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

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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 (TDpre/post), tumor volume (TVpre/post), SCC-Ag (SCCpre/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, TDpre/post, TVpre/post, TVRR, SCCpre/post and SCCRR showed significant association with OS and PFS (P < 0.05). On multivariate analysis, TDpre [Hazard ratio (HR) = 0.373, P = 0.028], TDpost (HR = 0.376, P = 0.003) and SCCpost (HR = 0.374, P = 0.001) were independent predictors of OS. TVRR (HR = 2.998, P < 0.001), SCCpre (HR = 0.563, P = 0.041), and SCCpost (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: TDpre/post, TVpre/post, TVRR, SCCpre/post, and SCCRR were prognostic factors in LACC. TDpre/post and SCCpost showed the most significant prognostic value. TVRR and SCCpre/post 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
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 (TDpre, TDpost), and pre-treatment tumor volume (TVpre). Furthermore, the prognostic relevance of post-treatment tumor volume (TVpost) 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 (SCCpre), post-treatment SCC-Ag (SCCpost), 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. Pre-treatment 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. TDpre and TDpost were measured by the related software modules, and then the TVpre, TVpost, and TVRR were calculated by 3D Slicer.

\[ TVRR = \frac{TV_{post} - TV_{pre}}{TV_{pre}} \times 100\% \]

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 tolerate 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/m² or nedaplatin in combination with paclitaxel 135 mg/m².

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, TDpre, TVpre, TDpost, TVpost, TVRR, SCCpre and SCCpost 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 TDpre and TDpost in our cohort were 4.5 cm (range, 1.7–9.7) and 2.1 cm (0.7–7.7), respectively; the median TVpre and TVpost were 45.08 cm³ (range, 4.80–328.71) and 6.52 cm³ (0.41–140.45); the median TVRR was 0.84% (range, 0–0.98); the median SCCpre and SCCpost 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 TDpre and TDpost (based on the Youden index) was 4.4 cm and 2.4 cm, respectively. The optimal cut-off value of TVpre and TVpost was 45.71 cm³ and 10.45 cm³, respectively. The optimal cut-off value of TVRR was 80.1%. The optimal cut-off value for SCCpre and SCCpost 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, SCC RR, FIGO staging, lymph node

Table 1 Patient and tumor characteristics

| Characteristics | n | %   |
|-----------------|---|-----|
| Age (years)     |   |     |
| < 54            | 108| 53.2|
| ≥ 54            | 95 | 46.8|
| FIGO stage      |   |     |
| Ia              | 14 | 6.9 |
| Ib              | 105| 51.7|
| IIa             | 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|
| TDpre (cm)      |   |     |
| ≤ 4.4           | 88 | 43.3|
| > 4.4           | 115| 56.7|
| TVpre (cm³)     |   |     |
| ≤ 45.71         | 105| 51.7|
| > 45.71         | 98 | 48.3|
| TDpost (cm)     |   |     |
| ≤ 2.4           | 127| 62.6|
| > 2.4           | 76 | 37.4|
| TVpost (cm³)    |   |     |
| ≤ 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|
| SCCpre (µg/L)   |   |     |
| ≤ 11.4          | 145| 71.4|
| > 11.4          | 58 | 28.6|
| SCCpost (µg/L)  |   |     |
| ≤ 1.9           | 180| 88.7|
| > 1.9           | 23 | 11.3|
| SCCRR (%)       |   |     |
| = 100           | 122| 60.1|
| < 100           | 24 | 11.8|

*Radiological characteristics
metastasis, and chemotherapy cycles all showed a significant association with OS ($P<0.05$). The 5-year OS rate in the TD$\text{pre} \leq 4.4$ cm group was significantly greater than that in the TD$\text{pre} > 4.4$ cm group (84.1% vs 58.3%, $P<0.001$). The 5-year OS rate in the TV$\text{pre} \leq 45.71$ cm$^3$ group was significantly greater than that in the TV$\text{pre} > 45.71$ cm$^3$ group (81.9% vs 56.1%, $P<0.001$). The 5-year OS rate in the TD$\text{post} \leq 2.4$ cm group and TD$\text{post} > 2.4$ cm group was 82.5% and 44.7%, respectively ($P<0.001$). The 5-year OS rate in the TV$\text{post} \leq 10.45$ cm$^3$ group and TV$\text{post} > 10.45$ cm$^3$ group was 81.9% and 56.1%, respectively ($P<0.001$). The 5-year OS rate 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$\text{pre} \leq 11.4$ μg/L group and SCC$\text{pre} > 11.4$ μg/L group was 75.2% and 55.2%, respectively ($P=0.001$). The 5-year OS rate in the SCC$\text{post} \leq 1.9$ μg/L group and SCC$\text{post} > 1.9$ μg/L was 75.3% and 34.5%, respectively ($P<0.001$). The 5-year OS rate 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$\text{pre}$, TD$\text{post}$, and SCC$\text{post}$ were identified as independent predictors of OS. The OS of patients with TD$\text{pre} \leq 4.4$ 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$\text{post} \leq 2.4$ 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$\text{post} \leq 1.9$ 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$\text{pre} \leq 4.4$ cm group showed a significantly better 5-year PFS rate than TD$\text{pre} > 4.4$ cm group (80.7% vs 52.2%, $P<0.001$). TV$\text{pre} \leq 45.71$ cm$^3$ group had better 5-year PFS than TV$\text{pre} > 45.71$ cm$^3$ group (78.1% vs 50.0%, $P<0.001$). The 5-year PFS of TD$\text{post} \leq 2.4$ cm group and TD$\text{post} > 2.4$ cm group were 79.5% and 39.5%, respectively ($P<0.001$). The 5-year PFS of TV$\text{post} \leq 10.45$ cm$^3$ group and TV$\text{post} > 10.45$ 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$\text{pre} \leq 11.4$ μg/L group and SCC$\text{pre} > 11.4$ μg/L group was 73.1% and 43.1%, respectively ($P<0.001$). The 5-year PFS of SCC$\text{post} \leq 1.9$ μg/L group and SCC$\text{post} > 1.9$ 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$\text{pre}$, and SCC$\text{post}$ 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$\text{pre} \leq 11.4$ μg/L was significantly better than that of patients with SCC$\text{pre} > 11.4$ μg/L (HR = 0.563, 95% CI 0.325–0.977, $P=0.041$). The PFS of patients with SCC$\text{post} \leq 1.9$ μg/L was also better than that of patients with SCC$\text{post} > 1.9$ 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$\text{pre}$ and SCC$\text{pre}$ showed the strongest correlation (Pearson = 0.37, $P<0.001$). In addition, there was a certain correlation between TD$\text{post}$ and SCC$\text{post}$, between TV$\text{pre}$ and SCC$\text{pre}$, between TV$\text{post}$ and SCC$\text{post}$, and between TVRR and SCCRR (Fig. 3).
Fig. 2 Results of receiver operating characteristic (ROC) curve analysis: a TD\textsubscript{pre} b TD\textsubscript{post} c TV\textsubscript{pre} d TV\textsubscript{post} e TVRR f SCC\textsubscript{pre} g SCC\textsubscript{post} h age
In this study, we investigated the prognostic value of tumor measurement parameters and SCC-Ag changes in patients with LACC. The study found that TDpre, TDpost, TVpre, TVpost, TVRR, SCCpre, SCCpost, 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 cm³, 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, SCCpre > 1.86 µg/L and SCCpost > 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 SCCpre and SCCpost

Table 2 (continued)

Table 2  Univariate analysis of OS and PFS

| Variable               | Univariate analysis | Univariate analysis | Univariate analysis |
|------------------------|---------------------|---------------------|---------------------|
|                        | 5-y OS (%)          | P                   | 5-y PFS (%)         | P                   |
| Age (years)            |                     |                     |                     |
| < 54                   | 65.7                | 0.201               | 59.3                | 0.118               |
| ≥ 54                   | 73.7                | 0.201               | 70.5                | 0.201               |
| FIGO stage             |                     |                     |                     |
| ≤ IIb                  | 78.2                | 0.001               | 73.1                | 0.002               |
| > IIb                  | 57.1                | 0.001               | 52.4                | 0.001               |
| Infection              |                     |                     |                     |
| Yes                    | 33.3                | <0.001              | 33.3                | 0.001               |
| No                     | 72.3                | 67.0                | 50.0                | 0.001               |
| Anemia                 |                     |                     |                     |
| Yes                    | 56.2                | <0.001              | 50.0                | <0.001              |
| No                     | 78.0                | 74.0                | 52.2                | 0.001               |
| Lymph node metastasis  |                     |                     |                     |
| Yes                    | 56.1                | 0.012               | 47.4                | <0.001              |
| No                     | 74.7                | 71.2                | 78.1                | <0.001              |
| TDpre* (cm)            |                     |                     |                     |
| ≤ 4.4                  | 84.1                | <0.001              | 80.7                | <0.001              |
| > 4.4                  | 58.3                | 6.6                 | 6.6                 | 0.001               |
| TVpre* (cm³)           |                     |                     |                     |
| ≤ 45.71                | 81.9                | <0.001              | 78.1                | <0.001              |
| > 45.71                | 56.1                | 4.0                 | 50.0                | 0.001               |
| TDpost* (cm)           |                     |                     |                     |
| ≤ 2.4                  | 84.3                | <0.001              | 79.5                | <0.001              |
| > 2.4                  | 44.7                | 3.9                 | 79.5                | <0.001              |
| TVpost* (cm³)          |                     |                     |                     |
| ≤ 10.45                | 82.5                | <0.001              | 78.1                | <0.001              |
| > 10.45                | 42.4                | 4.0                 | 78.1                | <0.001              |
| TVRR* (%)              |                     |                     |                     |
| ≤ 80.1                 | 46.2                | <0.001              | 41.0                | <0.001              |
| > 80.1                 | 84.0                | 79.2                | 79.2                | <0.001              |
| 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                |
| SCCpre (µg/L)          |                     |                     |                     |
| ≤ 11.4                 | 75.2                | 0.001               | 73.1                | <0.001              |
| > 11.4                 | 55.2                | 43.1                |
| SCCpost (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                | 20.8                | 0.001               |

Table 3  Multivariate analysis of OS and PFS

| Variable               | Multivariate analysis | Multivariate analysis | Multivariate analysis | Multivariate analysis | Multivariate analysis | Multivariate analysis |
|------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|                        | HR 95% CI             | P                     |
| OS                     |                       |                       |
| TDpre (cm)             | 0.373 0.155–0.898     | 0.028                 |
| TDpost (cm)            | 0.376 0.198–0.715     | 0.003                 |
| SCCpre (µg/L)          | 0.374 0.207–0.677     | 0.001                 |
| TVRR (%)               | 2.998 1.739–5.171     | <0.001                |
| SCCpre (µg/L)          | 0.563 0.325–0.977     | 0.041                 |
| SCCpost (µg/L)         | 0.253 0.143–0.447     | <0.001                |

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 TDpre, TDpost, TVpre, TVpost, TVRR, SCCpre, SCCpost, 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 cm³, 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, SCCpre > 1.86 µg/L and SCCpost > 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 SCCpre and SCCpost.
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\textsubscript{pre} and TD\textsubscript{post} were independent predictors of OS, while TVRR was an independent predictor of PFS. In a multicenter study [21], TD\textsubscript{pre} > 6 cm (P=0.0024) was an independent prognostic factor for LACC. However, in our study, the optimal TD\textsubscript{pre} cut-off value was 4.4 cm. We also found that patients with TD\textsubscript{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\textsubscript{pre} was identified as an important factor affecting the prognosis of CC. The current FIGO staging includes TD\textsubscript{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\textsubscript{post} cut-off value or reference range? In the study by Lee et al. [22], TD\textsubscript{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\textsubscript{post} ≤ 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\textsubscript{post} = 2.4 cm was the optimal cut-off value. The results suggest that patients with TD\textsubscript{post} ≤ 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 ≥ 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 ≥ 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

Fig. 3 Results of correlation analysis: a Correlation between TD\textsubscript{pre} and SCC\textsubscript{pre}; b TD\textsubscript{post} and SCC\textsubscript{post}; c TV\textsubscript{pre} and SCC\textsubscript{pre}; d TV\textsubscript{post} and SCC\textsubscript{post}; e TVRR and SCCRR
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 SCCpre = 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 SCCpre ≥ 4 µg/L were significantly lower than those of patients with SCCpre < 4 µg/L. In our study, the optimal cut-off value of SCCpre was 11.4 µg/L, and Cox regression multivariate analysis identified SCCpre as an independent predictor of PFS. In addition, we observed a significant positive correlation between SCCpre and TDpre (Pearson = 0.37, P < 0.001). The results of this study also suggest that SCCpre can be used to assess tumor burden and predict prognosis.

We believe that the SCCpost 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 SCCpost < 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 SCCpost as an important factor affecting prognosis. The 5-year PFS in the SCCpost ≤ 1.9 µg/L group and SCCpost ≥ 1.9 µg/L group was 70.6% and 17.4%, respectively (P < 0.001). In the study by Ryu et al. [19], SCCpost = 0.9 µg/L was the optimal cut-off value for predicting tumor recurrence. SCCpost was an independent predictor of DFS. Although the best cut-off value of SCCpost was different in each study, all studies have identified the prognostic value of SCCpost: patients who had SCCpost 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 ≤ 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, TDpre, TDpost, and SCCpost were independent predictors of OS of patients with CC. TVRR, SCCpre, and SCCpost were independent predictors of PFS. These tumor parameters and level of SCC-Ag were very good predictors of tumor response rate during treatment.

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**Authors’ contributions**

WJ wrote the manuscript and performed procedures; SY drafted conception and wrote the manuscript; XY, XIE and HM contributed to writing the manuscript and performing data analysis; YJ and XY XIA contributed to drafting conception and data analysis; PG contributed to drafting conception, writing the manuscript and design. All authors read and approved the final manuscript.

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**Availability of data and materials**

The data used or analyzed during the current study are available from the corresponding author on reasonable request.
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.

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