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Serum squamous cell carcinoma antigen level and magnetic resonance imaging for the prognosis of locally advanced cervical cancer

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Abstract. – OBJECTIVE: Squamous cell carcinoma antigen (SCC-ag) and magnetic resonance imaging (MRI) were explored to serve as biomarkers to predict the prognosis of cervical cancer (CC) patients treated with neoadjuvant chemotherapy (NACT) prior to radical surgery, with the aim of identifying the subgroup that least benefits from the combined therapy.

PATIENTS AND METHODS: All patients were treated with NACT prior to radical surgery and received MRI and SCC-ag examinations before and after NACT. For these three cycles of NACT, patients were treated with intravenous paclitaxel at 150 mg/m² over a period of 3 hours and carboplatin, with the area under the sera concentration-time curve of 5 over a period of 30 minutes on the first day of each cycle. Meanwhile, the blood pressure, ECG, and blood oxygen saturation of the patients were observed during the infusion. A discovery cohort and a validation cohort were applied to examine the prognostic performance of SCC-ag, MRI, and their combination. The endpoints of our study were overall survival (OS) and progression-free survival (PFS).

RESULTS: A total of 384 patients diagnosed between August 2006 and December 2010 were enrolled in our research, with 206 patients in the discovery cohort and 178 patients in the validation cohort. The high-risk group identified by MRI had a worse OS [hazard ratio (HR), 3.567; 95% confidence interval (CI), 1.466-8.677; log-rank p=0.0027) and PFS (HR, 4.062; 95% CI, 2.171-7.6; log-rank p<0.0001) than the low-risk group. Meanwhile, the SCC-RC could serve as a strong prognostic factor to predict OS (HR, 5.614; 95% CI, 2.473-12.744; log-rank p<0.0001) and PFS (HR, 7.481; 95% CI, 4.194-13.344; log-rank p<0.0001) for CC. In addition, the combined MRI and SCC-ag had greater prognostic efficiency and were used to divide the whole patient population into three groups. Compared with patients in the low-risk group, patients in the high-risk group had a worse OS (HR, 8.216; 95% CI, 2.98-22.651; log-rank p<0.0001) and PFS (HR, 11.757; 95% CI, 5.735-24.104; log-rank p<0.0001). Multivariate analyses revealed that MRI, SCC-ag, and their combination were independent prognostic factors.

CONCLUSIONS: SCC-ag and MRI, individually or in combination, were bound up with OS and PFS in CC. Additionally, the predictive efficiency improved when SCC-ag and MRI were combined in a risk model that predicted the OS and PFS of SCC compared with the predictive efficiency of either SCC-ag or MRI alone, revealing that the combination of these two biomarkers could help to ameliorate prognostic stratification and to guide personalized therapy for SCC patients.

Key Words:
Cervical cancer, Prospective cohort, SCC-ag, MRI, Prognostic stratification.

Introduction

Cervical cancer (CC) is the second most frequently diagnosed cancer and ranks third among the causes of cancer deaths for females in less developed countries[1]. There are approximately 500,000 newly diagnosed CC cases each year worldwide, with 80% of them being in developing countries[1]. In addition, CC deaths in developing countries account for nearly 90% of all CC deaths worldwide[1]. Despite a downward trend in developed nations, CC incidence has grown dramatically in China in recent years, which can be attributed to the country's low coverage of CC screening[2]. In developing countries, the majority of CC patients are diagnosed at a locally advanced stage[3], and most of the tumors belong to the squamous cell carcinoma subtype. Currently, neoadjuvant chemotherapy (NACT) followed

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by radical surgery has been confirmed to be an effective procedure for locally advanced CC[4,5]. Although this technique significantly improves the prognosis of patients with locally advanced CC, it is not appropriate for all patients, and some will have progressive or recurrent illnesses. Thus, it is critical to identify prognostic factors for local CC patients in the advanced stages treated with NACT plus radical surgery and to identify the subgroup that least benefits from the combined therapy[6,7].

Studies[8-14] have revealed that the response to NACT is an independent prognostic factor (IPF) for CC patients who received NACT followed by surgery, and NACT responders have favorable outcomes compared with non-responders. Serum squamous cell carcinoma antigen (SCC-ag) is a glycoprotein extracted from human cervical squamous cell carcinoma tissue and mainly exists in the cytoplasm of squamous cell carcinoma of the cervix and uterus. Its detection is highly correlated with the diagnosis of cervical cancer, which is currently considered the most clinically valuable serum marker. Magnetic resonance imaging (MRI) has achieved good results in the clinical diagnosis of various tumors due to its high tissue resolution and the ability to achieve multi-sequence imaging. Our previous study[15] demonstrated that the combination of SCC-ag and MRI predicted the CC response to NACT with high accuracy. Thus, we hypothesized that serum SCC-ag and MRI could serve as biomarkers to predict the prognosis of CC patients treated with NACT prior to radical surgery, given that these parameters reflect the response to NACT.

In this research, we evaluated the prognostic significance of SCC-ag and MRI for patients with squamous cervical cancer (SCC) who received NACT treatment and radical surgery using our prospective cohort with a follow-up time of nearly ten years.

Patients and Methods

Study Cohort

Between August 2006 and December 2010, all patients with a diagnosis of CC in the Department of Gynecology Oncology, the Affiliated Tumor Hospital of Harbin Medical University, were eligible for this protocol.

Prior to enrollment, informed consent was obtained from the patients. This study protocol was approved by the Hospital Ethics Committee of the Harbin Medical University Cancer Hospital with the ethics number FH-EU20100203. All procedures comply with the ethical guidelines of the Declaration of Helsinki.

The inclusive criteria were as follows: (1) SCC patients with Stage IB2-IIB disease on the basis of the Federation of Gynecology and Obstetrics (1998 FIGO staging system); (2) patients without prior metrectomy, pelvic radiation therapy, systemic chemotherapy or medical contraindications to chemotherapy; and (3) patients with the SCC histologic subtype. Patients who did not die of CC or abandoned treatments were excluded from our cohort.

All patients were treated with NACT prior to radical surgery and received MRI and SCC-ag examinations before and after NACT. In our study, the NACT regimen included three cycles of paclitaxel and carboplatin that were separated by three weeks. For these three cycles of NACT, patients were treated with intravenous paclitaxel at 150 mg/m^2 over a period of 3 hours and carboplatin, with the area under the sera concentration-time curve of 5 over a period of 30 minutes on the first day of each cycle. Meanwhile, the blood pressure, ECG and blood oxygen saturation of the patients were observed during the infusion.

The whole cohort was separated into two cohorts: the discovery cohort and the validation cohort. The discovery cohort included patients diagnosed between August 2006 and December 2009; the validation cohort included patients diagnosed between January 2010 and December 2010.

MRI Analysis and SCC-ag Array

MRI and diffusion-weighted image (DWI) scanning were initially carried out for all enrolled patients after NACT. The largest diameter (mm) of the target lesion was obtained. SCC-ag (ng/ml) was measured twice in fasting sera samples that were obtained at the first visit and after NACT treatment. The detailed protocol for MRI and SCC-ag can be found in our previous study[15].

NACT Response Evaluation

The NACT response was assessed according to the response evaluation criteria in solid tumors (RECIST) criteria (version 1.1). Complete response (CR) means complete disappearance of all lesions, and partial response (PR) means at least a 30% decrease in the sum of the largest diameter (LD) of the target lesion. Stable disease (SD) means neither a decrease in size that qual-

ified as PR nor a sufficient increase in size that qualified as progressive disease (PD), and PD was represented as at least a 20% increase in the sum of the LD of the target lesions. In our study, the overall response means CR and PR.

Pathological Evaluation

All specimens removed *via* radical surgery were pathologically analyzed, including the macroscopic measurement of the lesion size and the microscopic determination of the lesion boundary on the basis of frozen tissue samples.

Follow-up Evaluation

Pelvic MRI, color Doppler ultrasound of the liver and kidney, cervical smears, X-rays, and SCC-ag arrays were performed for each patient every 3 months for the first 2 years in the follow-up period, and thereafter, the patients received these examinations at 6-month intervals. The endpoints of our research were overall survival (OS) and progression-free survival (PFS). OS means the period from the first admission until death or to the time of the most recent follow-up; PFS means the period from the first admission to the occurrence of local recurrence or distant metastasis.

Statistical Analysis

The normality of the quantitative data was detected *via* the Shapiro-Wilk test[16]. The quantitative data are denoted as the mean and deviation if the data were normally distributed; otherwise, the data are reported as the median and interquartile. The qualitative data are presented as frequency counts and percentages. Two variables were created for each of these factors to evaluate the predictive ability of MRI and SCC-ag for prognosis. One represented the MRI absolute change (MRI-AC) and the SCC-ag absolute change (SCC-AC) before and after NACT treatment. The other represented the MRI relative change (MRI-RC) and the SCC-ag relative change (SCC-RC). MRI-AC or SCC-AC was obtained by subtracting the MRI or SCC-ag value after NACT from that before NACT. The MRI-RC or SCC-RC was obtained by dividing the MRI-AC or SCC-AC by the MRI or SCC-ag value before NACT. The optimum cutoff values for MRI and SCC-ag for prognosis prediction were determined by time-dependent receiver operative characteristic (ROC) curve analysis with a maximum delay of ten years in the discovery cohort[17]. The cut-off values were obtained with the maximum Youden index[18]. The area under the curve (AUC) value reflected the predictive ability for prognosis in ROC analyses. The AUC value was between 0.5 and 1, and a higher AUC value indicated that there was a better predictive ability for prognosis. Survival times between different groups were compared *via* Kaplan-Meier analysis and the log-rank test. Univariate and multivariate Cox proportional hazards models were used to assess the prognostic value of MRI and SCC-ag in terms of OS and PFS. Variables that were statistically significant in univariate analyses were fitted to multivariate Cox models. Meanwhile, the proportional hazards assumption was tested when establishing Cox proportional hazards models. All statistical analyses were performed in the R platform (version 3.6.0) (Auckland, New Zealand), and a two-sided p-value <0.05 was considered statistically significant.

Results

Patients

From August 2006 to December 2010, 397 patients who met the inclusion criteria were initially enrolled, and 13 patients were excluded from our study because they did not die of CC or abandoned treatments during follow-ups (**Supplementary Figure 1**). Therefore, 384 patients were eligible for final analyses. The median follow-up time was nine years. There were 206 and 178 patients in the discovery cohort and validation cohort, respectively. The detailed demographic and clinical information for the discovery and validation cohorts is presented in Table I.

The Prognostic Ability of NACT Response

Since our hypothesis of the usefulness of MRI and SCC-ag for predicting the prognosis of SCC was motivated by the fact that MRI and SCC-ag were sensitive and reliable biomarkers for predicting the SCC response to NACT in our previous study[15], we first assessed the predictive efficiency of NACT response.

In the discovery cohort, univariate analysis suggested that NACT response did not significantly predict the OS of the SCC patients (HR, 1.779; 95% CI, 0.78-4.058; log-rank p=0.16) (**Supplementary Figure 2A**). However, the NACT response was significantly bound up with PFS (HR,

Table I. Demographics and clinical characteristics of study patients.

Demographic or characteristic	Discovery cohort (n = 206)		Validation cohort (n = 178)	
	No. of patients	%	No. of patients	%
Age, years				
Mean ± sd	46 ± 8		49 ± 7	
Menopause				
Yes	138	67.99	91	51.12
No	68	33.01	87	48.88
FIGO Stage				
IB2	40	19.42	34	19.32
IIA	63	30.58	49	27.84
IIB	103	50	93	52.84
Lymph node metastasis				
Yes	19	9.22	31	17.42
No	187	90.78	147	82.58
Differentiation				
Well	41	19.9	24	13.48
Moderate	97	47.09	83	46.63
Poor	68	33.01	71	39.89
Postoperative radiotherapy				
Yes	71	34.47	83	46.63
No	135	65.53	95	53.37

FIGO Stage: International Federation of Gynecology and Obstetrics Stage.

4.474; 95% CI, 2.481-8.069; log-rank $p<0.0001$) (**Supplementary Figure 2B**). NACT response remained statistically significant for predicting PFS in a multivariate Cox model.

In the validation cohort, NACT response was significantly correlated with OS (HR, 3.905; 95% CI, 1.415-10.77; log-rank $p=0.0045$) and PFS (HR, 6.531; 95% CI, 3.101-13.75; log-rank $p<0.0001$) in the univariate analysis (**Supplementary Figure 2 C-D**). Multivariate models demonstrated that NACT response was an IPF for OS and PFS (Table II). Since no clinical and demographic variables were significantly associated with for PFS in univariate analysis, NACT response was considered an IPF for PFS without fitting the multivariate models.

The Prognostic Ability of MRI and SCC-ag in the Discovery Cohort

The ROC analyses in the discovery cohort showed that the MRI-AC had a slightly higher AUC value than the MRI-RC for predicting both the OS (0.675 *vs.* 0.67) and PFS (0.714 *vs.* 0.706), and the SCC-RC had a higher AUC value than the SCC-AC for predicting both the OS (0.697 *vs.* 0.675) and PFS (0.8 *vs.* 0.776) (**Supplementary Figure 3**). Therefore, the MRI-AC and SCC-RC were chosen to represent the MRI and SCC-ag, respectively, in the rest of the study. The optimal cutoff value was calculated using ROC analysis with reference to OS, which obtained optimal cutoff values of -14 and -0.167 for the MRI-AC and SCC-RC, respectively. Patients were assigned to two groups, high-risk and low-risk groups, according to the optimal cutoff values. Univariate analysis uncovered that the MRI-AC was obviously associated with the OS [hazard ratio (HR), 3.567; 95% confidence interval (CI), 1.466-8.677; log-rank $p=0.0027$] and PFS (HR, 4.062; 95% CI, 2.171-7.6; log-rank $p<0.0001$) for SCC in the discovery cohort (Figure 1A-B). The high-risk group separated by the MRI-AC had a significantly shorter survival rate than the low-risk group in terms of OS (five-year survival rate: 92.9% *vs.* 96.7%; ten-year survival rate: 81% *vs.* 93.5%) and PFS (five-year survival rate: 77.4% *vs.* 94.2%; ten-year survival rate: 61.9% *vs.* 88.4%) (Figure 1 A-B). Compared with the MRI-AC, the SCC-RC had a stronger predictive value for survival. Univariate analyses showed that the SCC-RC could serve as a strong prognostic factor for predicting OS (HR, 5.614; 95% CI, 2.473-12.744; log-rank $p<0.0001$) and PFS (HR, 7.481; 95% CI, 4.194-13.344; log-rank $p<0.0001$) for SCC in the discovery cohort (Figure 1 C-D). The survival rate of the patients in the high-risk group separated by the SCC-RC was obviously shorter than that in patients in the low-risk group in terms of OS

Table II. Univariate analyses in the validation cohort.

Variable	Overall survival			Progression-free survival		
	HR	HR 95% CI	*p*-value	HR	HR 95% CI	*p*-value
Age	0.98	0.917-1.048	0.5548	0.968	0.923-1.015	0.1839
Menopause (Yes *vs.* No)	1.47	0.523-4.13	0.4647	1.492	0.719-3.097	0.2833
FIGO Stage						
IB2	Ref					
IIA	0.442	0.074-2.643	0.3706	0.901	0.313-2.597	0.847
IIB	1.235	0.34-4.488	0.7485	0.985	0.385-2.517	0.9748
Lymph node metastasis (Yes *vs.* No)	3.559	1.266-10.006	**0.0161**	1.609	0.69-3.751	0.2705
Differentiation						
Well	Ref					
Moderate	0.774	0.205-2.917	0.7048	0.791	0.285-2.197	0.6535
Poor	0.467	0.105-2.087	0.3189	0.769	0.267-2.214	0.6267
Postoperative radiotherapy (Yes *vs.* No)	2.453	0.838-7.177	0.1015	1.889	0.91-3.921	0.0881
MRI-AC (High *vs.* Low)	3.376	1.154-9.879	**0.0264**	3.522	1.648-7.528	**0.0012**
SCC-RC (High *vs.* Low)	5.174	1.84-14.547	**0.0018**	8.178	3.969-16.851	**< 0.0001**
MRI-AC and SCC-RC						
Low	Ref					
Medium	2.954	0.834-10.47	0.0933	2.507	0.989-6.353	0.0527
High	8.411	2.256-31.359	**0.0015**	12.374	5.025-30.469	**< 0.0001**
NACT responsiveness (Responders *vs.* non-responders)	3.905	1.415-10.77	**0.0085**	6.531	3.101-13.75	**< 0.0001**

FIGO Stage: International Federation of Gynecology and Obstetrics Stage; MRI-AC: MRI absolute change; SCC-RC: SCC-ag relative change; NACT: Neoadjuvant chemotherapy.

(five-year survival rate: 85.3% *vs.* 97.1%; ten-year survival rate: 67% *vs.* 92.5%) and PFS (five-year survival rate: 60.8% *vs.* 92.4%; ten-year survival rate: 33.4% *vs.* 86%) (Figure 1 C-D).

The Prognostic Ability of MRI and SCC-ag in the Validation Cohort

We further assessed whether the MRI-AC and SCC-RC could act as prognostic biomarkers in the validation cohorts. The optimal cutoff values obtained in the discovery cohort were also used in the validation cohort, and the whole group of patients was assigned to high-risk and low-risk groups. The MRI-AC was significantly associated in univariate Cox analyses with OS (HR, 3.376; 95% CI, 1.154-9.879; log-rank p=0.018) and PFS (HR, 3.522; 95% CI, 1.648-7.528; log-rank p=0.0005) (Figure 2 A-B). The high-risk group of patients divided by the MRI-AC was associated with shorter survival than the low-risk group when evaluating OS (five-year survival rate: 88.3% *vs.* 98.2%; ten-year survival rate: 85.3% *vs.* 95.4%) and PFS (five-year survival rate: 75.1% *vs.* 92.6%; ten-year survival rate: 70.7% *vs.* 90.7%) (Figure 2A-B). The MRI-AC remained statistically significant in multivariate Cox models and was an IPF for OS and PFS (Table II and Table III). Since no clinical and demographic variables were significantly associated with PFS in univariate analysis, the MRI-AC was considered an IPF for PFS without fitting the multivariate models.

Similar to the discovery cohort, the SCC-RC also exhibited a stronger prognostic ability for survival than the MRI-AC in the validation cohort. The SCC-RC was significantly associated with OS (HR, 5.174; 95% CI, 1.84-14.547; log-rank p=0.0005) and PFS (HR, 8.178; 95% CI, 3.969-16.851; log-rank p<0.0001) in univariate analyses (Figure 2C-D). The high-risk group divided by the SCC-RC had a significantly shorter survival in terms of the predicted OS (five-year survival rate: 81.8% *vs.* 96.1%; ten-year survival rate: 72.7% *vs.* 94.2%) and PFS (five-year survival rate: 50% *vs.* 90.9%; ten-year survival rate: 36.4% *vs.* 89.6%) (Figure 2C-D). Multivariate analyses suggested that the SCC-RC was an IPF for OS and PFS (Table II and Table III). Since no clinical and demographic variables were significantly associated with PFS in univariate analysis, the SCC-RC was considered an IPF for PFS without fitting the multivariate models.

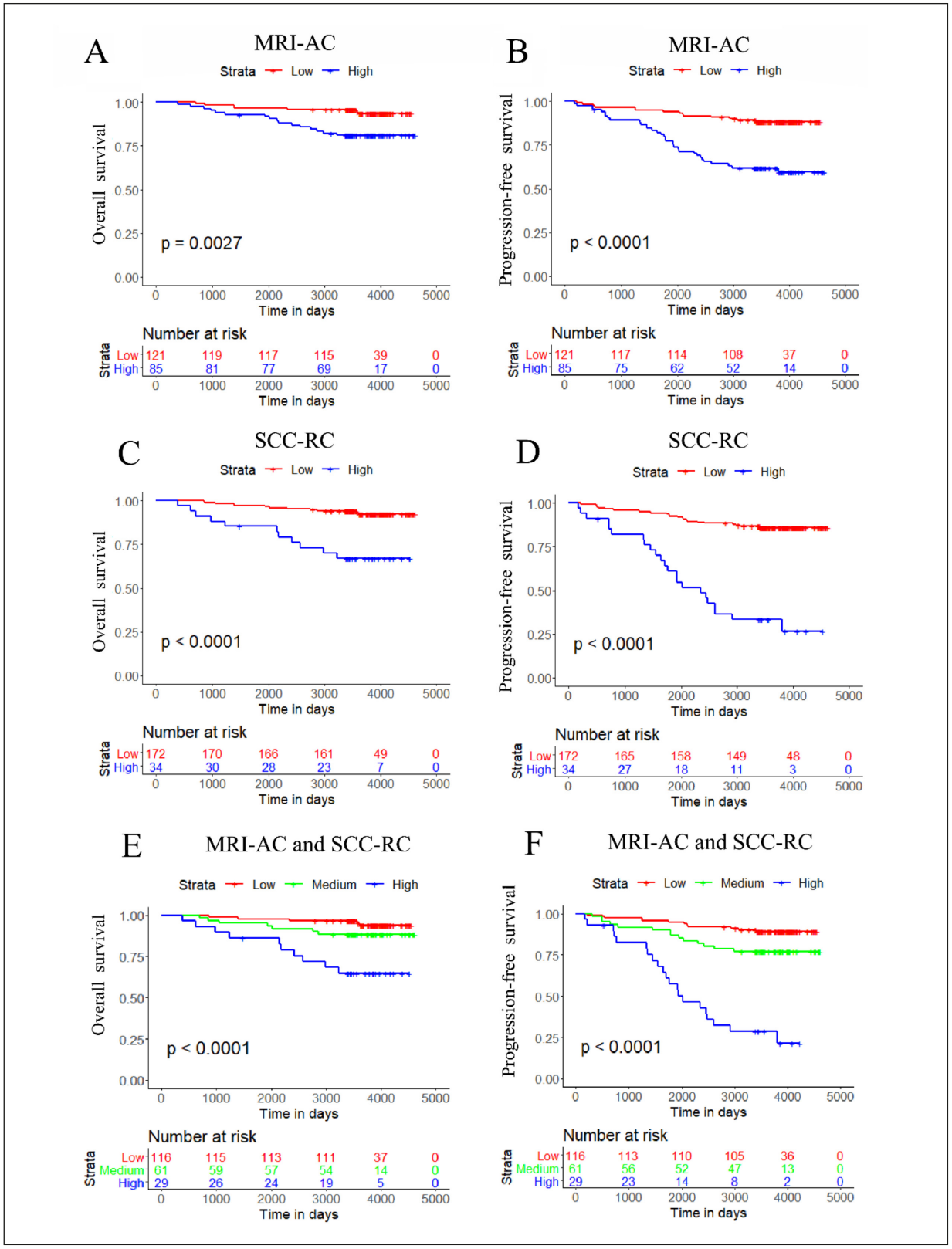

Figure 1. The prognostic value of MRI-AC and SCC-RC in the discovery cohort. **A**, MRI-AC for overall survival. **B**, MRI-AC for progression-free surviva. **C**, SCC-RC for overall survival. **D**, SCC-RC for progression-free survival. **E**, The combination of MRI-AC and SCC-RC for overall survival. **F**, The combination of MRI-AC and SCC-RC for progression-free survival.

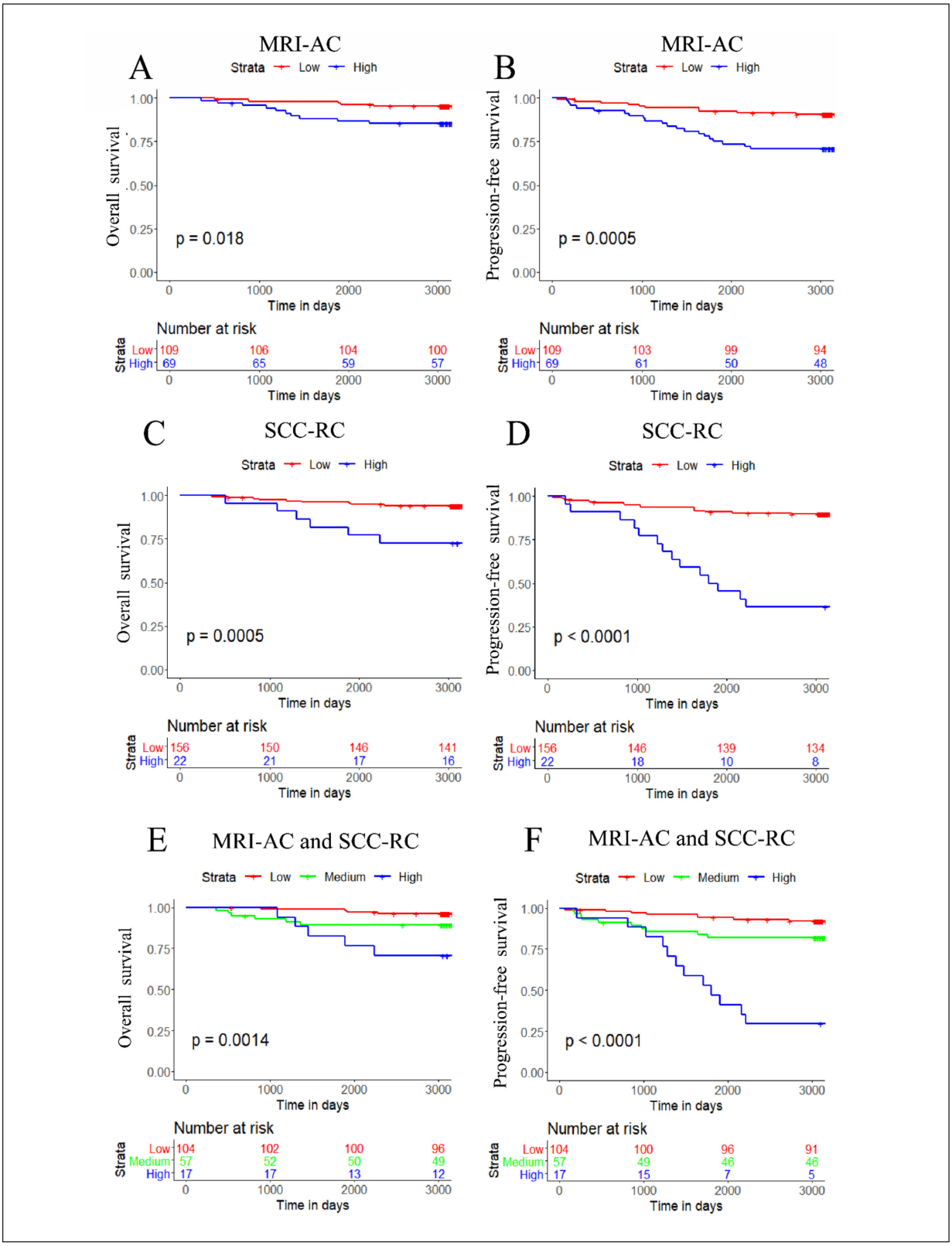

Figure 2. The prognostic value of MRI-AC and SCC-RC in the discovery cohort. **A**, MRI-AC for overall survival. **B**, MRI-AC for progression-free survival. **C**, SCC-RC for overall survival. **D**, SCC-RC for progression-free survival. **E**, The combination of MRI-AC and SCC-RC for overall surviva. **F**, The combination of MRI-AC and SCC-RC for progression-free survival.

Construction of a New Prognostic Risk Model Combining MRI with SCC-ag

As MRI and SCC-ag were strong predictors for OS and PFS, we hypothesized that the combination of these two biomarkers could further ameliorate the predictive efficiency for prognosis. We divided the whole cohorts into three groups, which generated the high-risk group with the MRI-AC high-risk group and SCC-RC high-risk group, the low-risk group with the MRI-AC low-risk group and the SCC-RC low-risk group, and the medium-risk group with either the MRI-AC high-risk group and the SCC-RC low-risk group or the MRI-AC low-risk group and the SCC-RC high-risk group.

For patients in the discovery cohort, univariate analyses demonstrated that the new combined risk model was obviously predictive of the OS and PFS (Figure 1E-F). Compared with patients in the low-risk group, patients in the high-risk group had a worse OS (HR, 8.216; 95% CI, 2.98-22.651; log-rank $p<0.0001$) and PFS (HR, 11.757; 95% CI, 5.735-24.104; log-rank $p<0.0001$). For OS, the five-year survival rates for the low-, medium-, and high-risk groups were 97.4%, 95.1%, and 86.2%, respectively, and the ten-year survival rates were 94.1%, 88.5%, and 64.7%, respectively (Figure 1E). For PFS, the five-year survival rates for the low-, medium-, and high-risk groups were 94.8%, 86.9%, and 57.3%, respectively, and the ten-year survival rates were 89.6%, 77%, and 28.6%, respectively (Figure 1F). The prognostic ability of the combined risk model was further verified in the validation cohort. The combined risk model was obviously predictive of OS and PFS in the univariate analyses (Table III; Figure 2E-F). Patients in the high-risk group had an obviously worse OS (HR, 8.411; 95% CI, 2.256-31.359; log-rank $p<0.0001$) and PFS (HR, 12.374; 95% CI, 5.025-30.469; log-rank $p<0.0001$) than patients in the low-risk group (Table III). For OS, the five-year survival rate for patients in the low-, medium-, and high-risk groups was 99%, 89.4%, and 82.4%, respectively, and the ten-year survival rate was 96.1%, 89.4%, and 70.6%, respectively (Figure 2E). For PFS, the five-year survival rates for the low-, medium-, and high-risk groups were 94.2%, 82.3%, and 47.1%, respectively, and the ten-year survival rates were 92.2%, 82.3%, and 29.4%, respectively (Figure 2F). Multivariate analyses revealed that the combined risk model was an IPF for OS and PFS (Table II and Table III). Since no clinical and demographic variables were statistically significantly associated in univariate analysis with PFS, the combined risk model was considered an IPF for PFS without fitting the multivariate models.

Therefore, the combined risk model generated a higher HR between the high-risk and low-risk groups than the MRI-AC, SCC-RC or NACT response. The combined risk model could further separate the extremely high- and low-risk group from the two groups formed by the MRI-AC and SCC-RC, which could be beneficial for increasingly individualized treatment for SCC.

Discussion

CC is one of the high-incidence cancers in women second to breast cancer, seriously endangering women's lives. Especially in the past decades, with the change of living habits and eating habits, coupled with the increase of work pressure and environmental pollution, CC has been increasingly affecting the physical and mental health of women. At present, with the progress of social informatization and the steady

Table III. Multivariate analyses in the validation cohort.

Variable	Overall survival		
	HR	HR 95% CI	p
MRI-AC (High *vs.* Low)	3.343	1.142-9.786	**0.0277**
SCC-RC (High *vs.* Low)	5.378	1.911-15.133	**0.0014**
MRI-AC and SCC-RC			
Low	Ref		
Medium	2.791	0.786-9.904	0.1123
High	9.141	2.443-34.2	**0.001**
NACT responsiveness (Responders *vs.* Non-responders)	3.542	1.277-9.827	**0.0151**

MRI-AC: MRI absolute change; SCC-RC: SCC-ag relative change; NACT: Neoadjuvant chemotherapy.

advancement of disease popularization, people's awareness of CC has been significantly improved. Although the pathogenesis of CC has not been fully elucidated, the genetics and environment factors have been identified. However, due to the problem of the individual's own immune system, it is unable to resist the invasion of viruses, which eventually leads to the growth of cancer cells and CC.

Although NACT followed by radical operation was confirmed to be an effective therapy for locally advanced CC, there were a subset of patients who experienced recurrence or metastases and had poor prognosis after treatment. Several studies[15,19-22] have focused on identifying biomarkers to predict the response to NACT in SCC patients treated with NACT plus radical surgery.

The progression of cervical cancer is a long process. If it can be diagnosed at an early stage and treated as soon as possible, it is of great significance to improve the prognosis of patients. However, few studies[19-22] have tried to identify prognostic factors for these patients and to identify the subset of patients who did not benefit from this treatment. To our knowledge, our study was the first to investigate the role of SCC-ag, MRI, and their combination as IPFs for SCC patients treated with NACT and radical surgery. Our study demonstrated that SCC-ag and MRI, individually or in combination, were bound up with OS and PFS in SCC. Additionally, the predictive efficiency improved when SCC-ag and MRI were combined into a risk model to predict OS and PFS in SCC compared with either of the individual SCC-ag or MRI, indicating that the combination of these two biomarkers could help to ameliorate prognostic stratification and guide personalized therapy for SCC patients. The FIGO stage is the most important prognostic factor for CC, but it was not statistically significant for prognostic prediction in our research, although it almost significant for predicting PFS in the discovery cohort (p=0.0429). Our conclusions were drawn from the discovery cohort and were validated in the validation cohort, suggesting that the optimal cutoff value of MRI and SCC-ag obtained from the discovery cohort could be used in clinical practice for prognostic stratification of SCC patients.

Many studies[8-14] demonstrated that the response to NACT was an IPF for SCC patients. However, NACT response was not statistically significant for predicting the OS in our discovery cohort. In addition, the predictive efficiency of NACT response was not only inferior to that of the combined risk model, but it was also inferior to that of SCC-ag. Therefore, although this study was motivated by the predictive ability of MRI and SCC-ag for NACT response, these two biomarkers had a stronger ability to predict prognosis than NACT response.

Sera SCC-ag is one of the most prevalent biomarkers for CC and has been confirmed[23-27] to be an important prognostic factor for CC. SCC-ag extracted from cervical squamous cell carcinoma is a marker of SCC, and its detection is highly correlated with the diagnosis of CC. Studies[28-32] have shown that it can provide detection value in combination with other indicators. Li et al[27] showed that posttreatment SCC-ag after NACT was an IPF affecting the OS and PFS for SCC patients treated with NACT and radical surgery. In our study, we used the same optimal cutoff value of SCC-ag as that in Li et al[27] study and found that the HR of posttreatment SCC-ag was only slightly higher than that of SCC-RC for predicting the OS in the validation cohort, and posttreatment SCC-ag had a significantly lower HR than SCC-RC for predicting OS and PFS in the discovery cohort and for predicting PFS in the validation cohort. Our study synthesized the effect of SCC-ag before and after NACT and evaluated the relative change, which displayed a stronger predictive efficiency than that of posttreatment SCC-ag alone. In addition, our study combined the effect of SCC-ag with MRI to form a new risk model, and this risk model performed better than either of the individual biomarkers.

The limitations of this study are as follows. This risk model only included data from patients in this study, and these patients were diagnosed between August 2006 and December 2010. We did not include subsequent data, which may lead to bias in the results. In addition, we did not perform *in vivo* or *in vitro* validation, which also needed further investigations.

Conclusions

Our study revealed that SCC-ag and MRI, individually or in combination, were IPFs of OS and PFS for locally advanced SCC patients treated with NACT followed by radical operation. SCC-ag in combination with MRI provided more precise prognostic stratification for SCC patients than either SCC-ag or MRI, which could help to guide individual treatment for these patients. Ad-

ditionally, the optimal cut-off values of the MRI-AC and SCC-RC obtained by our study could be applied in clinical practice to divide locally advanced SCC patients into several risk groups.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data Availability

All data generated or analyzed during this study are included in this published article.

Ethics Approval

This study protocol was approved by the Hospital Ethics Committee of the Harbin Medical Universtiy Cancer Hospital with the ethics number FH-EU20100203.

Informed Consent

All subjects were informed of the purpose, content, and procedure of the clinical study. All subjects have signed informed consent.

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