

Evaluation of Chemotherapy Response with Serum Squamous Cell Carcinoma Antigen Level in Cervical Cancer Patients: A Prospective Cohort Study

Mingzhu Yin^{1,3}, Yan Hou^{2,3}, Tao Zhang², Changyi Cui³, Xiaohua Zhou⁴, Fengyu Sun², Huiyan Li⁵, Xia Li⁶, Jian Zheng⁵, Xiuwei Chen¹, Cong Li⁷, Xiaoming Ning⁷, Kang Li^{2*}, Ge Lou^{1*}

1 Department of Gynecology and Oncology, The Affiliated Tumor Hospital of Harbin Medical University, Harbin, Heilongjiang Province, China, **2** Department of Epidemiology and Biostatistics, Harbin Medical University, Harbin, Heilongjiang Province, China, **3** Laboratory of Genetics, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, United States of America, **4** Department of Biostatistics, University of Washington, Seattle, Washington, United States of America, **5** Department of Radiotherapy Oncology, The Affiliated Tumor Hospital of Harbin Medical University, Harbin, China, **6** Department of Cardiology, The Second Affiliated Hospital of Harbin Medical University, Harbin, China, **7** Department of Pathology, The Affiliated Tumor Hospital of Harbin Medical University, Harbin, China

Abstract

MRI does not always reflect tumor response after chemotherapy. Therefore, it is necessary to explore additional parameters to more accurately evaluate tumor response for the subsequent clinical determination about radiotherapy or radical surgery. A training cohort and an external validation cohort were used to examine the predictive performance of SCC-ag to evaluate tumor response from teaching hospital of Harbin Medical University. The study included 397 women with SCC (age: 28–73 years). Patients consecutively enrolled between August 2008 and January 2010 ($n = 205$) were used as training cohort. Patients consecutively enrolled between February 2010 and May 2011 ($n = 192$) were used as validation cohort. A multivariate regression analysis of the data from the training cohort indicated that serum SCC-ag level is an independent factor for neo-adjuvant chemotherapy (NACT) response. Analysis of the data from the validation cohort suggested that chemotherapy response could be more accurately predicted by SCC-ag than by magnetic resonance imaging (MRI) (sensitivity (Se): 0.944 vs. 0.794; specificity (Sp): 0.727 vs. 0.636; positive predictive value (PPV): 0.869 vs. 0.806; negative predictive value (NPV): 0.873 vs. 0.618; the area under ROC curve (AUC): 0.898 vs. 0.734). Combining SCC-ag with MRI was more powerful than MRI alone (Se: 0.952 vs. 0.794; Sp: 0.833 vs. 0.636; PPV: 0.916 vs. 0.806; NPV: 0.902 vs. 0.618; AUC: 0.950 vs. 0.734). Our study indicates that serum SCC-ag level is a sensitive and reliable measure to evaluate cervical cancer response to chemotherapy. Using SCC-ag in combination with MRI findings further improves the predictive power.

Citation: Yin M, Hou Y, Zhang T, Cui C, Zhou X, et al. (2013) Evaluation of Chemotherapy Response with Serum Squamous Cell Carcinoma Antigen Level in Cervical Cancer Patients: A Prospective Cohort Study. *PLoS ONE* 8(1): e54969. doi:10.1371/journal.pone.0054969

Editor: Rui Medeiros, IPO, Inst Port Oncology, Portugal

Received: August 27, 2012; **Accepted:** December 18, 2012; **Published:** January 22, 2013

Copyright: © 2013 Yin et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: The study was supported by grants from the National Natural Science Foundation of China (NSFC 81172453 and 81172767), Wu LianDe Youth Innovation Fund (WLD-QN1105) and the Tumor Hospital of Harbin Medical University Fund (JJZ2011-08).

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: louge@ems.hrbmu.edu.cn (GL); likang@ems.hrbmu.edu.cn (KL)

These authors contributed equally to this work.

Introduction

Neoadjuvant chemotherapy (NACT) could create chances for curative resection of initially non-resectable tumors [1–4]. However, approximately 30% of the patients with squamous cervical cancer (SCC) are non-responsive to chemotherapy [5,6]. For patients not responding to neoadjuvant chemotherapy, attempt to remove the tumor with surgery could be disastrous.

MRI is the golden standard to evaluate tumor response to chemotherapy. For cervical cancer patients receiving neoadjuvant chemotherapy, MRI findings are used to determine eligibility of the patients for subsequent resection [7–9]. MRI is prone to false-positive results, i.e. tumor appears to be decreased in size upon MRI imaging, but actually did not change or even have increased in size based on post-surgical pathological examination, or false-negative results, e.g. in patients with “no residual disease” as judged by MRI imaging, histologic examination detected lesions that measured >1 cm in 8% of the case [10]. Integrated

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging improves the evaluation accuracy of tumor volume after chemotherapy [11]. The expense, however, has limited its use, especially in developing countries.

The squamous cell carcinoma antigen (SCC-ag), which serves as a serological marker for squamous cell cervical cancer, is a sub-fraction of the tumor antigen TA-4, which is a 48 kDa glycoprotein that was first isolated by Kato and Torigoe [12]. This antigen is reported to be closely related to clinical staging or the tumor spread as well as the tumor response of advanced squamous disease to radiation or chemotherapy [13–15] and can be used to predict the survival and tumor recurrence during the follow-up period [16–20].

In the current study, we examined the sensitivity and reliability of using serum SCC-ag level to evaluate response to chemotherapy in patients with cervical cancer. The study included a training cohort of 205 subjects and an external validation cohort of 192

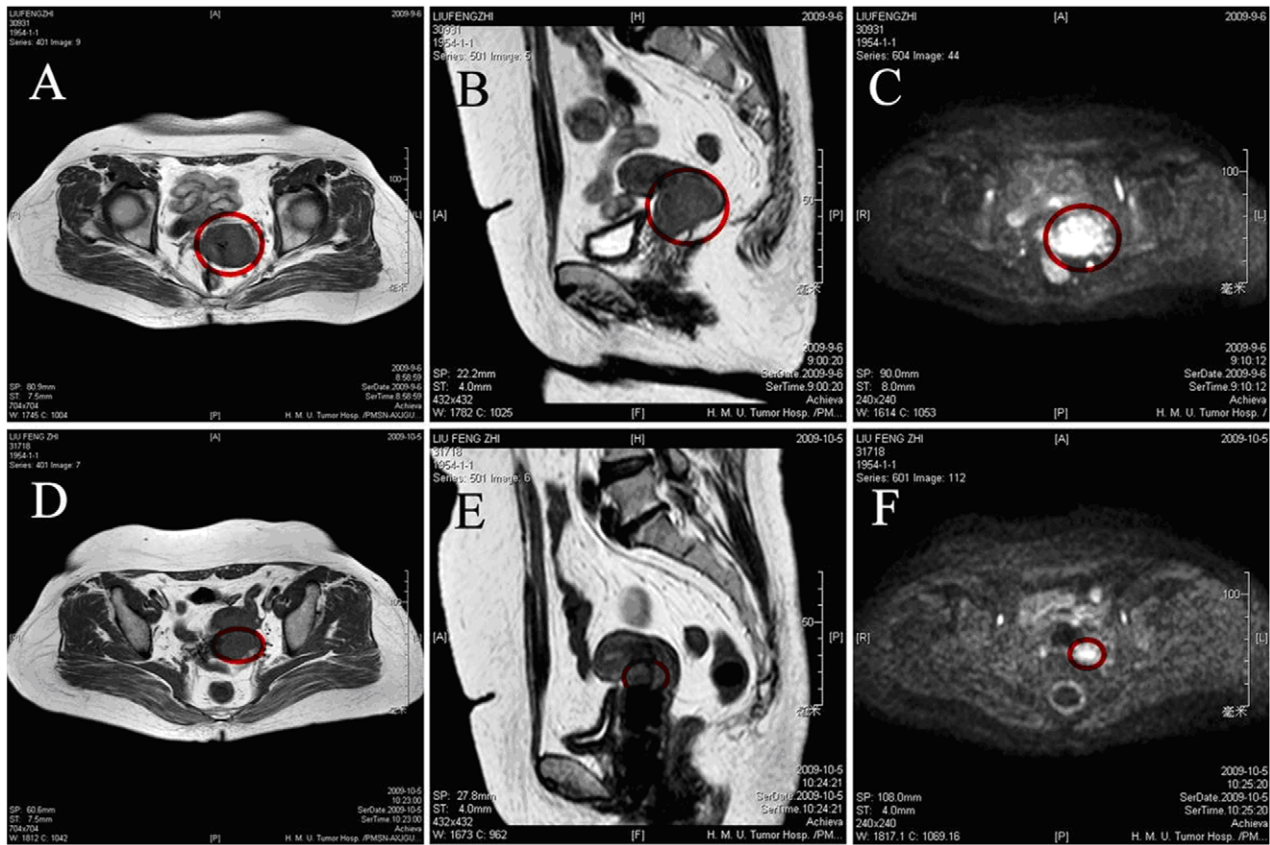


Figure 1. Conventional and DW-MRI of the same lesion from a 55-year-old woman undergoing NACT. (A)–(C): pretreatment axial (A) and sagittal (B) conventional MR images and diffusion-weighted MR image (C). (D)–(F): preoperative axial (D) and sagittal (E) conventional MR images and diffusion-weighted MR image (F). The red circles in (B)–(F) indicate the largest pretreatment and preoperative lesion as measured in different planes and using different MRI techniques.

doi:10.1371/journal.pone.0054969.g001

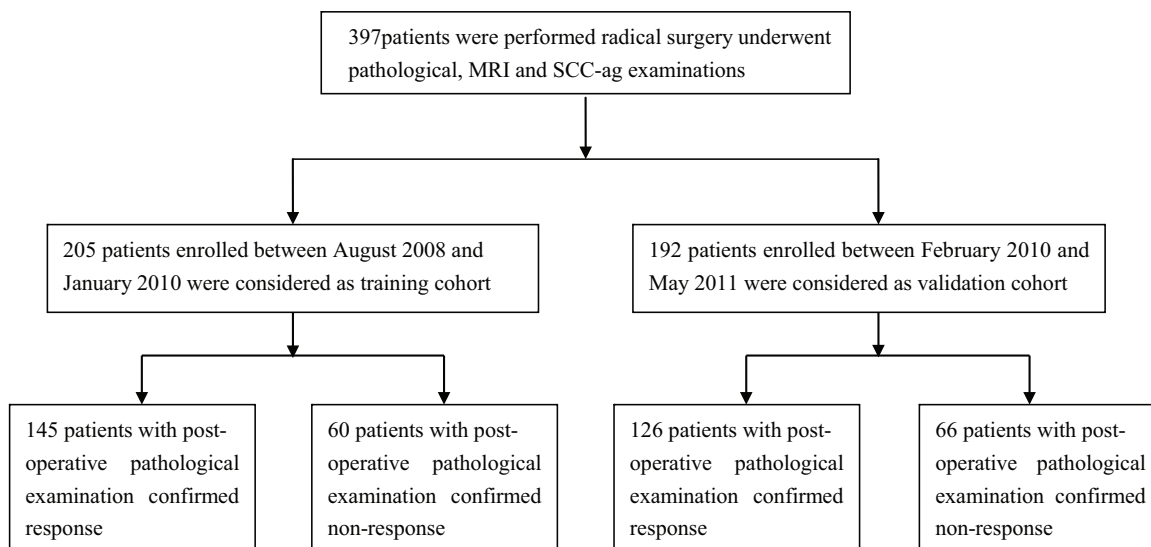


Figure 2. Number of patient enrollment.

doi:10.1371/journal.pone.0054969.g002

Table 1. Demographics and Clinical Characteristics of Eligible Patients in Prospective Cohort.

Characteristics	Training cohort (n = 205)		p value	Validation cohort (n = 192)		p value
	Non-response (n = 60)	Response (n = 145)		Non-response (n = 66)	Response (n = 126)	
Age						
Mean ± SD	47.65 ± 8.39	49.1 ± 8.42	0.2615	46.85 ± 8.45	46.28 ± 9.39	0.6870
Min-max	32–73	28–68		30–71	25–72	
Menses						
Non-menopause	25(41.67)	64(44.14)	0.7453	24(36.36)	41(32.54)	0.5949
menopause	35(58.33)	81(55.86)		42(63.64)	85(67.46)	
FIGO Stage						
IB2	16(26.67)	24(16.55)	0.0719	23(34.85)	22(17.46)	0.0389
IIA	12(20.00)	47(32.41)		18(27.69)	44(34.92)	
IIB	32(53.33)	74(51.03)		25(38.46)	60(47.62)	
Lymph node metastasis						
Negative	11(18.33)	46(31.72)	0.0515	35(53.03)	59(46.83)	0.4140
Positive	49(81.67)	99(68.28)		31(46.97)	67(53.17)	
Differentiation						
Well	9(15.00)	22(15.28)	0.9895	9(13.64)	32(25.4)	0.1668
Moderate	29(48.33)	68(47.22)		34(51.52)	57(45.24)	
Poor	22(36.67)	55(37.50)		23(34.85)	37(29.37)	

The values in the parentheses represented the percentage frequency;
doi:10.1371/journal.pone.0054969.t001

subjects. A random forest model was used to test the hypothesis that SCC-ag level in combination with MRI improves the evaluation of response to chemotherapy.

Materials and Methods

Inclusion Criteria

Patients were enrolled in this study if they satisfied all following inclusion criteria: 1) a diagnosis of stage IB2-IIB SCC (FIGO classification); 2) no prior hysterectomy, pelvic radiotherapy, systemic chemotherapy or medical contraindications to chemotherapy. All patients have signed up the written informed consent. The study was approved by the Institutional Review Board. All patients received NACT treatment following radical dissection, and underwent MRI and SCC-ag examinations. NACT regimen consisted of three cycles of paclitaxel and carboplatin treatment. On the first day of each cycle, patients received paclitaxel at 150 mg/m² intravenously (IV) over a period of 3 hours plus carboplatin (area under the serum concentration-time curve: 5) over a period of 30 minutes. Blood pressure, ECG and blood oxygen saturation were monitored during the infusion. Cycles were separated by 3 weeks.

Training and Validation Cohorts

The training cohort includes all patients with a diagnosis of stage IB2-IIB SCC between August 2008 and January 2010. The validation cohort included all patients diagnosed with stage IB2-IIB SCC between February 2010 and May 2011.

Magnetic Resonance Imaging

All patients underwent MRI scans at the initial visit using a 1.5-T NVi/CVi magnetic resonance machine (GE, Waukesha, Wisconsin, USA) with a standard phased array torso coil. An

additional MRI scan was carried out upon completion of NACT. Briefly, a sagittal T1- and T2-weighted fast spin echo acquisition was obtained with a 24 × 24 cm field of view (FOV), an echo time (TE) of 97.6 ms, and a repetition time (TR) of 1600 ms. Slices (4 mm) were acquired with 1-mm gap using a 256 × 256 matrix. The scan ranged from the iliac crests to the pubic symphysis. Based on the sagittal view, axial slices were obtained through the tumor using a T2-weighted fast recovery fast spin echo sequence with an FOV of 32 × 32 cm, a TE/TR of 83.6/4520 ms, 3-mm slices (no gap) and a 256 × 256 matrix.

Once the tumor was fully visualized, diffusion-weighted images (DWIs) were acquired in straight axial and sagittal planes (planned on the T2-weighted sagittal scan) and centered through the middle of the tumor using an epi-based diffusion tensor imaging sequence. The epi-based sequence was limited to straight axial slices. All slices were acquired with a 40 × 40-cm FOV, a 2-mm slice thickness, a TR/TE of 6800 ms/70 ms, and a 160 × 256 matrix. Data were acquired with a *b* value of 1000. The ADC value was obtained from diffusion tensor images on each slice.

Clinical Response Evaluation and Imaging Analysis

Clinical response was evaluated using the RECISR criteria for solid tumors (version 1.1).⁹ Complete response (CR) was defined as complete disappearance of all lesions; partial response (PR) was defined as at least a 30% decrease in the sum of the largest diameter (LD) of the targeted lesions; stable disease (SD) was defined as neither shrinkage that qualified as PR nor sufficient increase that qualified as progressive disease (PD); and PD was defined as at least a 20% increase in the sum of the LD of the target lesions. The overall response was defined as CR plus PR. The clinical response was evaluated based on imaging only. The images were evaluated by two experienced radiologists aware of patient diagnosis and treatment but not the results of other

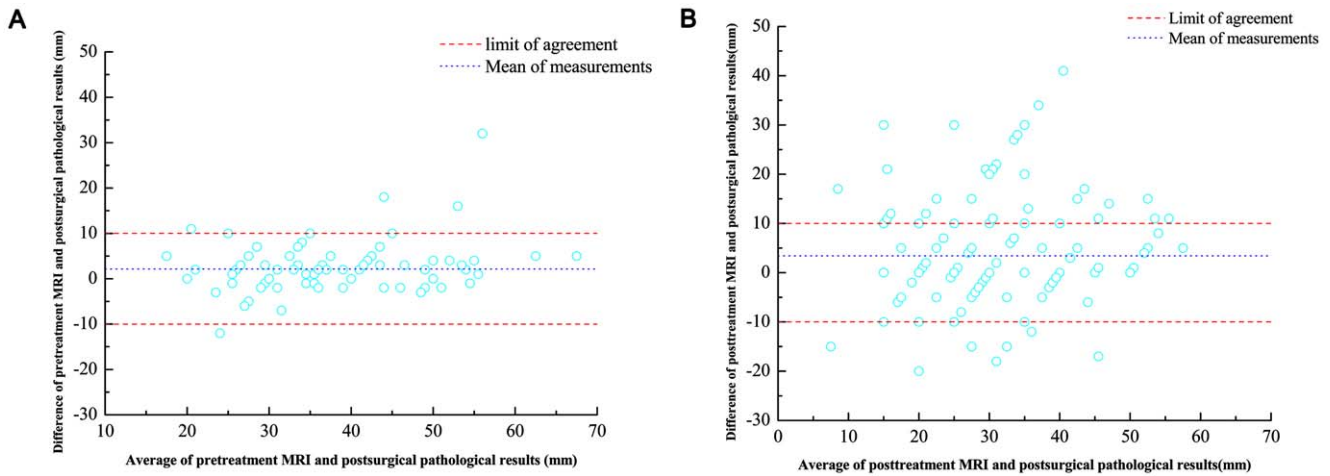


Figure 3. Agreement of tumor sizes, as measured by MRI versus postsurgical pathology. (A) Bland-Altman plot of tumor size measured by pretreatment MRI examination and postsurgical pathological results; 95% plots are within the limit of agreement (0 ± 10 mm), indicating a good agreement between pretreatment MRI results and postsurgical pathological measurement. (B) Bland-Altman plot of tumor size measured by posttreatment MRI and postsurgical pathology; almost 40% plots are out of the limit of agreement (0 ± 10 mm), which indicates a poor agreement between posttreatment MRI and postsurgical pathology, i.e. posttreatment MRI results may not be in place of postsurgical pathological measurement.

doi:10.1371/journal.pone.0054969.g003

imaging modalities. Upon discrepancy between the two readings, a third, independent experienced radiologist served as the final arbitrator. Representative MRI and DWI of a 55-year-old patient are shown in Figure 1.

SCC-ag Assay

Fasting serum samples were collected in duplicate at the initial visit and upon the completion of NACT. SCC-ag level was measured using an IMx SCC-ag microparticle enzyme immunoassay kit (Abbott Laboratories, Abbott Park, IL).

Pathological Assessment

All specimens removed by surgery were submitted for pathological analysis that included macroscopic measurement of the lesion size and microscopic determination of the lesion boundary based on frozen tissue.

Statistical Analysis

Categorical data are described as frequency counts and percentages, and the quantitative data were presented as mean \pm standard deviation ($\bar{X} \pm SD$). Comparisons between the clinopathological characteristics, e.g., FIGO staging, lymph node metastasis and differentiation in responsive and non-responsive patients, were performed using *Pearson's* chi-square test. Bland-Altman analysis was used to assess the agreement between MRI examinations and pathological findings and the Bland-Altman plot was used to visualize this agreement [21–23]. Univariate and multivariate logistic regression analyses were conducted to determine whether SCC-ag level was an independent factor in the evaluation of the NACT response Random forest (RF) analysis [24–27] was carried out in the validation cohort to verify the predictive performance and compare the evaluation accuracy of MRI findings in combination with SCC-ag vs. MRI results or SCC level alone. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and the area under receiver operating curve (AUC) were calculated using pathological results as reference standard.

All statistic analyses were carried using SAS version 9.1.3 (SAS, Cary, NC), with the exception of random forest analysis (R version 2.12).

Results

Demographic and Clinical Characteristics

Between August 2008 and October 2010, 446 subjects were enrolled. Among these, 397 patients received NACT followed by radical surgery (Figure 2). The demographic and clinical data were summarized in Table 1. The baseline characteristics were comparable across the datasets, with the exception of FIGO stage

Table 2. Univariate and Multivariate Logistic Analysis of SCC-ag Level and Response to Neoadjuvant Chemotherapy in a Prospective Cohort.

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Δ MRI*						
<0.30	1.00	–	–	–	–	–
≥ 0.30	13.30	6.40–27.63	<0.0001	10.28	3.86–27.37	<.0001
Δ SCC-ag [†]						
<0.30	1.00	–	–	–	–	–
[0.30, 0.50)	4.63	1.53–13.98	0.0158	3.62	1.01–2.93	0.0210
[0.50, 0.70)	30.06	10.35–87.36	0.0048	31.70	9.28–108.25	0.0025
≥ 0.70	112.54	28.18–449.40	<.0001	75.26	17.00–333.16	<.0001

* Δ MRI indicated the decrease percentage in tumor size before and after NACT with MRI.

[†] Δ SCC-ag indicated the decrease percentage in SCC-ag level before and after NACT.

doi:10.1371/journal.pone.0054969.t002

Table 3. Tumor sizes before and after neoadjuvant chemotherapy with the percent of SCC-ag decrease.

Group	Percent of SCC-ag decrease after NACT	Pretreatment		Posttreatment	
		$\bar{X} \pm SD$	Median(range)	$\bar{X} \pm SD$	Median(range)
Training cohort (n = 205)	<0.30	42.93 ± 13.77	44(20~75)	35.78 ± 14.95	37(0~61)
	[0.30, 0.50)	43.13 ± 12.84	40(24~73)	30.25 ± 14.75	28(0~61)
	[0.50, 0.70)	45.85 ± 10.33	44.5(25~68)	26.92 ± 14.36	28.5(0~51)
	≥0.70	47.49 ± 12.07	47(28~80)	24.01 ± 13.01	23.5(0~67)
Validation cohort (n = 192)	<0.30	42.68 ± 12.05	40(24~68)	36.51 ± 16.79	40(0~65)
	[0.30, 0.50)	41.00 ± 10.53	40(24~60)	28.43 ± 14.08	25(0~54)
	[0.50, 0.70)	44.56 ± 11.05	44(20~68)	27.47 ± 12.82	25(0~50)
	≥0.70	48.89 ± 11.41	50(24~80)	24.02 ± 13.56	22(0~67)

doi:10.1371/journal.pone.0054969.t003

in the validation cohort. Although the training cohort had many more lymph node positive metastases, there was no significantly statistical difference ($p = 0.0515$).

Agreement between MRI data and the Postsurgical Pathological Findings

The Bland-Altman plot was used to visualize the agreement between pretreatment or posttreatment MRI and the postsurgical pathological finding. In the Bland-Altman plot, the limit of agreement was the acceptably maximal difference of MRI and postsurgical pathological results, known from the clinical point of view, approximately 10 mm. The Bland-Altman analysis showed that the tumor size measured by pretreatment MRI and postsurgical pathology exhibited good agreement (Figure 3A) because 95% plots lies in the limits, whereas approximately 40% of

the plots were out of the limit of agreement (Figure 3B), indicating a poor agreement in tumor size measured by posttreatment MRI and postsurgical pathological examinations results.

SCC-ag Level and the Response to NACT

As mentioned above (see Introduction), SCC-ag is closely related to the extent of the disease as well as the response to treatment and can be used to predict the survival and tumor recurrence during the follow-up period. However, to our knowledge, few studies were performed to investigate the role of SCC-ag in the evaluation performance to chemotherapy response. Therefore, we tried to assess whether serum SCC-ag level measured before and after NACT can be a parameter for evaluation of tumor response. In this study, the 30, 50, and 70% decreases in SCC-ag levels were chosen as cutoffs to categorize the

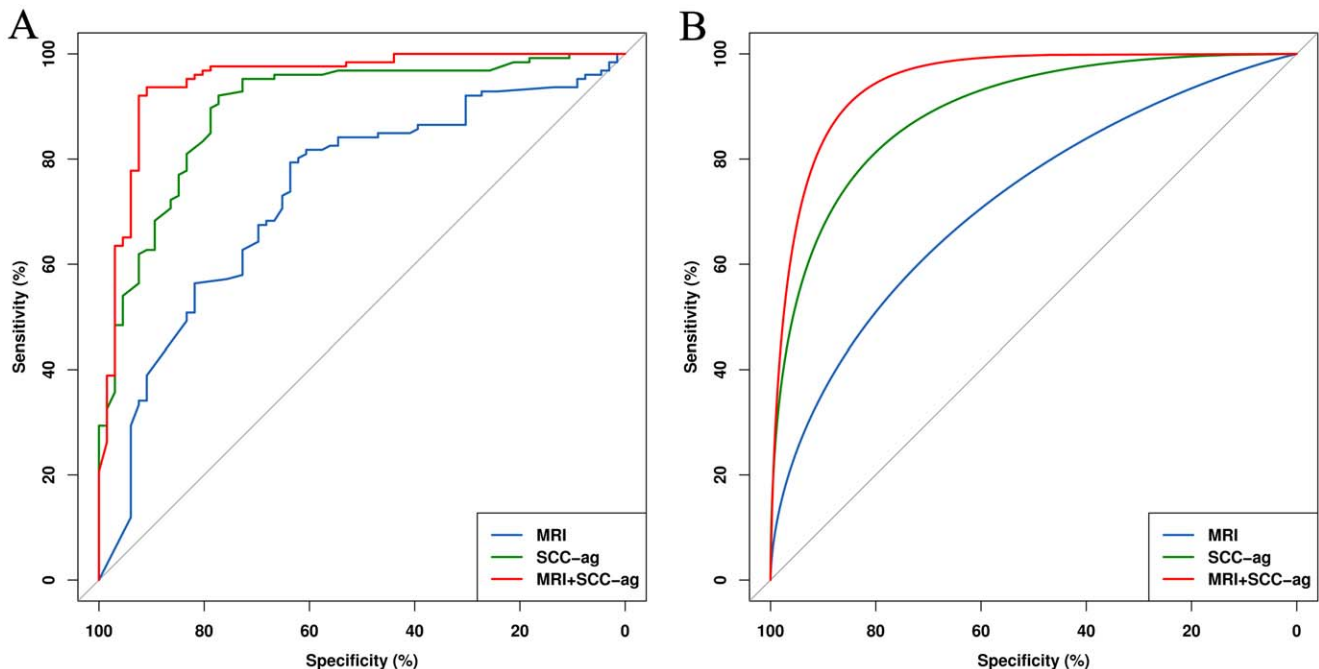


Figure 4. The empirical (A) and smooth (B) AUCs in the validation cohort. MRI in combination with serum SCC-ag vs. MRI or SCC-ag alone, respectively.

doi:10.1371/journal.pone.0054969.g004

Table 4. The Accuracy Estimation of NACT Response in an External Validation Cohort.

Evaluation indicator	Δ MRI		Δ SCC		MRI plus SCC	
	Estimator	95%CI	Estimator	95%CI	Estimator	95%CI
Sensitivity	0.80	0.72–0.87	0.94	0.90–0.98	0.95	0.91–0.98
Specificity	0.64	0.52–0.74	0.73	0.62–0.83	0.83	0.74–0.92
PPV	0.81	0.73–0.87	0.87	0.81–0.92	0.92	0.86–0.96
NPV	0.62	0.50–0.74	0.87	0.78–0.95	0.90	0.82–0.97
AUC	0.73	0.66–0.81	0.90	0.85–0.95	0.95	0.91–0.99

Abbreviation: Δ MRI: the decrease percentage in tumor size before and after NACT with MRI; Δ SCC-ag: the decrease percentage in SCC-ag level before and after NACT; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the ROC curve; The confidence interval was estimated based on exact test of binominal distribution.
doi:10.1371/journal.pone.0054969.t004

continuous pre- and post-treatment SCC-ag levels and find out the correlation between SCC-ag level and chemotherapy response in a more clear way. Univariate and multivariate logistic regression analyses of the chemotherapy response evaluation based on the MRI findings or SCC-ag levels alone were shown in Table 2. The mean and median of pre-treatment and post-treatment tumor sizes as well as range with the percent of SCC-ag decrease were presented in Table 3. Both MRI findings and SCC-ag level are independent factors for response to chemotherapy and the percent of MRI examination and SCC-ag level decrease positively correlated with chemotherapy response. From the multivariate logistic regression, we found that the percent of MRI above 30% increase the likelihood of chemotherapy response for patients by 10.28 times compared with 30% or less. The percent of SCC-ag decrease after chemotherapy exceeding 30, 50, 70% increase the possibility of chemotherapy response by 3.62, 31.70, 75.26 times compared with decrease percent below 30%, respectively.

Validation

Analysis of the data from the validation cohort using a random forest model demonstrated that chemotherapy response could be more accurately predicted by SCC-ag than by MRI in Table 4 (Se: 0.944 vs. 0.794; Sp: 0.727 vs. 0.636; PPV: 0.869 vs. 0.806; NPV: 0.873 vs. 0.618; AUC: 0.898 vs. 0.734). Combining SCC-ag with MRI was more powerful than MRI alone (Se: 0.952 vs. 0.794; Sp: 0.833 vs. 0.636; PPV: 0.916 vs. 0.806; NPV: 0.902 vs. 0.618; AUC: 0.950 vs. 0.734). Figure 4 presented the empirical and smooth AUCs for the external validation cohort with MRI plus SCC-ag, MRI and SCC-ag alone.

Discussion

The current study revealed good agreement of post-surgical pathological findings with MRI findings prior to, but not after

NACT. Possible factors that contributed to the poor agreement after chemotherapy include necrosis, granuloma formation, hyaline degeneration, tiny lesions and inflammation in the target lesions after the treatment. Diffusion-weighted MRI (DW-MRI) could improve the accuracy, but only to limited degree [28,29].

Serum SCC-ag, which is one of the most common biomarkers of cervical cancer, has been used to monitor the disease recurrence. Few studies, however, have investigated the role of the SCC-ag levels in the evaluation of NACT response in SCC patients. Hashimoto et al investigated the role of SCC-ag as a biomarker of chemotherapy response in patients with metastatic cervical cancer and reported that the patients with reduction in serum SCC-ag levels may be responsive to chemotherapy [30] and Kim et al demonstrate that there is a linear correlation between percent decrease in SCC-ag and that of tumor volume in cervical cancer patients [31], which are consistent with our results. Besides, we also demonstrates that the accuracy of the percent of SCC-ag decrease alone in the chemotherapy response evaluation is better than that of MRI alone, and SCC-ag level together with MRI examination is more powerful than MRI alone. Additionally, Reesink-Peter et al. recently reported that in the early-stage cervical cancer, serum SCC-ag level is more refined preoperative estimation of the likelihood for adjuvant radiotherapy [32]. SCC level may be useful in the evaluation of primary and recurrent SCC of cervix to radiation and chemotherapy [15], Ohara et al found that postradiotherapy SCC-ag can be used to predict tumor recurrence and not useful for evaluation radiotherapy response [33]. In this present study, we did not mention the relationship between radiotherapy response or metastasis and decrease percent of SCC-ag level, which needs to be further studied.

The ADC values from the DW-MRI data at each assessment (Table 5) did not differ between non-responsive and responsive patients, suggesting the limited value of DW-MRI.

In theory, the findings from the current study could be reasonably extrapolated to all malignant tumors that originate from squamous tissue. Such a speculation, however, requires extensive studies in the future.

In conclusion, our study indicates that serum SCC-ag level is a sensitive and reliable measure to evaluate cervical cancer response to chemotherapy. Using SCC-ag in combination with MRI findings further improves the predictive power. Chemotherapy response evaluation may benefit from this serum biomarker and help the oncologists to make optimal decision for cervical cancer patients.

Table 5. Apparent diffusion coefficient (ADC) values in the response and non-response patients before and after chemotherapy treatment ($\text{mm}^2\cdot\text{s}$).

	N	Pre-treatment	Post-treatment
Response	271	$0.92 \pm 0.22 \times 10^{-3}$	$1.03 \pm 0.16 \times 10^{-3}$ *
Non-response	126	$0.93 \pm 0.18 \times 10^{-3}$	$1.01 \pm 0.24 \times 10^{-3}$ *

*compare with pre-treatment ADC value, $p > 0.05$;
doi:10.1371/journal.pone.0054969.t005

Acknowledgments

We would like to thank all the reviewers for their valuable contribution and constructive feedback.

References

- Benedetti-Panici P, Maneschi F, Cutillo G, Greggi S, Salerno MG, et al. (1996) Modified type IV-V radical hysterectomy with systematic pelvic and aortic lymphadenectomy in the treatment of patients with stage III cervical carcinoma. Feasibility, technique, and clinical results. *Cancer* 78: 2359–2365.
- Iwasaka T, Fukuda K, Hara K, Yokoyama M, Nakao Y, et al. (1998) Neoadjuvant chemotherapy with mitomycin C, etoposide, and cisplatin for adenocarcinoma of the cervix. *Gynecol Oncol* 70: 236–240.
- deSouza NM, Soutter WP, Rustin G, Mahon MM, Jones B, et al. (2004) Use of neoadjuvant chemotherapy prior to radical hysterectomy in cervical cancer: monitoring tumor shrinkage and molecular profile on magnetic resonance and assessment of 3-year outcome. *Br J Cancer* 90: 2326–2331.
- Yin M, Zhao F, Lou G, Zhang H, Sun M, et al. (2011) The long-term efficacy of neoadjuvant chemotherapy followed by radical hysterectomy compared with radical surgery alone or concurrent chemoradiotherapy on locally advanced stage cervical cancer. *Int J Gynecol Cancer* 21: 92–99.
- Panici PB, Scambia G, Baiocchi G, Greggi S, Ragusa G, et al. (1991) Neoadjuvant chemotherapy and radical surgery in locally advanced cervical cancer. Prognostic factors for response and survival. *Cancer* 67: 372–379.
- Park DC, Kim JH, Lew YO, Kim DH, Namkoong SE (2004) Phase II trial of neoadjuvant paclitaxel and cisplatin in uterine cervical cancer. *Gynecol Oncol* 92: 59–63.
- Micheletti E, La Face B, Bianchi E, Caqna E, Apostoli P, et al. (1997) Continuous infusion of carboplatin during conventional radiotherapy treatment in advanced squamous carcinoma of the cervix uteri IIB-IIIIB (UICC). A phase I/II and pharmacokinetic study. *Am J Clin Oncol* 20: 613–620.
- Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, et al. (2000) Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 18: 1606–1613.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 45: 228–247.
- Vincens E, Balleyquier C, Rey A, Uzan C, Zareski E, et al. (2008) Accuracy of Magnetic Resonance Imaging in Predicting Residual Disease in Patients Treated for Stage IB2/II Cervical Carcinoma With Chemoradiation Therapy. *Cancer* 113: 2158–2165.
- Dimitrakopoulou-Strauss A, Strauss LG, Egerer G, Vasamiette J, Mechterheimer G, et al. (2010) Impact of dynamic 18F-FDG PET on the early prediction of therapy outcome in patients with high-risk soft-tissue sarcomas after neoadjuvant chemotherapy: a feasibility study. *J Nucl Med* 51(4): 551–558.
- Kato H, Torigoe T (1977) Radioimmunoassay for tumor antigen of human cervical squamous cell carcinoma. *Cancer* 40: 1621–1628.
- Kato H, Morioka H, Tsutsui H, Aramaki S, Torigoe T (1982) Value of tumor antigen (TA-4) of squamous cell carcinoma antigen in predicting the extent of cervical cancer. *Cancer* 50: 1294–1296.
- Scambia G, Benedetti Panici P, Foti E, Amoroso M, Salerno G, et al. (1994) Squamous cell carcinoma antigen: Prognostic significance and role in the monitoring of neoadjuvant chemotherapy response in cervical cancer. *J Clin Oncol* 12: 2309–2316.
- Yazigi R, Munoz AK, Richardson B, Risser R (1991) Correlation of squamous cell carcinoma antigen levels and treatment response in cervical cancer. *Gynecol Oncol* 41: 135–138.
- Ngan HYS, Chan SYW, Wong LC, Choy DTK, Ma HK (1990) Serum squamous cell carcinoma antigen in the monitoring of radiotherapy treatment response in carcinoma of the cervix. *Gynecol Oncol* 37: 260–263.
- Strauss HG, Laban C, Lautenschlager C, Buchmann J, Schmann J, et al. (2002) SCC antigen in the serum as an independent prognostic factor in operable squamous cell carcinoma of the cervix. *Eur J Cancer* 38: 1987–1991.
- Bae SN, Namkoong SE, Jung JK, Kim CJ, Park JS, et al. (1997) Prognostic significance of pre-treatment squamous cell carcinoma antigen and carcinoembryonic antigen in squamous cell carcinoma of the uterine cervix. *Gynecol Oncol* 64: 418–424.
- Massuger LF, Koper NP, Thomas CM, Dom KF, Schijf CP (1997) Improvement of clinical staging in cervical cancer with serum squamous cell carcinoma antigen and CA 125 determinations. *Gynecol Oncol* 64: 473–476.
- Chou CY, Wang ST, Kuo HC, Tzeng CC, Yao BL (1994) Serum level of squamous cell carcinoma antigen and tumor size are useful to identify preoperatively patients at high risk of cervical cancer. *Cancer* 74: 2497–2501.
- Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1: 307–310.
- Hüttmann EM, Greulich T, Hattesoehl A, Schmid S, Noeske S, et al. (2011) Comparison of two devices and two breathing patterns for exhaled breath condensate sampling. *PLoS One* 6: e27467.
- Er F, Ederer S, Nia AM, Caglayan E, Dahlem KM, et al. (2011) Accuracy of Doppler-echocardiographic mean pulmonary artery pressure for diagnosis of pulmonary hypertension. *PLoS One* 5: e15670.
- Breiman L (2001) Random Forest. *Machine Learning* 45: 5–32.
- Khondoker MR, Bachmann TT, Mewissen M, Dickinson P, Dobrzalecki B, et al. (2010) Multi-factorial analysis of class prediction error: estimating optimal number of biomarkers for various classification rules. *J Bioinform Comput Biol* 8: 945–965.
- Borgia JA, Basu S, Faber LP, Kim AW, Coon JS, et al. (2009) Establishment of a multi-analyte serum biomarker panel to identify lymph node metastases in non-small cell lung cancer. *J Thorac Oncol* 4: 338–347.
- Hamby SE, Hirst JD (2008) Prediction of glycosylation sites using random forests. *BMC Bioinformatics* 9: 500.
- Kwee TC, Takahara T, Ochiai R, Nieuvelstein RA, Luijten PR (2008) Diffusion-weighted whole-body imaging with background body signal suppression (DWIBS): features and potential applications in oncology. *Eur Radiol* 18: 1937–1952.
- Koh DM, Cook GJ, Husband JE (2003) New horizons in oncologic imaging. *N Engl J Med* 348: 2487–2488.
- Hashimoto K, Yonemori K, Katsumata N, Hirakawa A, Hirata T, et al. (2011) Use of squamous cell carcinoma antigen as a biomarker of chemotherapy response in patients with metastatic cervical carcinoma. *Eur J Obstet Gynecol Reprod Biol* 159(2): 394–398.
- Kim BG, Kim JH, Park SY, Lee JH, Lee ED, et al. (1996) Relationship between squamous cell carcinoma antigen levels and tumor volumes in patients with cervical carcinomas undergoing neoadjuvant chemotherapy. *Gynecol Oncol* 63: 105–113.
- Reesink-Peters N, van der Velden J, Ten Hoor KA, Boezen HM, de Vries EG, et al. (2005) Preoperative Serum Squamous Cell Carcinoma Antigen Levels in Clinical Decision Making for Patients With Early-Stage Cervical Cancer. *J Clin Oncol* 23: 1455–1462.
- Ohara K, Tanaka Y, Tsunoda H, Nishida M, Sugahara S, et al. (2002) Assessment of Cervical Cancer Radioresponse by Serum Squamous Cell Carcinoma Antigen and Magnetic Resonance Imaging. *Obstet Gynecol* 100: 781–787.

Author Contributions

Designed the software used in analysis: FS. Conceived and designed the experiments: MY YH CC XZ GL KL. Performed the experiments: MY YH HL JZ XC XL CL XN GL. Analyzed the data: YH TZ XZ FS KL. Contributed reagents/materials/analysis tools: MY YH CC XZ GL KL HL JZ CL XN. Wrote the paper: MY YH KL GL.