High expression of survivin predicts poor prognosis in cervical squamous cell carcinoma treated with paclitaxel and carboplatin

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Abstract

Lack of effective biomarkers is one of the challenges in current neoadjuvant chemotherapy to predict drug response and sensitivity of cervical squamous cell carcinoma (CSCC). The present study was designed to investigate the correlation of the expression of survivin, an inhibitor of apoptosis with the prognosis of CSCC patients undergoing neoadjuvant chemotherapy.

A total of 117 CSCC patients treated with paclitaxel and carboplatin between May 2015 and April 2017 in the Second Hospital of Lanzhou University were retrospectively analyzed. The pathologic diagnosis and classification of CSCC were based on the Guidelines of the International Federation of Gynaecology and Obstetrics (FIGO). The efficacy was defined as complete remission (CR), partial remission (PR), and stability disease (SD). The expressions of survivin, vascular endothelial growth factor (VEGF), and Ki67 were determined with immunohistochemistry. Data were analyzed with SPSS software.

Univariate analysis showed that survivin expression had no correlation with ages, FIGO stage, macroscopic type, lymphovascular invasion, depth of lymphovascular invasion, lymph node metastasis, and tumor size among 117 CSCC patients. However, survivin expression was positively correlated with pathological grade (R=0.691, P<.001). Multivariate analysis revealed that survivin expression was independently correlated with grades (R<.001). In addition, the analysis of correlation indicated that survivin expression is positively correlated with VEGF expression (R=0.820, P<.001) and Ki67 expression (R=0.673, P<.001). The numbers (percentages) of complete remission (CR), partial remission (PR), and stability disease (SD) were 11 (9.4%), 91 (77.8%), and 15 (12.8%) respectively after the treatment of paclitaxel and carboplatin. Univariate analysis showed that efficacy of treatment was negatively correlated with pathological grade (R=0.513, P<.001), Ki67 expression (R=0.586, P<.001), VEGF expression (R=0.476, P<.001) and survivin expression (R=0.519, P<.001). Multivariate analysis revealed that efficacy of treatment was independently correlated with grades (R=.028), Ki67 (P<.001), and survivin expression (P=.015).

The results suggested that survivin expression is negatively correlated with the prognosis of CSCC patients treated with paclitaxel and carboplatin. Therefore, survivin expression might be a marker for prognosis in CSCC following neoadjuvant chemotherapy.

Abbreviations: AUC = area under curve, CR = complete remission, CSCC = cervical squamous cell carcinoma, FIGO = International Federation of Obstetrics and Gynecology, IgG = immunoglobulin G, PD = progress disease, PR = partial remission, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stability disease, SP = streptavidin-peroxidase, TVS = transvaginal ultrasound, VEGF = vascular endothelial growth factor.

Keywords: carboplatin, cervical squamous cell carcinoma, efficacy, paclitaxel, survivin

1. Introduction

Cervical cancer is the second most common malignant tumor in women worldwide, and the second most common cause of cancer-related death in women.[1,2] The International Federation of Obstetrics and Gynecology (FIGO) reported that although surgical techniques, radiotherapy equipment, and techniques have been greatly improved and developed, the survival rate of cervical cancer has not improved since 1950, and the overall 5-year survival rate keeps around 40%.[3] There are 2 clinical variants including cervical squamous cell carcinomas (CSCC) occupying 85% to 90% and adenocarcinoma carcinomas comprising 10% to 15% of cases.[4] In recent years, with the rapid development of basic and clinical research of tumor chemotherapy, chemotherapy has exerted good effect on cervical cancer. Paclitaxel is a new anti-tumor drug, which acts on G2/M phase of tumor cells, promotes tubulin polymerization, inhibits its depolymerization, and finally forms stable non-functional microtubules, thus inhibiting the mitosis of tumor cells and promoting apoptosis of tumor cells.[5] Frei et al[6] proposed and began the first neoadjuvant chemotherapy including paclitaxel for cervical cancer in 1982. Several studies have showed that neoadjuvant chemotherapy has a good therapeutic effect on high-risk cervical cancer with adverse prognostic factors, that is, locally advanced cervical cancer, stage Ib2–Ia2 massive cervical cancer, and early parametrial invasion of stage IIb.[6–9] Neoadjuvant chemotherapy can reduce the size of local tumor,
decrease the degree of parauterine invasion, and improve the surgical resection rate. However, neoadjuvant chemotherapy may delay the time of radical surgery or radiotherapy for CSCC patients if the curative effect is unsatisfactory. How to predict chemosensitivity and evaluate efficacy and to avoid delays in surgery and radiotherapy is critically important.

Survivin is a microtubule-binding inhibitor of apoptosis protein.\(^\text{[10]}\) The specific expression of survivin in G2/M phase blocks cell apoptosis caused by apoptosis genes and chemotherapy drugs mainly through direct or indirect inhibition of the activation of apoptosis-effector protease caspase-3, caspase-7.\(^\text{[6]}\) Survivin can be detected in most human tumors, and the high expression of survivin is closely related to poor prognosis of cervical cancer and resistance to chemotherapy.\(^\text{[10–12]}\) Study has shown that survivin can bind to the caspase activator released by tumor cells during chemotherapy of paclitaxel, thereby blocking the binding of the latter to apoptosis inhibitors, and thus inhibiting cell apoptosis.\(^\text{[13]}\) It can be speculated that the expression of survivin may be closely related to the resistance mechanism of paclitaxel to CSCC.

The present study was designed to investigate the correlation of the expressions of survivin with the prognosis of CSCC patients treated with paclitaxel and carboplatin.

## 2. Materials and methods

### 2.1. Patients and specimens

All 117 CSCC specimens and relevant clinical data were obtained from the Department of Gynaecology, the Second Hospital of Lanzhou University (Lanzhou, China), between May 2015 and April 2017. Tumor tissues were collected during the cervical biopsy. The size of tumor was measured by transvaginal ultrasound (TVS). All patients were diagnosed with locally advanced CSCC with tumor size of >4cm and were not treated with chemotherapy or radiotherapy before neoadjuvant chemotherapy. Clinicopathological characteristics of the patients are summarized in Table 1. All specimens included in this study were classified as squamous cell carcinoma by the experienced pathologists. The histological classification and grading were performed according to FIGO and World Health Organization histological grading criteria, respectively. This study was approved by the Review Board of the Second Hospital of Lanzhou University. Written informed consent was obtained from each participant.

### 2.2. Treatment protocol

All patients received 3 courses (interval time: 21 days) of intravenous drip infusion of paclitaxel (135–175 mg/m²) and carboplatin (area under curve, AUC=4–5) for 3 weeks. Two weeks after the end of chemotherapy, all patients received radical hysterectomy accompanied with pelvic lymphadenectomy surgery.

### Table 1

Demographic and clinicopathologic characteristics in patients with CSCC.

| Variables                      | No. of cases | % of cases |
|-------------------------------|--------------|------------|
| Ages                          |              |            |
| <45                           | 51           | 43.6       |
| ≥45                           | 66           | 56.4       |
| FIGO stage                    |              |            |
| Ib2                           | 53           | 45.3       |
| Ia2                           | 64           | 54.7       |
| Macroscopic types             |              |            |
| Cervical canal type           | 13           | 11.1       |
| Ulcerative type               | 15           | 12.8       |
| Endophytic type               | 22           | 18.8       |
| Exogenous type                | 67           | 57.3       |
| Grades                        |              |            |
| G1                            | 41           | 35.0       |
| G2                            | 56           | 47.9       |
| G3                            | 20           | 17.1       |
| Lymphovascular invasion       |              |            |
| Absence                       | 68           | 58.1       |
| Presence                      | 49           | 41.9       |
| Depth of lymphovascular invasion |           |            |
| <1/2                          | 80           | 68.4       |
| ≥1/2                          | 37           | 31.6       |
| Lymph node metastasis         |              |            |
| Absence                       | 61           | 52.1       |
| Presence                      | 56           | 47.9       |
| Tumor size, cm (mean, SD)     | 5.8          | 0.7        |

CSCC = cervical squamous cell carcinoma, FIGO = International Federation of Obstetrics and Gynecology.
2.3. Efficacy evaluation

The clinical efficacy was evaluated 2 weeks after the end of chemotherapy according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.[14] Briefly, complete remission (CR) is defined as the complete disappearance of visible lesions with tumor size of zero under TVS after the chemotherapy; partial remission (PR) is defined as that the products of maximum diameter and maximum vertical transverse diameter of the tumor after the chemotherapy are decreased by at least 30% compared with that before chemotherapy; stability disease (SD) is defined as that the aforementioned products are increased by at most 20% or decreased by at most 30% respectively; and progress disease (PD) is defined as that the aforementioned products are increased by at least 20% or that new tumor appears.

2.4. Immunohistochemistry

The expression of Ki67, survivin, and vascular endothelial growth factor (VEGF) in CSCC tissues was detected using immunohistochemistry streptavidin-perosidase (SP) method as described previously.[15] Briefly, the tissues were embedded in paraffin using standard histological procedures, incubated with primary antibodies against human Ki67, survivin, and VEGF (dilution 1:1000). After washing with PBS, sections were incubated with horseradish peroxidase (HRP) labeled IgG (1:500) secondary antibody. Diaminobenzidine (DAB) substrate kits were used to reveal the immunohistochemical reaction followed by staining with hematoxylin (HE).

The positive cells expressed as brown-yellow particles in the cytoplasm and/or nucleus after staining. A combination of the rate of the positive cells in similar cells and tinctorial strength of the positive cells was taken into consideration. Semiquantitative method was applied to estimate the results. Positive intensity was divided into 4 scales based on the degree of coloration: no coloration (negative, 0 point), light yellow (weak positive, 1 point), brown-yellow (moderate positive, 2 points), and chocolate brown (strong positive, 3 points). Other scores were based on the proportion of the positive cells: <5% (0 point), 5%–25% (1 point), 26%–50% (2 points), 51%–75% (3 points), and >75% (4 points). The comprehensive evaluation was calculated by 2 kinds of scales: 0 point is negative (−); 1 to 4 points are regarded as weak positive (+); 5 to 8 points are taken as moderate positive (++); 9 to 12 points are recognized as strong positive (++++).

2.5. Statistical analysis

Statistical analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL). The difference was compared between groups by using the Student t test for continuous variables and the chi-square test for categorical variables. Spearman rank-correlation test (α = 0.05, 2 side) was used to analyze the correlation. P < .05 was used for determining the significance.

3. Results

3.1. Demographic and clinicopathologic characteristics in patients with CSCC

As shown in Table 1, 51 (43.6%) cases were <45 years old among 117 CSCC patients. There were 53 (45.3%) cases of FIGO stage Ib2 and 64 (54.7%) of stage Ia2, respectively. The percentages of different macroscopic types are 11.1%, 12.8%, 18.8%, and 57.3% for cervical canal type, ulcerative type, endophytic type, and exogenous type, respectively. In addition, 41 (35.0%) cases were classified as grade 1, 56 (47.9%) cases as grade 2, and 20 (17.1%) cases as grade 3, respectively. Sixty eight (58.1%) cases had no lymphovascular invasion and 80 (68.4%) cases had 1/2 in depth of lymphovascular invasion. Sixty one (52.1%) cases had lymph node metastasis. The mean tumor size of CSCC was 5.8 cm.

3.2. Correlation of survivin expression with demographic and clinicopathologic characteristics in patients with CSCC

Univariate analysis showed that survivin expression had no correlation with ages, stage, macroscopic type, lymphovascular invasion, depth of lymphovascular invasion, lymph node metastasis, and tumor size (Table 2). However, survivin expression was positively correlated with pathological grade ($\chi^2=74.924, P<.001$). Multivariate analysis revealed that survivin expression was independently correlated with grades ($\chi^2=82.976, P<.001$) (Table 3).

3.3. Expressions and correlation between survivin and VEGF in patients with CSCC

Among 117 CSCC patients, the negative (−) expression of survivin was found in 26 (22.2%) cases (Table 4). The weak positive (+) expression of survivin was in 27 (23.1%) cases, moderate positive (+++) in 28 (23.9%) cases, and strong positive (++++) in 36 (30.8%) cases (Fig. 1). Regarding VEGF expression, the cases were 6 (5.1%), 40 (34.2), 37 (31.6%), and 34 (29.1) for negative, weak positive, moderate positive, and strong positive, respectively. As shown in Table 4, for 26 cases with negative expression of survivin, 3 (11.5%) and 23 (88.5%) indicated negative and weak positive expression of VEGF, respectively. However, for 36 cases with strong positive expression of survivin, 8 (22.2%) and 28 (77.8%) indicated moderate and strong positive expression of VEGF, respectively. The analysis of correlation indicated that survivin expression is positively correlated with VEGF expression ($\chi^2=111.491, P<.001$; $R=0.820, P<.001$).

3.4. Correlation between survivin and Ki67 in patients with CSCC

With increases in survivin expression from negative to strong positive expression, the expression of Ki67 were increased from 37.7%, 46.7%, 61.4% to 67.5% (Table 5). The analysis of correlation indicated that survivin expression is positively correlated with Ki67 expression ($F=32.433, P<.001$; $R=0.673, P<.001$).

3.5. Efficacy of treatment with paclitaxel and carboplatin in patients with CSCC

Among 117 patients with CSCC, the numbers (percentages) of CR, PR, and SD were 11 (9.4%), 91 (77.8%), and 15 (12.8%) respectively after the treatment of paclitaxel and carboplatin (Table 6).

3.6. Correlation of efficacy of treatment with demographic and clinicopathologic characteristics and expressions of Ki67, VEGF and survivin patients with CSCC

Univariate analysis showed that efficacy of treatment had no correlation with ages, stage, macroscopic type, lymphovascular...
invasion, depth of lymphovascular invasion, lymph node metastasis, and tumor size (Table 7). However, efficacy of treatment was negatively correlated with pathological grade ($\chi^2 = 40.920, P < .001; R = .513, P < .001$), Ki67 expression ($\chi^2 = 30.232, P < .001; R = .586, P < .001$), VEGF expression ($\chi^2 = 30.458, P < .001; R = .476, P < .001$), and survivin expression ($\chi^2 = 44.119, P < .001; R = .519, P < .001$). Multivariate analysis revealed that efficacy of treatment was independently correlated with grades ($\chi^2 = 10.484, P = .028$), Ki67 ($\chi^2 = 19.973, P < .001$), and survivin expression grades ($\chi^2 = 15.555, P = .015$) (Table 8).

4. Discussion
The present study indicated that survivin expression is negatively correlated with the prognosis of patients with CSCC treated with paclitaxel and carboplatin. Therefore, survivin expression might be a marker for prognosis in CSCC following neoadjuvant chemotherapy.

It has been recently reported that in a phase II nonrandomized study, the clinical responses of locally advanced cervical cancer to neoadjuvant chemotherapy (paclitaxel 80 mg/m², carboplatin AUC 2) were 5 (11.1%), 34 (75.5%), 5 (11.1%), and 1 (2.2%) for CR, PR, SD, and PD, respectively.[3] Another prospective multicenter phase II trial (paclitaxel 80 mg/m², cisplatin 75 mg/m²) study has been revealed that the clinical outcomes of the locally advanced cervical cancer to the treatment was 17 (34.0%), 30 (58%), and 3 (6%) for CR, PR, and SD, respectively.[16] Similarly, the present study found that the numbers (percentages) of CR, PR, and SD were 11 (9.4%), 91 (77.8%), and 15 (12.8%), respectively after the treatment of paclitaxel and carboplatin. Taken together, the aforementioned

### Table 2
Univariate analysis of correlation between survivin expression with clinicopathologic characteristics in CSCC.

| Variables                  | – | + | ++ | +++ | $\chi^2$ or $F$ | $P$ | Pearson $R$ | $P$ |
|----------------------------|---|---|----|-----|----------------|-----|-----------|-----|
| Ages $<45$                 | 9 (34.9) | 15 (55.6) | 12 (42.9) | 15 (41.7) | 2.484 | .478 | –.011 | .904 |
| $\geq 45$                  | 17 (65.4) | 12 (44.4) | 16 (57.1) | 21 (58.3) | 2.987 | .394 | –.008 | .294 |
| FIGO stage                 |   |   |    |     | 9.525 | .390 | .076 | .417 |
| Ib2                        | 8 (30.8) | 14 (51.9) | 14 (60.0) | 17 (47.2) | 74.924 | .<.001 | 0.691 | <.001 |
| Iia2                       | 18 (69.2) | 13 (48.1) | 14 (60.0) | 19 (52.8) | 5.022 | .170 | –.230 | .808 |
| Macroscopic types          |   |   |    |     | 12.458 | .230 | –.001 | .371 |
| Cervical canal type        | 5 (19.2) | 2 (7.4) | 5 (17.9) | 1 (2.8) | 5.972 | .320 | –.100 | .225 |
| Ulcerative type            | 2 (7.7) | 2 (7.4) | 4 (14.3) | 7 (19.4) | 2.753 | .034 | –.001 | .743 |
| Endophytic type            | 6 (23.1) | 6 (22.2) | 5 (17.9) | 5 (13.9) | 4.753 | .094 | –.006 | .371 |
| Exogenous type             | 13 (50.0) | 17 (63.0) | 14 (60.0) | 23 (63.9) | 7.253 | .064 | .031 | .743 |
| Grades                     |   |   |    |     | 3.085 | .001 | –.220 | .100 |
| G1                         | 25 (96.2) | 10 (37.0) | 4 (14.3) | 2 (5.6) | 5.022 | .170 | –.230 | .808 |
| G2                         | 1 (3.8) | 16 (59.3) | 20 (71.4) | 19 (52.8) | 4.753 | .094 | –.006 | .371 |
| G3                         | 0 (0) | 1 (3.7) | 4 (14.3) | 15 (41.7) | 2.753 | .034 | –.001 | .743 |
| Lymphovascular invasion    |   |   |    |     | 3.153 | .369 | –.001 | .371 |
| Absence                    | 19 (73.1) | 13 (48.1) | 12 (42.9) | 24 (66.7) | 5.022 | .170 | –.230 | .808 |
| Presence                   | 7 (26.9) | 14 (51.9) | 16 (57.1) | 12 (33.3) | 4.753 | .094 | –.006 | .371 |
| Depth of lymphovascular invasion |   |   |    |     | 11.710 | .379 | –.001 | .371 |
| <1/2                       | 20 (76.9) | 16 (59.3) | 16 (57.1) | 28 (77.8) | 6.249 | .100 | .225 | .100 |
| ≥1/2                       | 6 (23.1) | 11 (40.7) | 12 (42.9) | 8 (22.2) | 5.022 | .170 | –.230 | .808 |
| Lymph node metastasis      |   |   |    |     | 0.972 | .379 | –.001 | .371 |
| Absence                    | 17 (65.4) | 11 (40.7) | 11 (39.3) | 22 (61.1) | 0.972 | .379 | –.001 | .371 |
| Presence                   | 9 (34.6) | 16 (59.3) | 17 (60.7) | 14 (38.9) | 0.972 | .379 | –.001 | .371 |
| Tumor size, cm (mean, SD)  |   |   |    |     | 36.8 (2.9) | 36.2 (2.2) | 38.4 (3.1) | 39.3 (3.5) |

CSCC = cervical squamous cell carcinoma, FIGO = International Federation of Obstetrics and Gynecology.

### Table 3
Multivariate analysis of correlation between survivin expression with clinicopathologic characteristics in CSCC.

| Variables                  | $\chi^2$ | $P$ |
|----------------------------|----------|-----|
| Ages $<45$                 | 2.261    | .520 |
| $\geq 45$                  | 3.085    | .379 |
| FIGO stage                 | 11.710   | .230 |
| Grades                     | 82.976   | <.001 |
| Lymphovascular invasion    | 3.153    | .369 |
| Depth of lymphovascular invasion | 1.116 | .773 |
| Lymph node metastasis      | 0.972    | .808 |
| Tumor size, cm (mean, SD)  | 2.678    | .444 |

CSCC = cervical squamous cell carcinoma, FIGO = International Federation of Obstetrics and Gynecology.

### Table 4
Expressions of survivin and VEGF in patients with CSCC.

| Variables                  | No. of cases | % of cases |
|----------------------------|--------------|------------|
| Survivin expression        |              |            |
| –                          | 26           | 22.2       |
| +                          | 27           | 23.1       |
| ++                         | 28           | 23.9       |
| +++                        | 36           | 30.8       |
| VEGF expression            |              |            |
| –                          | 6            | 5.1        |
| +                          | 40           | 34.2       |
| ++                         | 37           | 31.6       |
| +++                        | 34           | 29.1       |

CSCC = cervical squamous cell carcinoma, VEGF = vascular endothelial growth factor.
studies and the present study suggested that neoadjuvant chemotherapy exhibit a good effect for most of the patients with advanced cervical cancer. However, approximately 6% to 12.8% patients are resistant to the neoadjuvant chemotherapy. The mechanisms underlying the resistance remain largely unclear.

In a meta-analysis study including 11 eligible studies with a total of 865 patients with cervical carcinoma, the authors found that survivin overexpression was closely related to lymph node metastasis, but was not significantly associated with tumor grade.\cite{17} The authors also found that the survivin expression was significantly associated with poor survival in cervical

### Table 5

| Variables          | Survivin expression (n [%]) | \(\chi^2\) or F | P     | Pearson R | P    |
|--------------------|----------------------------|----------------|-------|-----------|------|
| VEGF expression    |                            |                |       |           |      |
| –                  | 3 (11.5)                   | 111.491        | <.001 | 0.820     | <.001|
| +                  | 23 (88.5)                  |                |       |           |      |
| ++                 | 11 (40.7)                  |                |       |           |      |
| +++                | 0 (0.0)                    |                |       |           |      |
| Ki67, %, mean (SD) | 37.7 (12.4)                | 32.433         | <.001 | 0.673     | <.001|

CSCC= cervical squamous cell carcinoma, VEGF = vascular endothelial growth factor.

### Table 6

| Variables          | No. of cases | % of cases |
|--------------------|--------------|------------|
| Efficacy of treatment |              |            |
| CR                 | 11           | 9.4        |
| PR                 | 91           | 77.8       |
| SD                 | 15           | 12.8       |

CR= complete remission, CSCC= cervical squamous cell carcinoma, PR= partial remission, SD= stability disease.

### Table 7

| Variables          | Efficacy of treatment (n [%]) | \(\chi^2\) or F | P     | Pearson R | P    |
|--------------------|-------------------------------|----------------|-------|-----------|------|
| Ages               |                              |                |       |           |      |
| <45                | 5 (45.5)                      | 0.737          | .692  | 0.064     | .494 |
| ≥45                | 6 (54.5)                      |                |       |           |      |
| FIGO stage         |                              |                |       |           |      |
| Ib2                | 6 (54.5)                      | 2.621          | .270  | 0.139     | .134 |
| Ila2               | 5 (45.5)                      |                |       |           |      |
| Macroscopic types  |                              |                |       |           |      |
| Cervical canal type| 3 (27.3)                     | 8.029          | .236  | 0.054     | .563 |
| Ulcerative type    | 0 (0.0)                       |                |       |           |      |
| Endophytic type    | 2 (18.2)                      |                |       |           |      |
| Exogenous type     | 6 (54.5)                      |                |       |           |      |
| Grades             |                              |                |       |           |      |
| G1                 | 9 (81.8)                      | 40.920         | <.001 | 0.513     | <.001|
| G2                 | 2 (18.2)                      |                |       |           |      |
| G3                 | 0 (0.0)                       |                |       |           |      |
| Lymphovascular invasion |                      |                |       |           |      |
| Absence            | 6 (54.5)                      | 1.067          | .586  | 0.049     | .601 |
| Presence           | 5 (45.5)                      |                |       |           |      |
| Depth of lymphovascular invasion |          |                |       |           |      |
| <1/2               | 7 (63.6)                      | 4.109          | .128  | 0.107     | .251 |
| ≥1/2               | 4 (36.4)                      |                |       |           |      |
| Lymph node metastasis |                      | 0.486          | .765  | 0.003     | .973 |
| Absence            | 5 (45.5)                      |                |       |           |      |
| Presence           | 6 (54.5)                      |                |       |           |      |
| Ki67, %, mean (SD) | 30.0 (8.9)                    | 30.232         | <.001 | 0.586     | <.001|
| VEGF expression    |                              |                |       |           |      |
| –                  | 2 (18.2)                      | 30.458         | <.001 | 0.476     | <.001|
| +                  | 8 (72.7)                      |                |       |           |      |
| ++                 | 1 (9.1)                       |                |       |           |      |
| +++                | 0 (0.0)                       |                |       |           |      |
| Survivin expression|                              |                |       |           |      |
| –                  | 9 (81.8)                      | 44.119         | <.001 | 0.519     | <.001|
| +                  | 1 (9.1)                       |                |       |           |      |
| ++                 | 1 (9.1)                       |                |       |           |      |
| +++                | 0 (0.0)                       |                |       |           |      |

CR= complete remission, CSCC= cervical squamous cell carcinoma, FIGO = International Federation of Obstetrics and Gynecology, PR= partial remission, SD= stability disease.
Table 8: Multivariate analysis of correlation between efficacy of paclitaxel with clinicopathologic characteristics in patients with cervical squamous cell carcinoma.

| Variables               | $\chi^2$ | $P$ |
|-------------------------|----------|-----|
| Ages                    | 0.938    | .626|
| FIGO stage              | 1.168    | .558|
| Macroscopic types       | 5.756    | .451|
| Grades                  | 10.848   | .028|
| Lymphovascular invasion | 0.482    | .786|
| Depth of lymphovascular invasion | 5.300 | .022 |
| Lymph node metastasis   | 2.037    | .361|
| K67, %, Mean (SD)       | 19.973   | <.001|
| Tumor size, cm (mean, SD)| 4.358   | .226|
| VEGF expression         | 1.348    | .969|
| Survivin expression     | 15.555   | .015|

FIGO = International Federation of Obstetrics and Gynecology, VEGF = vascular endothelial growth factor.

Survivin expression was significantly associated with poor survival in cervical carcinoma patients who had undergone either surgery or radiotherapy and adjuvant chemotherapy in the aforementioned meta-analysis study and only squamous cell carcinoma is included in our study. Consistently, both the aforementioned study and the present study indicated that survivin expression was significantly associated with poor survival in cervical carcinoma patients who had undergone either surgery or radiotherapy and adjuvant chemotherapy in the aforementioned study or poor prognosis treated with neo-adjuvant chemotherapy for CSCC in the present study. Taken together, the aforementioned studies and the present study indicated that high survivin expression might be at least partly responsible for the resistance of cervical carcinoma to the neoadjuvant chemotherapy. However, how survivin gets involved in the resistances needs to be further investigated.

Survivin is a microtubule-binding inhibitor of apoptosis protein. The specific expression of survivin in G2/M phase, mainly through direct or indirect inhibition of the activation of apoptosis-effector protease caspase-3, caspase-7 to block cell apoptosis caused by apoptosis genes, and chemotherapy drugs. Studies have shown that survivin can bind to the caspase activator released by tumor cells during chemotherapy of paclitaxel, thereby blocking the binding of the latter to apoptosis inhibitors, and thus inhibiting cell apoptosis. It can be speculated that the inhibition of the activation of apoptosis-effector protease caspase-3, caspase-7 by survivin may be closely related to the resistance mechanism of paclitaxel to CSCC.

VEGF is an over-expressed endothelial-cell-selective growth factor in many human tumors, which can promote angiogenesis of tumor tissue. In breast cancer, survivin expression is significantly correlated with VEGF expression. The coexpression of survivin and VEGF-C is more statistically significant to assess lymphatic metastasis in breast cancer. Over-expression of survivin and VEGF in small-cell lung cancer may predict the poorer prognosis. However, the relationship between survivin and VEGF and their roles in CSCC have not been reported. The present study revealed that survivin expression is positively correlated with VEGF expression in cervical squamous cell tissue. Regarding the relationship between survivin and VEGF, it has been reported that survivin protein expression in hepatocarcinoma tissues was positively correlated with VEGF expression, indicating survivin may inhibit the apoptosis of hepatocarcinoma cells and promote tumor angiogenesis by upregulating the expression of VEGF protein, thus accelerating the occurrence and development of hepatocarcinoma.

The present study has several limitations. Firstly, the sample size of patients was relatively small. Secondly, the study was based on 1 center. Lastly, this study did not compare CSCC with adenocarcinoma carcinomas. These limitations can be solved in the future by increasing the sample size, expanding to multicenters investigation and comparing CSCC with adenocarcinoma carcinomas.

5. Conclusions

The results suggested that survivin expression is negatively correlated with the prognosis of patients with CSCC treated with paclitaxel and carboplatin. Therefore, survivin expression might be a marker for prognosis in CSCC following neoadjuvant chemotherapy and a new therapeutic target for CSCC.

Author contributions

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