Original Article
Correlation of RAGE/S100A14 expression to sensitivity of neo-adjuvant intra-arterial chemotherapy in cervical squamous cell carcinoma

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Abstract: Objective: The aim of this study was to explore the RAGE/S100A14 expression in cervical squamous cell carcinoma (CSCC) between pre- and post-neo-adjuvant intra-arterial chemotherapy and their correlation with chemotherapy sensitivity. Methods: Paired tumor samples (pre- and post-chemotherapy) were obtained from 40 patients who were treated with cisplatin based neo-adjuvant intra-arterial chemotherapy and radical hysterectomy at The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Central Hospital. Normal cervical epithelial tissue samples were obtained from 35 patients with uterine myoma treated by hysterectomy as the control group. The neo-adjuvant chemotherapy response was evaluated according to response evaluation criteria in solid tumors of the WHO. The expression of RAGE and S100A14 mRNA was analyzed by Real time PCR and the expression of RAGE and S100A14 protein was examined by Western blot (WB), and immunohistochemical assay (IHC). Results: After neo-adjuvant chemotherapy, 25 cases responded to chemotherapy, 15 cases were non-responsive; with the total effective rate of 62.5%. The expression of RAGE and S100A14 in cervical cancer tissue was statistically higher than that of normal cervical epithelial tissue (P<0.05). The expression of RAGE and S100A14 in tumor cells was statistically enhanced after exposure to neo-adjuvant chemotherapy (*P*<0.05). The expression of RAGE and S100A14 in cervical cancer tissue before chemotherapy was statistically lower in the response group than that in the non-responsive group (*P*<0.05). Significant positive correlations were identified between RAGE and S100A14 protein expression of cervical cancer cases in the prior chemotherapy group ($r_{Spearman}$=0.679, *P*<0.05), post chemotherapy group ($r_{Spearman}$=0.587, *P*<0.05), response group ($r_{Spearman}$=0.731, *P*<0.05) and non-responsive group ($r_{Spearman}$=0.81, *P*<0.05). Conclusion: RAGE and S100A14 were highly expressed in cervical squamous carcinoma tissue compared to normal cervical epithelial specimens. RAGE and S100A14 expression was associated with the response to neo-adjuvant arterial chemotherapy, and may be used as potential biomarkers for neo-adjuvant arterial chemotherapy response.

Keywords: RAGE, S100A14, cervical squamous cell cancer, neo-adjuvant intra-arterial chemotherapy

Introduction

Cervical cancer is one of the most common gynecological malignancies worldwide, ranking fourth in female carcinomas and the seventh in human all malignancies. The incidence and mortality of cervical cancer in females are second only to breast cancer [1]. In 2018, an estimated 485,000 new cases and 236,000 deaths worldwide were found [2]. There are more than 150,000 new cases diagnosed in China each year, of which about 20,000-30,000 people die of this disease or related complications. In the past 40 years, with the wide application of large-scale screening pro-grams for cervical cancer, the mortality of cervical cancer has declined gradually. However, cervical cancer patients are younger in recent years. At present, 16% of all cervical cancer patients in China are under 35 years old [3].

Neo-adjuvant chemotherapy was proposed by Fried in 1982. It refers to chemotherapy (2-3 courses) before an operation or radiotherapy in order to achieve the following effects: 1) reducing tumor stage (stage I b-IV a tumors), providing conditions for radical surgery; 2) reducing tumor volume (local mass > 4 cm), improving the surgical resection rate of tumors, young patients can effectively retain the function of
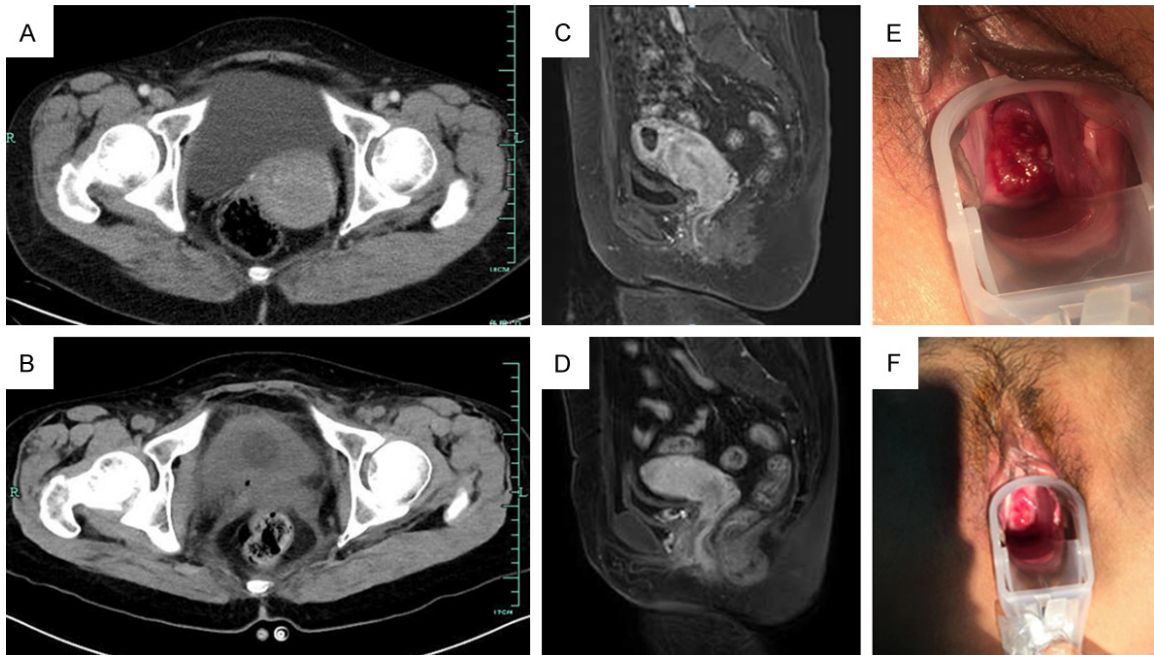
Figure 1. Squamous cervical cancer diagnosed by colposcopy, computer tomography and MIR. (A. Pelvix CT image prior neo-adjuvant chemotherapy; B. Pelvix CT image post neo-adjuvant chemotherapy; C. Pelvix MRI image prior neo-adjuvant chemotherapy; D. Pelvix MRI image post neo-adjuvant chemotherapy; E. Colposcopy image prior neo-adjuvant chemotherapy; F. Colposcopy image post neoadjuvant chemotherapy).

their vagina or ovaries; 3) enhance the sensitivity of radiotherapy; 4) evaluate the chemotherapeutic drug sensitivity of patients, provide certain clues for the prognosis of patients, and provide a basis for future treatment; 5) eliminate subclinical lesions, reduce postoperative recurrence and metastasis, and improve the prognosis; 6) when the treatment is repeated, the incidence of complications of patients with recurrence after NACT + surgery is clearly less than the recurrence after radiotherapy. However, there are great individual differences in the sensitivity of neo-adjuvant arterial chemotherapy. Therefore, how to predict the sensitivity or resistance of tumor to chemotherapy drugs before neo-adjuvant arterial chemotherapy, avoid the use of non-sensitive drugs and decrease the side effects of chemotherapy drugs, has become a hot research topic.

RAGE, as a receptor of S100 protein, plays an important role in intracellular signal transduction. S100A protein has been found to interact with RGAE, including S100A1, S100A2, S100A4, S100A5, S100A6, S100A7, S100A8/A9, S100A11, S100A12, S100A13 and S100A14. Research had demonstrated that S100A14 could regulate cell proliferation and apoptosis by binding to its receptor RAGE.

Recent studies have confirmed that S100A14 induces cell cycle arrest, apoptosis, or metastasis in oral and esophageal squamous cell carcinoma in a p53 dependent or receptor-dependent manner [4, 5]. The role of S100A14 and RAGE in tumor progression and chemosensitivity is not clear yet. In recent years, S100A14 and RAGE were found to be moderately and highly expressed in many malignant tumors, and their expression level is closely related to the invasive ability of malignant tumors. It has been reported that S100A14 and RAGE can promote tumor progression, such as tumor growth, survival, metastasis and diffusion, and participate in chemotherapy tolerance of malignant tumors. However, the interaction of S100A14 in neo-adjuvant arterial chemotherapy for cervical squamous cell carcinoma has not been reported yet [6].

Material and methods

Patients

Forty patients with massive cervical squamous cell carcinoma (tumor diameter > 4 cm, FIGO stage I, B2 and II, A2) treated in our hospital were included in the present work from October 1, 2014 to March 1, 2017, **Figure 1**. After neo-
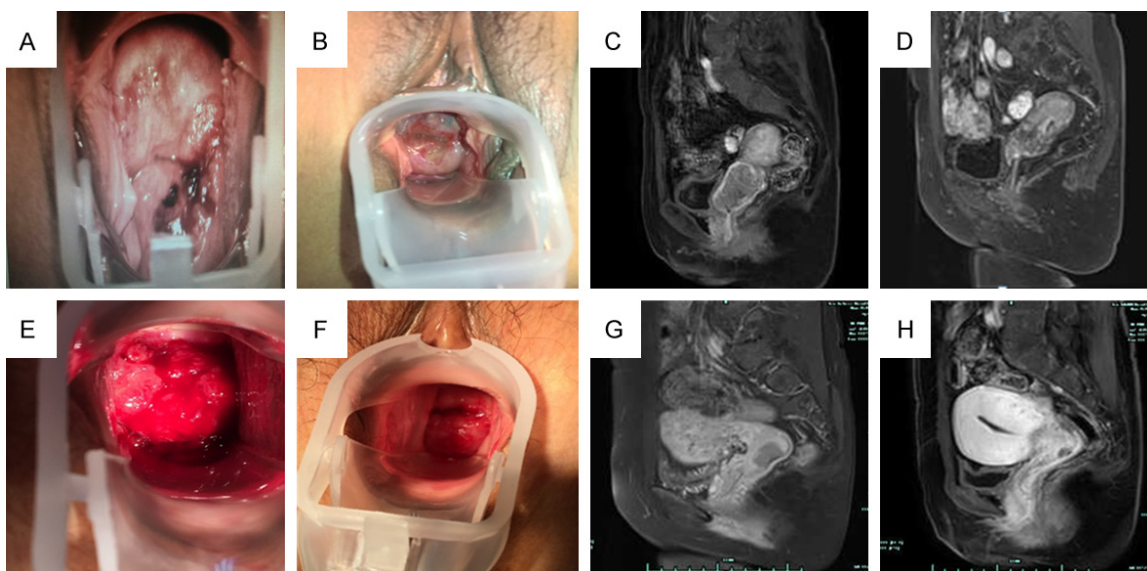
Figure 2. Colposcopy and MIR image prior and post neo-adjuvant chemotherapy. (A, E. Colposcopy of the cervical carcinoma prior neo-adjuvant chemotherapy; B. F. Colposcopy of the cervical carcinoma post neo-adjuvant chemotherapy; C, G. MRI image prior neo-adjuvant chemotherapy; D, H. MRI image post neo-adjuvant chemotherapy).

adjuvant arterial chemotherapy, 40 patients underwent radical surgery or radiotherapy for cervical cancer treatment. Another 35 normal cervical tissue samples from patients treated with hysteromyoma were selected as the control group. The average age of the 40 patients with cervical cancer was 45 ± 9 years. The stage of the tumor is determined by two or more doctors at the level of deputy director and above who are engaged in gynecological tumors, **Figure 2**. According to the clinical stage of cervical cancer in FIGO 2009, 23 cases (57.5%) were in stage IB_2 and 17 cases (42.5%) in stage IIA_2 (**Table 1**). The study was approved by the ethics committee of The Fifth Affiliated Hospital of Wenzhou Medical University, Lishui Central Hospital. An informed consent was obtained from all the include subjects.

Neo-adjuvant chemotherapy

All patients received cisplatin plus bleomycin combined neo-adjuvant arterial chemotherapy through Seldinger puncture method. After the right femoral artery was successfully accessed, the guide wire, 5F catheter sheath and 5FCobra catheter were introduced respectively. If necessary, 3F Terumo SP microcatheter was selected. After successful catheterization, DSA was performed to show the blood supply of the tumor. Then the catheters were inserted into the uterine arteries, and chemotherapy drugs were injected into the catheters. A single dose

of cisplatin 45 mg, and bleomycin 15 mg was given. Under TV monitoring, a bottle of 500-700 μm embolization microsphere was injected, and the two uterine arteries were embolized by gelatin sponge particles. The two uterine arteries were divided again. The branches and abnormal staining disappeared, and the operation ended after the development of the main uterine artery. According to the effect of chemotherapy, 1-2 cycles of chemotherapy were given. The interval between the two chemotherapy applications was 2-3 weeks. In order to protect the kidney, all patients were hydrated after chemotherapy: the daily infusion volume was 3000 ml-4000 ml, the continuous infusion volume was 3 days, and the urine volume was calculated for 24 h. According to the volume of infusion and urine volume, if necessary, furosemide 20 mg intravenous injection was given.

Neo-adjuvant chemotherapy response evaluation

Before chemotherapy, the size of tumor was measured by gynecological and imaging examination. Then, 2-3 weeks after the end of arterial chemotherapy, the therapeutic effect of chemotherapy was evaluated according to the WHO standard for short-term efficacy evaluation of solid tumors [7]. The tumor diameter before and after chemotherapy was mainly determined by gynecological examination, ultrasound and/or MRI examination to decide

Table 1. The general characteristics of the response and non-response groups

Group	n	Age (year)	Stage		Differentiation			Diameter (cm)
			IB$_2$	IIA$_2$	Well	Moderate	Poor	
Responsive	25	46±8	14	11	6	15	4	5.31±1.24
Non-responsive	15	44±10	9	6	3	9	3	5.64±1.35

whether to carry out surgery or radiotherapy. All the therapeutic effects and pre-treatment stages were determined by two or more senior doctors. The maximum diameter and the maximum vertical transverse diameter of the lesions were measured by B-ultrasound and/or MRI, and the product of the two was used to evaluate the change of the tumor volume.

Real-time PCR assay

The total RNA of the specimens from cervical cancer and controls was extracted from cells using TRIzol® reagent (Life Technology), according to the manufacturer's instructions and then reversed transcribed into microRNA cDNAs with reverse Transcriptase M-MLV (RNase H-) (TaKaRa) by using specific primers. qRT-PCR was subsequently performed using the SYBR® Premix Ex Taq™ II kit (Takara) with the primer: RAGE-F: AGG AGG AAG AGG AGG AGC GTA; RAGE-R: TGG CAA GGT GGG GTT ATA CAG; S100A14-F: TCA CCA AAG GAC CAG ACA CAC; S100A14-R: GCC CTC TCC ACA TCA CTG AAT.

Immunohistochemistry assay

The paraffin embedded tissue was cut into sections with a thickness of 4 μm, and fished with poly lysine anti desquamation glass. After dewaxing and gradient alcohol hydration, pH 6.0 citric acid was used to repair antigen under high temperature and high pressure. Then 3% hydrogen peroxide was used to remove endogenous enzyme activity for 10 minutes. Reagent A was applied and sealed at room temperature for 10 minutes. Primary and secondary antibodies were added by dripping after the antigen was retrieved. The tissues were developed and mounted for microscopic examination.

Western blot assay

Total protein was extracted through radioimmunoprecipitation lysis buffer. Thirty μg samples were separated on 10% sodium dodecyl sulfatepolyacrylamide gel electrophoresis (SDS-PAGE) and transferred to nitrocellulose (NC) membrane (Millipore). The membranes were incubated with the specific antibodies of RAGE and S100A14 overnight at 4°C. After incubation with secondary antibodies (Beyotime, Beijing, P. R. China) for 1 hr at room temperature, the blots were detected using an enhanced chemiluminescence detection system. GAPDH was used as an internal control.

Statistical analysis

SPSS19.0 statistical software was used for data analysis. The data was first tested for Shapirowilk normality distribution. The data of a normal distribution was represented by mean ± standard deviation and the comparison of means of the two samples was done with a t-test of independent samples. The count data was analyzed by Fisher exact probability analysis and the comparison of independent sample grade data of the two groups was done with Wilcoxon two sample rank sum test. The statistical data of rages before and after chemotherapy and S100A14 before and after chemotherapy were all non-normal distribution data. The median (p25-p75) was used to express its distribution. Because of the proportioning relationship between the tissues before and after chemotherapy, Wilcoxon matched rank sum test was used to compare the expression levels of related proteins in cervical squamous cell carcinoma before and after chemotherapy. The comparison of various proteins before chemotherapy between the effective group and the ineffective group was tested by Mann Whitney U method. The correlation between the expression of RAGE and S100A14 in cervical cancer, the expression before and after chemotherapy, the expression in the chemotherapy effective group and the chemotherapy ineffective group was analyzed by Spearman rank correlation. Two tailed P<0.05 was considered a statistical difference.
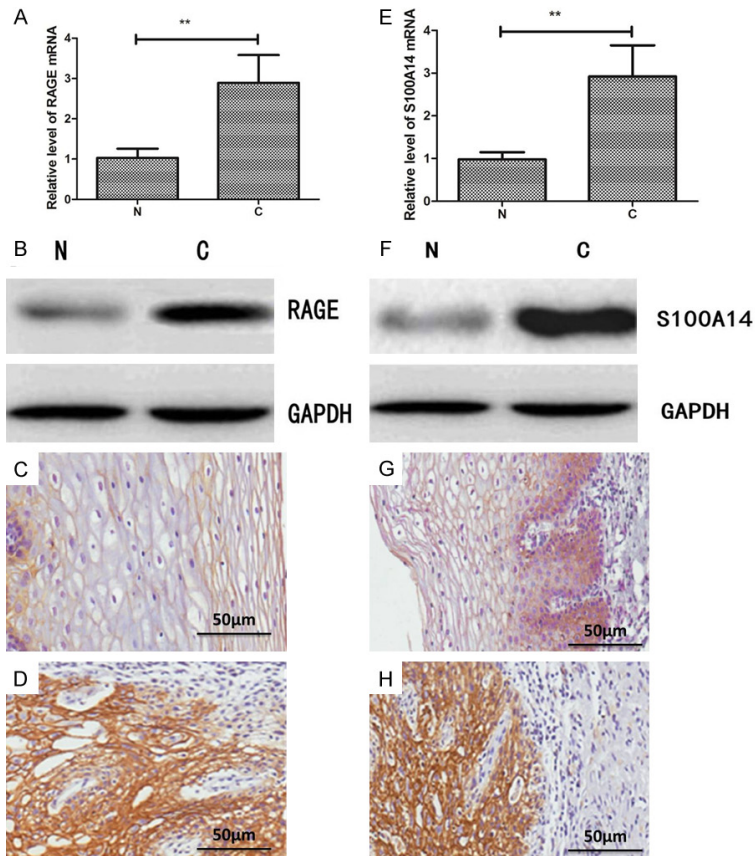
Results

Neo-adjuvant intra-arterial chemotherapy response

For the included 40 patients with cervical squamous cell carcinoma, 12 (30%) were completely responsive, 13 (32.5%) were partially responsive, 11 (27.5%) were stable disease and 4

Figure 3. RAGE and S100A14 expression in cervical cancer and normal cervical tissue prior treatment. (A. RAGE mRNA relative expression; B. S100A14 mRNA relative expression; C. RAGE protein expression detected by WB assay; D. S100A14 protein expression detected by WB assay; E. RAGE protein expression detected by IHC in normal tissue; F. S100A14 protein expression detected by IHC in normal tissue; G. RAGE protein expression detected by IHC in cervical cancer tissue; H. S100A14 protein expression detected by IHC in cervical cancer tissue).

Table 2. RAGE and S100A14 protein expression in normal and cancer tissue

Group	n	RAGE	S100A14
Normal tissue	24	2.29 (1.35-3.17)	1.36 (0.58-1.96)
Cancer tissue	40	6.30 (4.43-8.47)	6.87 (4.53-8.86)
Z		-3.316	-3.796
P		0.008	0.002

tissue and cervical cancer tissue was 1.03 ± 0.23 and 2.89 ± 0.69, respectively, **Figure 3A**. The relative expression of S100A14 mRNA was 0.98 ± 0.17 and 2.95 ± 0.73 for normal and cancer tissue, respectively, **Figure 3B**. The expression of RAGE and S100A14 mRNA in cervical cancer was significantly higher than that in normal cervical tissue ($P<0.05$). Western blot assay indicated that RAGE and S100A-14 protein was up-regulated in cancer tissue compared to normal tissue, (**Figure 3C**, **3D**). RAGE and S100A14 protein was positive in 26 (**Figure 3E**) and 24 samples (**Figure 2F**) in normal tissue. However, all the 40 cancer specimens had positive expression of RAGE and S100A14 protein (**Figure 3G**, **3H**). The RAGE protein expression score in normal cervical tissue was 2.29 (1.35-3.17), which was significantly lower than that in cervical cancer tissue 6.30 (4.43-8.47), ($z=-3.316$, $P<0.05$). S100A14 expression in normal cervical tissue and cervical cancer tissue was 1.36 (0.58-1.96), and 6.87 (4.53-8.86) respectively, with significant statistical difference ($z=-3.796$, $P<0.05$), **Table 2**.

RAGE and S100A14 expression prior and post neoadjuvant intra-arterial chemotherapy

Real time PCR demonstrated that the relative expression of RAGE mRNA in cervical squamous cell carcinoma before and after neoadjuvant chemotherapy was 1.09 ± 0.25 and 1.57 ± 0.31, respectively, with significant statistical difference ($z=-2.193$, $P<0.05$), **Figure 4A**. The relative expression of S100A14 mRNA in cervical squamous cell carcinoma before and after chemotherapy was 0.92 ± 0.34 and 1.61 ± 0.42, with significant statistical difference ($z=-2.387$, $P<0.05$) (**Figure 4E**). Western blot assay indicated

(10%) developed as progression of disease. The total objective response (OR) effective rate was 62.5%.

RAGE and S100A14 expression in cervical cancer and normal cervical tissue prior treatment

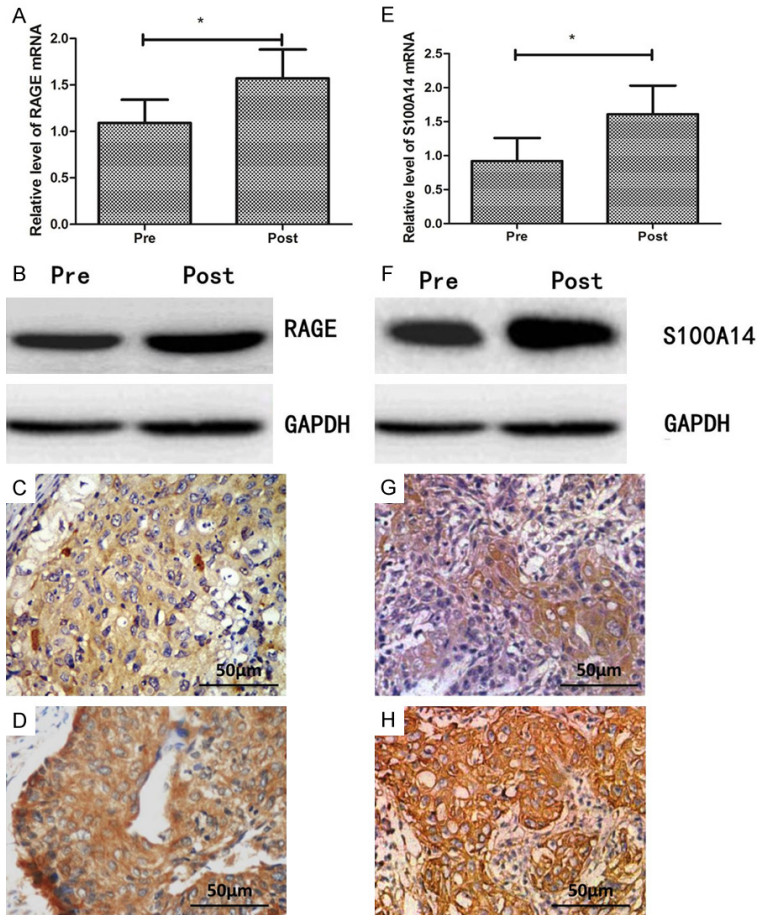Real time PCR assay showed that the relative expression of RAGE mRNA in normal cervical

Figure 4. RAGE and S100A14 expression for prion and post neo-adjuvant intra-arterial chemotherapy in cervical cancer patients. (A. RAGE mRNA relative expression; B. RAGE protein expression detected by WB assay prior and post chemotherapy; C. RAGE protein expression detected by IHC assay before chemotherapy; D. RAGE protein expression detected by IHC assay post chemotherapy; E. S100A14 mRNA relative expression; F. S100A14 protein expression detected by WB assay prior and post chemotherapy; G: S100A14 protein protein expression detected by IHC assay before chemotherapy; H: S100A14 protein expression detected by IHC assay post chemotherapy).

Table 3. RAGE and S100A14 protein expression between prior and post neoadjuvant chemotherapy groups

Groups	n	RAGE	S100A14
Prior chemotherapy	40	6.30 (4.43-8.47)	6.87 (4.53-8.86)
Post chemotherapy	37	9.36 (5.22-13.13)	9.56 (5.12-12.84)
Z		-2.017	-2.117
P		0.039	0.034

found in 3 patients after neo-adjuvant chemotherapy, and the expression of RAGE and S100A14 protein could be seen in the remaining 37 tumor samples. RAGE and S100A14 protein expression score was shown in **Table 3**, which indicated significant statistical difference between prior and po0 st neo-adjuvant chemotherapy ($P<0.05$).
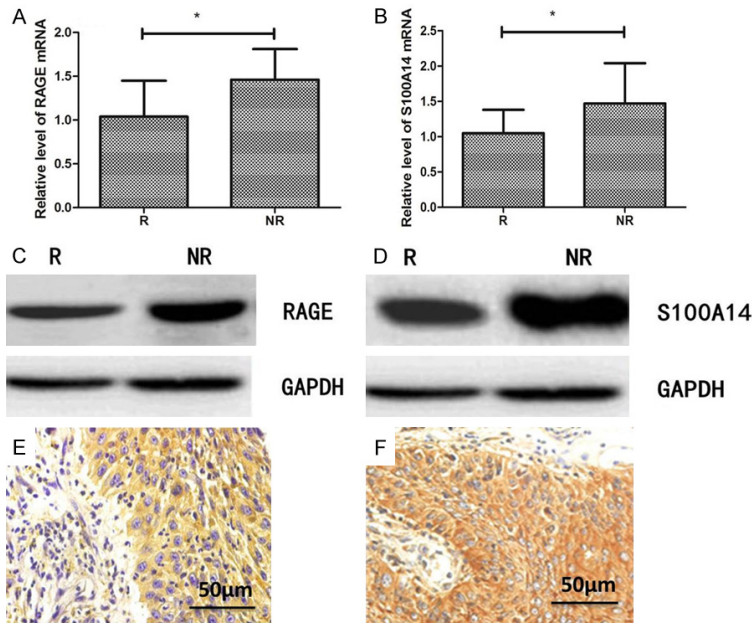
RAGE and S100A14 expression between response and non-responsive group

The relative expression of RAGE and S100A14 mRNA was 1.04 ± 0.41 and 1.05 ± 0.33 in cervical squamous cell carcinoma before chemotherapy in the response group (**Figure 5A**), while the RAGE and S100A14 mRNA in cervical squamous cell carcinoma before chemotherapy in the non-responsive group was 1.46 ± 0.35 and 1.47 ± 0.57 (**Figure 5B**), with statistical significant difference ($P<0.05$). Western blot assay indicated that RAGE and S100A14 protein was up-regulated in non-responsive group compared to response group after neoadjuvant chemotherapy, (**Figure 5C**, **5D**). The RAGE and S100A14 protein scores of the response group were 5.01 (4.13-6.76) and 5.31 (3.93-6.43) (**Figure 5E**, **5F**), respectively, while those of the non-response group were 8.52 (7.33-9.78) and 9.37 (7.41-11.16), respectively with statistical significant difference ($P<0.05$), **Table 4**.

Correlation between RAGE and S100A14 expression

Significant positive correlations were identified between RAGE and S100A14 protein expression in different groups ($P<0.05$), **Table 5**.

that RAGE and S100A14 protein was up-regulated after neo-adjuvant chemotherapy, (**Figure 4B**, **4F**). In cervical cancer, there was no difference for the location of RAGE **Figure 4C**, **4D** and S100A14 **Figure 4G**, **4H** protein before and after chemotherapy. No cancer tissue was

Figure 5. RAGE and S100A14 expression for response and non-response neo-adjuvant intra-arterial chemotherapy in cervical cancer patients. (A. RAGE mRNA relative expression between response and non-response group; B. S100A14 mRNA relative expression between response and non-response group; C. RAGE protein expression detected by WB assay between response and non-response group; D. S100A14 protein expression detected by WB assay between response and non-response group; E. RAGE protein expression detected by IHC assay of response group; F. S100A14 protein expression detected by IHC assay of response group).

Table 4. RAGE and S100A14 protein expression in response and non-response groups

Groups	n	RAGE	S100A14
Responsive	25	5.01 (4.13-6.76)	5.31 (3.93-6.43)
Non-responsive	15	8.52 (7.33-9.78)	9.37 (7.41-11.16)
Z		-2.048	-2.625
P		0.041	0.022

Table 5. Correlation between RAGE and S100A14 expression in different groups

Group	n	r_s	P
Prior chemotherapy	40	0.679	0.00
Post chemotherapy	37	0.587	0.004
Responsive	25	0.731	0.008
Non-responsive	15	0.81	0.013

RAGE and S100A14 protein expression validated by protein database

RAGE and S100A14 were also found positive in cervical squamous cancer tissue according to the human protein atlas, **Figure 6**.

Discussion

In this study, we used western blot, RT-PCR and immunohistochemistry assay to compare the expression of two proteins (RAGE and S100A14) in normal cervical epithelium and cervical squamous cell carcinoma. Western blot was applied to analyze the expression of two proteins (RAGE and S100A14 protein) in normal cervical epithelial tissue and cervical squamous cell carcinoma tissue, before and after neo-adjuvant chemotherapy, and in the effective and ineffective chemotherapy groups. We found that the protein expression in cervical squamous cell carcinoma was significantly higher than that in normal tissue epithelium, suggesting that the two proteins had specific expression in cancer and may play an important role in cervical cancer development. At the same time, we also found that RAGE and S100A14 expression in cervical squamous cell carcinoma after chemotherapy was higher than that before chemotherapy, and in cervical squamous cell carcinoma in the chemotherapy ineffective group was higher than that in the chemotherapy effective group. We also used RT-PCR assay to detect the expression of the two kinds of proteins in tissues, and verified the above findings, which again suggested the specific expression of the two kinds of proteins in cancer and the differential expression in different observation groups. Furthermore, the patients with low expression of RAGE and S100A14 protein were found to have better response rates than those with high expression, which indicated that RAGE and S100A14 protein may be potential biomarkers for the prognosis of neo-adjuvant chemotherapy.

Human RAGE gene is located on chromosome 6 [8] and encodes in the main histocompatibil-
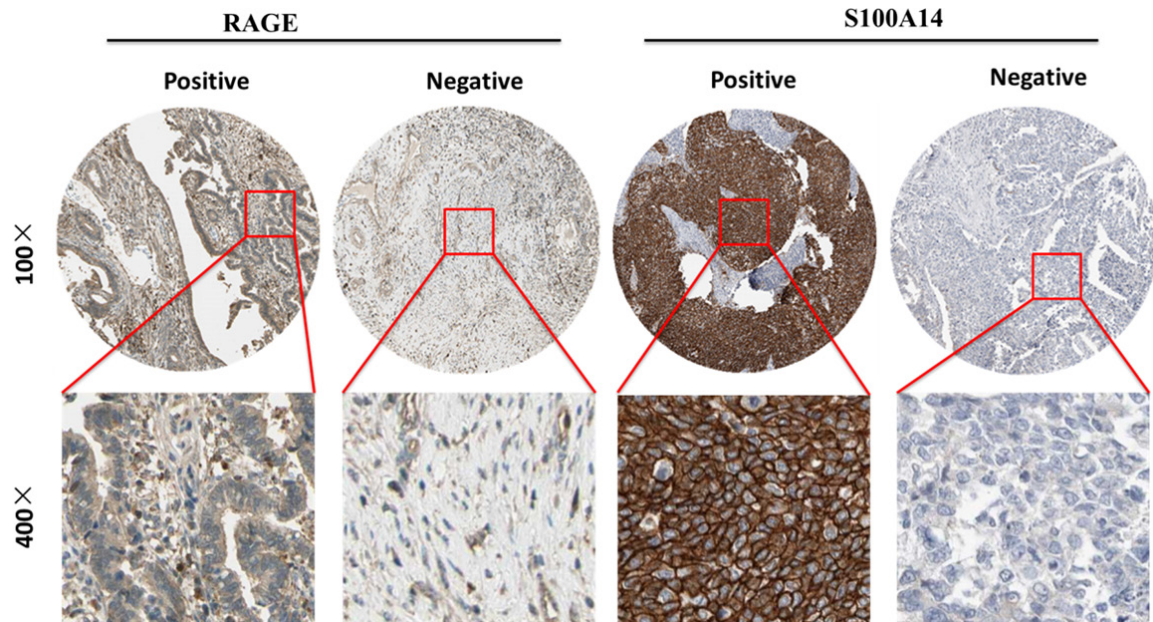
Figure 6. The RAGE and S100A14 protein expression in cervical squamous cell carcinoma demonstrated by the human protein atlas.

ity complex class III region [9, 10]. RAGE is a member of the cell surface molecular immunoglobulin superfamily, which is a single transmembrane, multi ligand pattern recognition receptor. RAGE expression depends on the type and state of tissue and cell [11]. In normal state, RAGE is abundant in the lung, while in other kinds of tissue cells, such as smooth muscle cells, monocytes, lymphocytes, liver stars. In the pathological state, such as tumor and inflammation, the expression of RAGE in cells can increase rapidly, and it can be combined with corresponding ligands to induce gene expression regulation through divergent signaling pathway [12, 13], and participate in cell proliferation, differentiation and inflammatory response.

In recent years, more and more studies have shown that the relationship between the expression of RAGE and the invasion and metastasis of malignant tumor cells, mainly in the research of gastric cancer, colorectal cancer, cholangiocarcinoma, pancreatic cancer, liver cancer, lung cancer and other adenocarcinoma [14]. In addition to the decreased expression of RAGE protein in lung cancer compared with normal tissues, the study of other adenocarcinomas showed that the expression of RAGE protein was up-regulated in tumor cells, and it was positively correlated with the invasion

depth and lymph node metastasis of cancer cells. Luo found that HMGB1 released from necrotic tumor cells treated with necrosis inducer enhanced the regeneration and metastasis of residual cancer cells through the activation of RAGE [15]. Recently, it has been found that the RAGE-PR3 interaction between human prostate cancer cells and bone marrow microenvironment mediates bone metastasis during prostate cancer progression, which has a potential impact on treatment and prognosis intervention [16]. In addition, in the study of osteosarcoma, it has been shown that RAGE is overexpressed in tumor tissue and has a significant correlation with clinical pathological features such as clinical stage and distant metastasis. It is a potential diagnostic biomarker and treatment target of the disease [17]. However, there are few reports on RAGE and chemotherapy of squamous cell carcinoma. Zhao Z et al. found that RAGE is widely expressed in tongue squamous cell carcinoma and related to drug-induced chemotherapy tolerance. RAGE blocking + cisplatin treatment can inhibit the progress of tongue squamous cell carcinoma by reducing autophagy and regulating Wnt/β-Catenin to improve the chemotherapy effect [18]. However, the relationship between rage and neoadjuvant arterial chemotherapy has not been reported.

S100A14 is a relatively new member of the calcium binding protein family. It is a new member of S100 family discovered by Pietas (2002) and other researchers through the comparative genomic hybridization of lung cancer. It is located in the q2l region of chromosome l. S100A14 protein expression is not consistent in various cancers, such as lung cancer, gastric cancer, bladder cancer, breast cancer, ovarian cancer, but is low in renal cancer, colorectal cancer and esophageal squamous cell carcinoma [19]. The expression of S100A14 protein is also different in normal tissues, such as normal esophageal epithelium and colorectal epithelium, which is moderately expressed in normal tissues of the lung, liver and kidney, and heart, but not expressed in brain, spleen and peripheral blood leukocytes [20].

It has been found that S100A14 can promote cell proliferation in hepatoma cells [21], while it can inhibit cell proliferation and promote cell invasion by inducing G1 phase arrest in oral and esophageal cancers [22]. S100A14 overexpression is associated with the prognosis of gastric cancer, colorectal cancer, and small bowel cancer [23]. Low S100A14 expression was associated with high colorectal cancer metastasis potential [24]. S100A14 has been identified as a potential new marker to predict distant metastasis of breast cancer cells [25]. S100A14 was up-regulated in basal breast cancer, which was significantly related to the outcome of patients [26]. However, there are few reports on S100A14 and tumor chemotherapy. Qian et al. reported that S100A14 may participate in the tolerance of ovarian cancer patients to platinum based chemotherapy [27]. However, there is no report about the relationship between S100A14 and neo-adjuvant arterial chemotherapy for giant cervical squamous cell carcinoma.

At present, the understanding of S100A14 and RAGE involved in signal transduction pathways is still unclear yet. The recognized ligands of RAGE include amphoterin, S100 family proteins and amyloid p-peptide. RGAE binds to ligands and is related to some important signaling pathways, such as MAPK, CDC42, NaCl, NF-κB, and is closely related to cell proliferation, migration and differentiation. The interaction between RAGE and many ligands plays an important role in the process of inflammation and tumor progression. RAGE can induce the activation of important signaling pathways including p21/Ras, RAC, p44/42, Akt, JNK, p38 MAPK and NF-κB, thus regulating gene expression.

In conclusion

RAGE and S100A14 were highly expressed in cervical squamous carcinoma tissue compared to normal cervical epithelial specimen. RAGE and S100A14 expression was associated with the response to neoadjuvant arterial chemotherapy, which may be used as potential biomarkers for neoadjuvant arterial chemotherapy response. This finding provides a basis for further study of rage/S100A on the signal transduction pathway related to cisplatin resistance regulation of cervical cancer chemotherapy drugs, and finally provides a valuable reference for how to make better evaluation indexes and individualized treatment strategies for neoadjuvant arterial chemotherapy of cervical cancer patients.

Disclosure of conflict of interest

None.

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