	< 0.001
> 45.71	56.1		50.0	
TD_{post}* (cm)				
≤ 2.4	84.3	< 0.001	79.5	< 0.001
> 2.4	44.7		39.5	
TV_{post}* (cm^3)				
≤ 10.45	82.5	< 0.001	78.1	< 0.001
> 10.45	42.4		36.4	
TVRR* (%)				
< 80.1	46.2	< 0.001	41.0	< 0.001
≥ 80.1	84.0		79.2	
Radiotherapy				
IMRT	72.4	0.371	64.2	0.928
CRT	65.0		65.0	
Total dose of radiotherapy (Gy)				
≤ 84	71.0	0.783	62.6	0.497
> 84	67.7		66.7	
Number of chemotherapy cycles				
< 4	55.4	0.004	52.3	0.026
≥ 4	76.1		70.3	
SCC_{pre} (μg/L)				
≤ 11.4	75.2	0.001	73.1	< 0.001
> 11.4	55.2		43.1	
SCC_{post} (μg/L)				
≤ 1.9	75.3	< 0.001	70.6	< 0.001
> 1.9	34.5		17.4	
SCCRR (%)				
= 100	75.4	< 0.001	69.7	< 0.001
< 100	33.3		20.8	

Table 2 (continued)

*Radiological characteristics

Table 3 Multivariate analysis of OS and PFS

Variable		Multivariate analysis		
		HR	95% CI	P
OS	TD_{pre} (cm)	0.373	0.155–0.898	0.028
	≤ 4.4/ > 4.4			
	TD_{post} (cm)	0.376	0.198–0.715	0.003
	≤ 2.4/ > 2.4			
	SCC_{post} (μg/L)	0.374	0.207–0.677	0.001
	≤ 1.9/ > 1.9			
PFS	TVRR (%)	2.998	1.739–5.171	< 0.001
	< 80.1/ ≥ 80.1			
	SCC_{pre} (μg/L)	0.563	0.325–0.977	0.041
	≤ 11.4/ > 11.4			
	SCC_{post} (μg/L)	0.253	0.143–0.447	< 0.001
	≤ 1.9/ > 1.9			

Discussion

In this study, we investigated the prognostic value of tumor measurement parameters and SCC-Ag changes in patients with LACC. The study found that TD_{pre}, TD_{post}, TV_{pre}, TV_{post}, TVRR, SCC_{pre}, SCC_{post}, and SCCRR were all prognostic factors for CC. With the advances in imaging and radiotherapy technology, exploring the prognostic relevance of tumor diameter, volume, TVRR, and other measurement parameters in patients with cervical cancer is a key imperative. Lee et al. [17] conducted a retrospective study of 40 patients with CC. They found that pre-radiotherapy tumor volume > 55 cm^3, tumor diameter during radiotherapy > 4 cm, and TVRR < 90% groups showed significantly poor PFS (5-year PFS: 69.7% vs 94.4%; 47.1% vs 88.0%; 61.3 vs 93.3%, respectively; $P < 0.05$). Ryu et al. [19] found that pre-treatment and post-treatment SCC-Ag values can predict the therapeutic efficacy and survival outcomes of patients with CC. In their study, SCC_{pre} > 1.86 μg/L and SCC_{post} > 0.9 μg/L groups had a longer median disease-free survival (DFS) than the respective control groups (median DFS: 132 months vs 148.5 months and 108 months vs. 147.5 months, respectively). The findings of Lee et al. and Ryu et al. indicated the prognostic value of tumor volume-related parameters and SCC-Ag in patients with CC. Therefore, it is worth further exploring the prognostic relevance of these indices. We used the 3D Slicer software system to accurately measure and calculate the pre- and post-treatment tumor parameters of each patient. In addition, we collected the SCC_{pre} and SCC_{post}

Chen *et al. Radiation Oncology* (2022) 17:6

Page 7 of 10

Fig. 3 Results of correlation analysis: **a** Correlation between TD_{pre} and SCC_{pre}; **b** TD_{post} and SCC_{post}; **c** TV_{pre} and SCC_{pre}; **d** TV_{post} and SCC_{post}; **e** TVRR and SCCRR
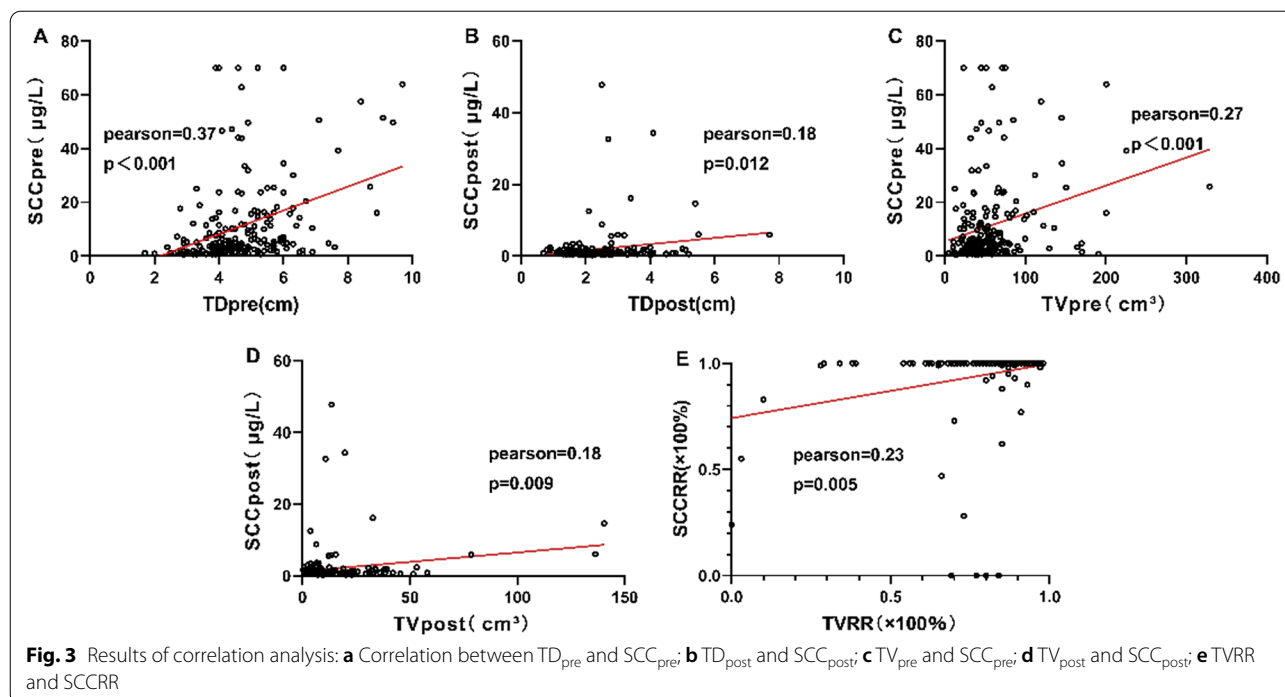
values of each patient and calculated the SCCRR. Statistical analysis provided more robust data to identify the relevant prognostic factors of CC in order to guide clinical treatment.

Studies have shown considerable inter-individual variability with respect to the initial pre-treatment tumor volume and post-treatment residual volume. Currently, the optimal values of tumor diameter, volume, and TVRR are not clear, and no studies have identified the best time-point to measure the related parameters during treatment [20]. In our study, we performed ROC curve analysis to determine the optimal cut-off values of tumor measurement parameters and SCC-Ag. After adjusting for age, stage, and other prognostic factors, we found that TD_{pre} and TD_{post} were independent predictors of OS, while TVRR was an independent predictor of PFS. In a multicenter study [21], $TD_{pre} > 6$ cm ($P = 0.0024$) was an independent prognostic factor for LACC. However, in our study, the optimal TD_{pre} cut-off value was 4.4 cm. We also found that patients with $TD_{pre} > 4.4$ cm had poorer 5-year OS and 5-year PFS rates (58.3% vs. 84.1% and 52.2% vs. 80.7%, respectively; $P < 0.001$). Despite the different cut-off values of the parameters selected in each study, TD_{pre} was identified as an important factor affecting the prognosis of CC. The current FIGO staging includes $TD_{pre} = 4$ cm as one of the staging standards for IB and IIA stages, which is similar to the optimal cut-off level identified in our study.

However, can we also determine the optimal TD_{post} cut-off value or reference range? In the study by Lee et al. [22], $TD_{post} = 1.8$ cm was identified as the optimal cut-off value on ROC curve analysis. The 5-year OS and PFS in the $TD_{post} \leq 1.8$ cm group and the control group was 96.2% vs 81.8% and 85.5% vs 58.8%, respectively ($P < 0.05$). In the present study, $TD_{post} = 2.4$ cm was the optimal cut-off value. The results suggest that patients with $TD_{post} \leq 2.4$ cm have better 5-year OS and PFS (84.3% vs 44.7% and 79.5 vs 39.5%, respectively; $P < 0.001$). Moreover, it was an independent predictor of OS.

In this study, TVRR was found to be an important determinant of OS and PFS. Moreover, it was an independent predictor of PFS. The optimal cut-off value of TVRR was 80.1%. The 5-year OS and PFS were significantly better in patients with $TVRR \geq 80.1\%$ (84% vs 46.2% and 79.2 vs 41%, respectively; $P < 0.001$). In the study by Lee et al. [23], TVRR was an independent predictor of OS (HR = 3.435, 95% CI 1.062–11.106, $P = 0.039$), and the 5-year OS rate in the TVRR > 87% group was significantly greater than that in the control group (96.5% vs 78%, $P = 0.0003$). Lee et al. [17] found that patients with $TVRR \geq 90\%$ had better 5-year PFS (93.3% vs 61.3%, $P = 0.031$). The differences in the study population and the analysis time-points do not permit a direct comparison of the results of various studies. Nonetheless, all studies have identified the prognostic relevance of TVRR in CC. The smaller the TVRR, the worse is the prognosis of patients. Therefore, we also discuss the

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 8 of 10

reasons why TVRR affects the prognosis of CC. Tewari et al. [22] found that chemotherapy can improve the tumor sensitivity to radiotherapy in patients undergoing concurrent chemoradiation, while radiotherapy further improves the local control rate. Some researchers found that the shrinkage of tumor after chemotherapy directly reflects the sensitivity of tumor cells to chemotherapy to a certain extent. Lack of obvious tumor shrinkage implies poor tumor control. In this setting, there is a likelihood of micrometastasis in the circulatory system, which may eventually lead to recurrence or metastasis [24–27].

In addition, we also assessed the prognostic value of SCC-Ag in patients with CC. SCC-Ag is used as one of the diagnostic markers for squamous cell carcinoma. SCC-Ag can be used to judge the prognosis of CC and predict the possibility of recurrence [15]. At present, the critical level for defining normal SCC-Ag is also different between different studies (≤ 1.5 μg/L vs ≤ 2.0 μg/L) [28, 29]. SCC-Ag cut-off value in our study was 2.0 μg/L. It should be noted that SCC-Ag often needs to be used in combination with other factors to evaluate the prognosis of CC. Choi et al. [11] retrospectively analyzed 304 patients with CC who received concurrent chemoradiation. They found that $SCC_{pre} = 4.0$ μg/L was the best cut-off value, and the results showed that the 3-year RFS rates (56.6% vs 80.2%, $P < 0.001$) and OS rates (72.1% vs 86.8%, $P = 0.005$) of patients with $SCC_{pre} \geq 4$ μg/L were significantly lower than those of patients with $SCC_{pre} < 4$ μg/L. In our study, the optimal cut-off value of SCC_{pre} was 11.4 μg/L, and Cox regression multivariate analysis identified SCC_{pre} as an independent predictor of PFS. In addition, we observed a significant positive correlation between SCCpre and TD_{pre} (Pearson = 0.37, $P < 0.001$). The results of this study also suggest that SCC_{pre} can be used to assess tumor burden and predict prognosis.

We believe that the SCC_{post} value may play an important role in the decision-making of follow-up treatment of CC [19, 30, 31]. Kawaguchi et al. [30] evaluated the SCC-Ag value at 1 month after treatment. They found that the prognosis of patients with $SCC_{post} < 1.15$ μg/L was significantly better than that of patients with SCCpost ≥ 1.15 μg/L (3-year OS: 90.7% vs 36.6%; 3-year PFS: 74.7% vs 19.5%, $P < 0.001$). Our study also identified SCC_{post} as an important factor affecting prognosis. The 5-year PFS in the $SCC_{post} \leq 1.9$ μg/L group and $SCC_{post} > 1.9$ μg/L group was 70.6% and 17.4%, respectively ($P < 0.001$). In the study by Ryu et al. [19], $SCC_{post} = 0.9$ μg/L was the optimal cut-off value for predicting tumor recurrence. SCC_{post} was an independent predictor of DFS. Although the best cut-off value of SCC_{post} was different in each study, all studies have identified the prognostic value of SCC_{post}; patients who had SCC_{post} higher than normal had poor prognosis.

In addition, we also found that the SCC-Ag of most patients with CC was significantly reduced after concurrent chemoradiation. Therefore, it is also very important to evaluate the predictive value of SCCRR for therapeutic efficacy. Markovina et al. [32] found that SCC-Ag gene knockout increased the radiosensitivity of CC cells cultured in vitro; this showed that SCCRR can indeed increase the radiotherapeutic efficacy. Therefore, many scholars believe that SCCRR can be used to predict the tumor response rate or survival of CC patients after receiving chemoradiation [17, 32]. In the study by Lee et al. [22], SCCRR showed an independent association with OS ($P = 0.003$); the 5-year OS of patients with SCCRR $\leq 93.3\%$ and SCCRR $> 93.3\%$ was 74.9% and 95.4%, respectively ($P < 0.0001$). We found that SCCRR was one of the prognostic factors influencing the OS and PFS of patients with LACC. Indeed, there was also a certain correlation between SCCRR and TVRR. However, since the correlation between SCCRR and TVRR was not very strong (Pearson = 0.23, $P = 0.005$), further studies are required to obtain more definitive evidence.

There are several limitations in this retrospective study. Firstly, the nature of a retrospective study certainly served as an inherited and fundamental limitation. Secondly, the study lacks of a verification cohort. Finally, we didn't perform the same prognostic analysis by subgroups stratifying by stage of disease.This will be the direction of our future research.

Conclusions

In this study, TD_{pre}, TD_{post}, and SCC_{post} were independent predictors of OS of patients with CC. TVRR, SCC_{pre}, and SCC_{post} were independent predictors of PFS. These tumor parameters and level of SCC-Ag were very good predictors of tumor response rate during treatment.

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 9 of 10

Declarations

Ethical approval and consent to participate
This study was approved by the medical ethical committee review board of the Fujian Cancer Hospital (No. SQ2020-080-01).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References

1. Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, Jhingran A, Kitchener HC, Mileshkin LR, Viswanathan AN, Gaffney DK. Cervical cancer: a global health crisis. Cancer. 2017;123(13):2404–12.
2. Shrivastava S, Mahantshetty U, Engineer R, Tongaonkar H, Kulkarni J, Dinshaw K. Treatment and outcome in cancer cervix patients treated between 1979 and 1994: a single institutional experience. J Cancer Res Ther. 2013;9(4):672–9.
3. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, Clark R, Cohn D, Crispens MA, Damast S, Dorigo O, Eifel PJ, Fisher CM, Frederick P, Gaffney DK, Han E, Huh WK, Lurain JR, Mariani A, Mutch D, Nagel C, Nekhlyudov L, Fader AN, Remmenga SW, Reynolds RK, Tillmanns T, Ueda S, Wyse E, Yashar CM, McMillian NR, Scavone JL. Cervical cancer, Version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw JNCCN. 2019;17(1):64–84.
4. Mazzola R, Ricchetti F, Fiorentino A, Levra NG, Fersino S, Di Paola G, Ruggieri R, Alongi F. Weekly cisplatin and volumetric-modulated arc therapy with simultaneous integrated boost for radical treatment of advanced cervical cancer in elderly patients: feasibility and clinical preliminary results. Technol Cancer Res Treat. 2017;16(3):310–5.
5. Luvero D, Plotti F, Aloisi A, Capriglione S, Ricciardi R, Miranda A, Lopez S, Scaletta G, De Luca G, Benedetti-Panici P, Angioli R. Patients treated with neoadjuvant chemotherapy + radical surgery + adjuvant chemotherapy in locally advanced cervical cancer: long-term outcomes, survival and prognostic factors in a single-center 10-year follow-up. Med Oncol (Northwood, London, England). 2016;33(10):110.
6. Rose PG, Java J, Whitney CW, Stehman FB, Lanciano R, Thomas GM, DiSilvestro PA. Nomograms predicting progression-free survival, overall survival, and pelvic recurrence in locally advanced cervical cancer developed from an analysis of identifiable prognostic factors in patients from NRG oncology/gynecologic oncology group randomized trials of chemoradiotherapy. J Clin Oncol. 2015;33(19):2136–42.
7. Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. Gynecol Oncol. 2004;93(2):458–64.
8. Eifel PJ. Problems with the clinical staging of carcinoma of the cervix. Semin Radiat Oncol. 1994;4(1):1–8.
9. Kovalic JJ, Perez CA, Grigsby PW, Lockett MA. The effect of volume of disease in patients with carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys. 1991;21(4):905–10.
10. Gadducci A, Tana R, Cosio S, Genazzani AR. The serum assay of tumour markers in the prognostic evaluation, treatment monitoring and follow-up of patients with cervical cancer: a review of the literature. Crit Rev Oncol Hematol. 2008;66(1):10–20.
11. Choi KH, Lee SW, Yu M, Jeong S, Lee JW, Lee JH. Significance of elevated SCC-Ag level on tumor recurrence and patient survival in patients with squamous-cell carcinoma of uterine cervix following definitive chemoradiotherapy: a multi-institutional analysis. J Gynecol Oncol. 2019;30(1):e1.
12. Jeong BK, Choi DH, Huh SJ, Park W, Bae DS, Kim BG. The role of squamous cell carcinoma antigen as a prognostic and predictive factor in carcinoma of uterine cervix. Radiat Oncol J. 2011;29(3):191–8.
13. Pras E, Willemse PH, Canrinus AA, de Bruijn HW, Sluiter WJ, ten Hoor KA, Aalders JG, Szabo BG, de Vries EG. Serum squamous cell carcinoma antigen and CYFRA 21–1 in cervical cancer treatment. Int J Radiat Oncol Biol Phys. 2002;52(1):23–32.
14. Verma J, Monk BJ, Wolfson AH. New strategies for multimodality therapy in treating locally advanced cervix cancer. Semin Radiat Oncol. 2016;26(4):344–8.
15. Xu F, Li Y, Fan L, Ma J, Yu L, Yi H, Chen X, Wei W, Wu P, Liang L, Hu H, Xing H, Wang W. Preoperative SCC-Ag and thrombocytosis as predictive markers for pelvic lymphatic metastasis of squamous cervical cancer in early FIGO stage. J Cancer. 2018;9(9):1660–6.
16. Salvatici M, Achilarre MT, Sandri MT, Boveri S, Vanna Z, Landoni F. Squamous cell carcinoma antigen (SCC-Ag) during follow-up of cervical cancer patients: role in the early diagnosis of recurrence. Gynecol Oncol. 2016;142(1):115–9.
17. Lee KC, Kim HJ, Sung K, Choi YE, Lee SH, Lim S, Lee KB, Shin JW, Park CY, Kim YS, Sym SJ, Shim YS, Choi SJ. The predictive value of tumor size, volume, and markers during radiation therapy in patients with cervical cancer. Int J Gynecol Cancer. 2017;27(1):123–30.
18. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin JC, Pujol S, Bauer C, Jennings D, Fennessy F, Sonka M, Buatti J, Aylward S, Miller JV, Pieper S, Kikinis R. 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging. 2012;30(9):1323–41.
19. Ryu HK, Baek JS, Kang WD, Kim SM. The prognostic value of squamous cell carcinoma antigen for predicting tumor recurrence in cervical squamous cell carcinoma patients. Obstet Gynecol Sci. 2015;58(5):368–76.
20. Wang JZ, Mayr NA, Zhang D, Li K, Grecula JC, Montebello JF, Lo SS, Yuh WT. Sequential magnetic resonance imaging of cervical cancer: the predictive value of absolute tumor volume and regression ratio measured before, during, and after radiation therapy. Cancer. 2010;116(21):5093–101.
21. Kyung MS, Kim HB, Seoung JY, Choi IY, Joo YS, Lee MY, Kang JB, Park YH. Tumor size and lymph node status determined by imaging are reliable factors for predicting advanced cervical cancer prognosis. Oncol Lett. 2015;9(5):2218–24.
22. Lee JH, Lee SW, Kim JR, Kim YS, Yoon MS, Jeong S, Kim JH, Lee JY, Eom KY, Jeong BK, Lee SH. Tumour size, volume, and marker expression during radiation therapy can predict survival of cervical cancer patients: a multi-institutional retrospective analysis of KROG 16–01. Gynecol Oncol. 2017;147(3):577–84.
23. Tewari KS, Monk BJ. Evidence-based treatment paradigms for management of invasive cervical carcinoma. J Clin Oncol. 2019;37(27):2472–89.
24. Du K, Huang Q, Bu J, Zhou J, Huang Z, Li J. Circulating tumor cells counting act as a potential prognostic factor in cervical cancer. Technol Cancer Res Treat. 2020;19:1533033820957005.
25. Zhang J, Shi H, Jiang T, Liu Z, Lin PP, Chen N. Circulating tumor cells with karyotyping as a novel biomarker for diagnosis and treatment of nasopharyngeal carcinoma. BMC Cancer. 2018;18(1):1133.
26. Okabe H, Tsunoda S, Hosogi H, Hisamori S, Tanaka E, Tanaka S, Sakai Y. Circulating tumor cells as an independent predictor of survival in advanced gastric cancer. Ann Surg Oncol. 2015;22(12):3954–61.
27. Hugenschmidt H, Labori KJ, Brunborg C, Verbeke CS, Seeberg LT, Schirmer CB, Renolen A, Borgen EF, Naume B, Wiedswang G. Circulating tumor cells are an independent predictor of shorter survival in patients undergoing resection for pancreatic and periampullary adenocarcinoma. Ann Surg. 2020;271(3):549–58.
28. Ohara K, Tanaka Y, Tsunoda H, Nishida M, Sugahara S, Itai Y. Assessment of cervical cancer radioresponse by serum squamous cell carcinoma antigen and magnetic resonance imaging. Obstet Gynecol. 2002;100(4):781–7.
29. Hong JH, Tsai CS, Wang CC, Lai CH, Chen WC, Lee SP, Chang TC, Tseng CJ. Comparison of clinical behaviors and responses to radiation between squamous cell carcinomas and adenocarcinomas/adenosquamous carcinomas of the cervix. Chang Gung Med J. 2000;23(7):396–404.
30. Kawaguchi R, Furukawa N, Kobayashi H, Asakawa I. Posttreatment cut-off levels of squamous cell carcinoma antigen as a prognostic factor in patients with locally advanced cervical cancer treated with radiotherapy. J Gynecol Oncol. 2013;24(4):313–20.
31. Charakorn C, Thadanipon K, Chaijindaratana S, Rattanasiri S, Numthavaj P, Thakkinstian A. The association between serum squamous cell carcinoma

Chen *et al. Radiation Oncology*   (2022) 17:6

Page 10 of 10

antigen and recurrence and survival of patients with cervical squamous cell carcinoma: a systematic review and meta-analysis. Gynecol Oncol. 2018;150(1):190–200.

32. Markovina S, Wang S, Henke LE, Luke CJ, Pak SC, DeWees T, Pfeifer JD, Schwarz JK, Liu W, Chen S, Mutch D, Wang X, Powell MA, Siegel BA, Dehdashti F, Silverman GA, Grigsby PW. Serum squamous cell carcinoma antigen as an early indicator of response during therapy of cervical cancer. Br J Cancer. 2018;118(1):72–8.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.