Systemic Immune-Inflammation Index Predicts Prognosis of Patients With Esophageal Squamous Cell Carcinoma Undergoing Radical Radiotherapy: A Propensity Score-Matched Analysis

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Research

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Abstract

Background

The systemic immune-inflammation index (SII) was recently investigated as a prognostic predictor in several kinds of solid tumors, including esophageal squamous cell carcinoma (ESCC) after esophagectomy. However, just few studies regarding SII in patients with ESCC undergoing radical radiotherapy are available. In addition, there has been hardly any report investigating the change trend of SII during radiotherapy. The aim of this study was to identify the prognostic value of SII in ESCC patients undergoing radical radiotherapy.

Methods

We retrospectively reviewed 303 ESCC patients undergoing radical radiotherapy. The change trend of SII was assessed by the box plot and curve fitting method. The time-dependent receiver operating characteristics was used to determine the optimal cutoff value of the SII. The association between SII and survival was determined by Kaplan-Meier method and Cox regression model. Propensity score matching (PSM) was applied to imbalance the baseline characteristics.

Results

High SII was associated with poor overall survival (OS) and progression-free survival (PFS) in patients with ESCC undergoing radical radiotherapy. Multivariate analysis showed that SII was a significant predictor for OS and PFS, whether before or after PSM. In addition, SII displayed an exponential increase trend during radiotherapy. The change of SII was also associated with OS and PFS.

Conclusions

The SII is a significant and independent predictor for OS and PFS of ESCC patients undergoing radical radiotherapy. Based on simple and inexpensive standard laboratory measurements, SII can be a promising marker for ESCC patients.

Introduction

Esophageal cancer is the eighth most common cancer worldwide in incidence and the sixth most common cause in mortality [1]. Esophageal squamous cell carcinoma (ESCC) is the most common pathological type in China, accounting for 90% of cases [2]. Although multidisciplinary treatment is commonly applied, including surgery combined with radiotherapy and chemotherapy, the 5-year overall survival remains poor. Therefore, assessing dependable prognostic predictors in ESCC remains very important.

During the past decade, there has been an increasing interest in the associations between systemic inflammatory response, immune status and long-term outcomes of several malignancies for many clinical researchers [3-7]. Some inflammatory and immune response biomarkers, such as platelet-lymphocyte ratio (PLR), neutrophil-lymphocyte ratio (NLR), and monocyte-lymphocyte ratio (MLR), have been demonstrated to be associated with postoperative prognosis in various cancers, including esophageal cancer, lung cancer, gastric cancer, et al [8-11]. However, these inflammatory biomarkers only integrate two kinds of cells. Recently, a novel indicator, systemic immune-inflammation index (SII), based on lymphocyte, neutrophil and platelet counts, has been proved as a powerful prognostic indicator for survival in various types of cancers [12-15]. Some previous studies have showed that preoperative SII is a prognostic marker for esophageal cancer undergoing esophagectomy [16-20]. However, to our best knowledge, just few studies regarding SII in patients with ESCC undergoing radical radiotherapy are available. In addition, there has been hardly any report investigating the change trend of SII during radiotherapy. Thus, the aim of this study was to investigate the prognostic value of SII in predicting survival in ESCC patients undergoing radical radiotherapy. Meanwhile, the change trend of SII during radiotherapy was analyzed. To reduce biases due to the different distributions of co-variables among the comparable groups and to increase statistical power, propensity score matching (PSM) was applied.

Materials And Methods

Patients

This retrospective analysis was conducted in 303 patients with ESCC who underwent radical radiotherapy from January 2011 to December 2017 at Fourth Hospital of Hebei Medical University in Shijiazhuang, China. All of the patients enrolled in the analysis met the following inclusion criteria: ESCC confirmed by histopathology; Karnofsky score ≥70 points; neither chemotherapy nor other anti-tumor therapy before radiotherapy; no history of malignant disease. All subjects gave their written informed consent to the study protocol, which was approved by the ethics committee of Fourth Hospital of Hebei Medical University, Shijiazhuang, China. According to TNM stage system issued by the American Joint Committee on cancer (AJCC; 7th edition), 30 patients with Stage I, 118 patients with Stage II and 155 patients with Stage III were included in this study. The characteristics of the patients are summarized in Table 1.

Treatment

In this study, all patients received intensity-modulated radiotherapy, including 180 patients undergoing involved-field irradiation and 123 patients undergoing elective node irradiation. The gross tumor volume (GTV), clinical tumor volume, and planned tumor volume were outlined in the RT treatment planning system, according to computed tomography simulation scan, barium esophagram, electronic gastroscopy and/or computed tomography-positron emission tomography. The primary tumor and positive regional lymph nodes were defined as GTV. The prescribed dose was set at 54-68 Gy (in 27-34 fractions over a range of 5-7 weeks). The elective node region was irradiated at the prescribed dose of 46-52 Gy. The patients undergoing adjuvant chemotherapy mainly received cisplatin combined with paclitaxel or 5-fluorouracil for 1 to 6 cycles.

Calculation of SII

SII = platelet counts × neutrophil counts/ lymphocyte counts. The optimal cutoff value for SII was calculated using the time-dependent receiver operating characteristics (ROC).

Follow-up

At our institution, follow-up examinations were performed every 3-month intervals in the first 2 years, then 6-month intervals. The routine examination included physical examination, blood tests, biological investigations, tumor markers, thoracic CT scanning, and barium esophagram.

Statistical analysis

All recorded data were analyzed using SPSS (version 23.0, IBM Corporation, Armonk, NY, USA). The change trend of SII was assessed by the box plot and curve fitting method. Pearson chi-square test was used to assess the correlation between different categorical variables. The OS rate was calculated using the Kaplan-Meier method, and a log-rank test was used to assess survival differences between groups. Cox proportional hazards regression analysis was performed to identify independent variables. PSM was carried out to reduce biases due to the different distributions of co-variables among the comparable groups. P values <0.05 indicated statistical significance.

Results

Correlation between SII and clinicopathological characteristics before and after propensity score matching

The optimal cutoff value for SII levels was set at 586 in this study, based on the OS (sensitivity: 60.5%; specificity: 56.9%; AUC of the ROC curve: 0.602; *P*=0.012). Based on their SII values, patients were categorized as high SII group (more than 586) or low SII group (586 or less).

The characteristics of 303 ESCC patients undergoing radical radiotherapy are presented in Table 1. Among the 303 patients, 178 (58.7%) were male and 125 (41.3%) were female. The median age was 67 years (range, 41-90 years). Patients with high SII in complete databases were more likely to be middle cancer (*P*=0.010), advanced T stage (*P*=0.001) and TNM stage (*P*=0.006).

Table 1 The Correlation between SII and characteristics in 303 ESCC patients before and after PSM

Characteristics	Total patients	Before PSM (n=303)			Total patients	After PSM (n=222)		
		SII≤586 (n=131)	SII>586 (n=172)	*P*		SII≤586 (n=111)	SII>586 (n=111)	*P*
Sex				0.235				0.130
Male	178	82	96		135	73	62	
Female	125	49	76		87	38	49	
Age				0.493				0.415
≤65	132	60	72		94	50	44	
>65	171	71	100		128	61	67	
Tumor location				0.010				0.271
Cervical+Upper	101	54	47		59	34	25	
Middle	135	46	89		103	46	57	
Lower	67	31	36		60	31	29	
T stage				0.001				0.296
T1+T2	83	47	36		61	27	34	
T3	103	48	55		85	48	37	
T4	117	36	81		76	36	40	
N stage				0.958				0.457
N0	93	40	53		63	29	34	
N+	210	91	119		159	82	77	
TNM stage				0.006				0.485
	30	18	12		19	7	12	
	118	59	59		97	50	47	
	155	54	101		106	54	52	

SII systemic immune-inflammation index, *ESCC* esophageal squamous cell carcinoma, *PSM* propensity score matching

SII and survival in all patients

Overall, the 1-, 3- and 5-year OS rates were 74.9%, 35.5% and 25.0%, respectively. The 1-, 3- and 5-year PFS rates were 57.1%, 27.6% and 19.9%, respectively. For the patients with a high SII (n=172), the 1-, 3- and 5-year OS rates were 65.7%, 28.4% and 18.7%, respectively. The corresponding rates in patients with a low SII (n=131) were 87.0%, 44.8% and 33.2%, respectively. In the high SII group and the low SII group, the 1-, 3-, 5-year PFS rates were 46.5%, 20.1%, 12.8% and 71.0%, 37.3%, 29.2%, respectively. Kaplan-Meier analysis showed that overall the high SII group had poorer OS and PFS compared with the low SII group (Fig. 1).

Univariate and multivariate survival analysis in all patients

In univariate analyses, the age, tumor location, T stage, lymph node metastasis, irradiation method, radiotherapy dose, adjuvant chemotherapy and the SII level were significantly associated with OS and PFS. Multivariate analyses identified the T stage, lymph node metastasis, adjuvant chemotherapy and SII as independent prognostic factors for OS (Table 2) and PFS (Table 3).

Table 2 Univariate and multivariate analyses of prognostic factors for OS in 303 ESCC patients

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	*P*	HR	95%CI
Sex (male/female)	0.979	1.003	0.776~1.298			
Age(≤65/>65)	0.016	1.378	1.062~1.789	0.467	1.116	0.830~1.502
Tumor location (cervical,upper/middle,lower)	0.006	1.481	1.121~1.956	0.826	1.035	0.764~1.402
T stage(T1,T2/T3,T4)	<0.001	2.057	1.516~2.792	0.001	1.733	1.268~2.366
Lymph node metastasis(negative/positive)	0.010	1.456	1.093~1.940	0.011	1.463	1.090~1.964
irradiation method (IFI/ENI)	<0.001	0.574	0.439~0.750	0.117	0.788	0.584~1.062
RT dose (≤60Gy/>60Gy)	0.005	0.693	0.538~0.893	0.326	0.870	0.659~1.149
Adjuvant chemotherapy (no/yes)	<0.001	0.611	0.474~0.788	0.016	0.701	0.524~0.937
SII (≤586/>586)	<0.001	1.667	1.284~2.163	0.011	1.420	1.083~1.860

OS overall survival, *ESCC* esophageal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval, *IFI* involved-field irradiation, *ENI* elective node irradiation, *RT* radiotherapy, *SII* systemic immune-inflammation index

Table 3 Univariate and multivariate analyses of prognostic factors for PFS in 303 ESCC patients

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	*P*	HR	95%CI
Sex (male/female)	0.781	1.037	0.805~1.334			
Age(≤65/>65)	0.034	1.316	1.020~1.697	0.563	1.088	0.818~1.445
Tumor location (cervical,upper/middle,lower)	0.013	1.409	1.075~1.848	0.905	0.982	0.730~1.321
T stage(T1,T2/T3,T4)	<0.001	1.947	1.448~2.617	0.001	1.642	1.212~2.225
Lymph node metastasis(negative/positive)	0.005	1.489	1.124~1.971	0.006	1.492	1.120~1.988
irradiation method (IFI/ENI)	<0.001	0.566	0.436~0.735	0.065	0.758	0.564~1.018
RT dose (≤60Gy/>60Gy)	0.006	0.707	0.552~0.907	0.411	0.891	0.676~1.174
Adjuvant chemotherapy (no/yes)	<0.001	0.630	0.491~0.809	0.025	0.726	0.549~0.961
SII (≤586/>586)	<0.001	1.658	1.284~2.140	0.012	1.411	1.079~1.845

PFS progression-free survival, *ESCC* esophageal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval, *IFI* involved-field irradiation, *ENI* elective node irradiation, *RT* radiotherapy, *SII* systemic immune-inflammation index

Changes of SII and survival in all patients

Based on the SII values before-, during-, and after the radiotherapy, the box plot showed the increasing trend of SII. Based on weekly averages for SII, the fitting curve and the function ($Y=787e^{0.197x}$, $P<0.001$) indicated that the mean SII displayed an exponential increase trend during radiotherapy (Fig. 2).

The median of SII after radiotherapy was 1457. On the basis of SII after radiotherapy, the two groups were divided into four subgroups: high-high (baseline SII > 586 and SII after radiotherapy > 1457); high-low (baseline SII > 586 and SII after radiotherapy ≤ 1457); low-high (baseline SII ≤ 586 and SII after radiotherapy > 1457); and low-low (baseline SII ≤ 586 and SII after radiotherapy ≤ 1457). Table 4 showed the relationships between changes of SII and survival according to these four groups.

Table 4 Relationships between changes of SII and survival in 303 ESCC patients

Baseline SII	SII after RT	N	Overall survival			Progression-free survival		
			Median (95%CI)	HR (95%CI)	*P*	Median (95%CI)	HR (95%CI)	*P*
High	High	108	14.7 (12.0~17.3)	1	-	10.2(7.8~12.5)	1	-
High	Low	64	21.2 (14.9~27.4)	0.841 (0.604~1.171)	0.306	12.6 (4.8~20.3)	0.841 (0.604~1.171)	0.306
Low	High	43	33.1 (23.2~43.1)	0.515 (0.341~0.778)	0.002	23.4 (12.2~34.6)	0.515 (0.341~0.778)	0.002
Low	Low	88	32.1(19.6~44.5)	0.587 (0.430~0.803)	0.001	25.0 (17.8~32.1)	0.587(0.430~0.803)	0.001

SII systemic immune-inflammation index, *ESCC* esophageal squamous cell carcinoma, *RT* radiotherapy, *CI* confidence interval, *HR* hazard ratio

SII and survival in propensity score matched patients

Considered the tumor location, T stage and TNM stage were imbalance between high SII group and low SII group (Table 1), we applied a 1:1 ratio propensity score matching (PSM). After PSM, there were 222 patients in all, and the clinicopathological characteristics were balanced and evenly distributed between two groups (*P*>0.05, Table 1). The Kaplan-Meier survival curves in the matched patients showed that the high SII group had poorer OS and PFS compared with the low SII group (Fig. 3).

Univariate and multivariate survival analysis in propensity score matched patients

A univariate analysis revealed that the age, T stage, irradiation method, radiotherapy dose, adjuvant chemotherapy and SII were significant predictors of OS. In multivariate analysis, the T stage, irradiation method and SII were identified as independent prognostic factors for OS (Table 5).

Univariate analysis identified the T stage, irradiation method, radiotherapy dose, adjuvant chemotherapy and SII as significant risk factors for PFS. In the multivariate analysis, the T stage, irradiation method, adjuvant chemotherapy and SII were conformed as independent prognostic factors for PFS (Table 6).

Table 5 Univariate and multivariate analyses of prognostic factors for OS in propensity score matched 222 ESCC patients

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	*P*	HR	95%CI
Sex (male/female)	0.601	1.082	0.806~1.452			
Age(≤65/>65)	0.029	1.395	1.035~1.881	0.601	1.095	0.779~1.540
Tumor location (cervical,upper/middle,lower)	0.591	1.095	0.788~1.521			
T stage(T1,T2/T3,T4)	<0.001	1.948	1.389~2.733	<0.001	2.322	1.634~3.300
Lymph node metastasis(negative/positive)	0.232	1.223	0.879~1.700			
irradiation method (IFI/ENI)	<0.001	0.518	0.380~0.706	0.026	0.689	0.496~0.957
RT dose (≤60Gy/>60Gy)	0.005	0.658	0.492~0.879	0.090	0.767	0.564~1.042
Adjuvant chemotherapy (no/yes)	<0.001	0.540	0.403~0.724	0.051	0.710	0.503~1.001
SII (≤586/>586)	<0.001	1.893	1.415~2.533	<0.001	2.222	1.634~3.021

OS overall survival, *ESCC* esophageal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval, *IFI* involved-field irradiation, *ENI* elective node irradiation, *RT* radiotherapy, *SII* systemic immune-inflammation index

Table 6 Univariate and multivariate analyses of prognostic factors for PFS in propensity score matched 222 ESCC patients

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95%CI	*P*	HR	95%CI
Sex (male/female)	0.565	1.088	0.816~1.450			
Age(≤65/>65)	0.070	1.306	0.979~1.744			
Tumor location (cervical,upper/middle,lower)	0.916	0.983	0.716~1.350			
T stage(T1,T2/T3,T4)	<0.001	1.888	1.363~2.617	<0.001	2.155	1.537~3.021
Lymph node metastasis(negative/positive)	0.225	1.218	0.886~1.675			
irradiation method (IFI/ENI)	<0.001	0.536	0.398~0.723	0.028	0.699	0.508~0.962
RT dose (≤60Gy/>60Gy)	0.003	0.657	0.495~0.871	0.073	0.763	0.567~1.026
Adjuvant chemotherapy (no/yes)	<0.001	0.571	0.430~0.758	0.027	0.714	0.530~0.963
SII (≤586/>586)	<0.001	1.656	1.247~2.198	<0.001	1.865	1.384~2.515

PFS progression-free survival, *ESCC* esophageal squamous cell carcinoma, *HR* hazard ratio, *CI* confidence interval, *IFI* involved-field irradiation, *ENI* elective node irradiation, *RT* radiotherapy, *SII* systemic immune-inflammation index

Discussion

During the past decade, there has been an increasing interest in the associations between systemic inflammation and outcomes of several malignancies [5-7]. However, just few studies regarding SII in patients with ESCC undergoing radical radiotherapy are available. In the present study, 303 ESCC patients received radical radiotherapy were analyzed retrospectively. The results showed that elevated SII was associated with tumor location, T stage and TNM stage. The OS and PFS were poorer in the high SII group than in the low SII group. SII was an independent prognostic factor for OS and PFS in ESCC patients treated with radical radiotherapy. To the best of our knowledge, this is the first report focused on the change trend of SII and the associations between change of SII and survival. The results showed that SII increased significantly during radiotherapy, and the change of SII was associated with OS and PFS. Moreover, it was worth mentioning that PSM was applied in the present study to reduce biases due to the different distributions of co-variables among the comparable groups and to increase statistical power. In 222 propensity matched ESCC patients, SII retained prognostic significance for OS and PFS.

Many studies have described the role of preoperative SII in the prognosis of various malignancies. SII has been demonstrated to be associated with postoperative survival in colorectal cancer, lung cancer, breast cancer, hepatocellular carcinoma, et al [12-15]. Moreover, in esophageal carcinoma, the preoperative SII was confirmed to be an independent predictor for survival and quality of life. Geng et al. [16] initially reported prognostic value of SII in patients with ESCC. Based on the retrospective study of 916 patients with ESCC who underwent radical surgery, they demonstrated that SII was an independent risk factor for OS and the prognostic value of SII is superior to PLR, NLR and MLR. Wang et al. [17] reported that higher SII was associated with advanced T stage, N stage and TNM stage, and the preoperative SII was a promising biomarker for predicting survival and quality of life of patients with ESCC. Similar results were shown in another study. Gao et al. [20] retrospectively analyzed 468 ESCC patients who underwent curative esophagectomy with R0 resection. Their result showed that a high SII was an independent predictor for both OS and DFS in patients with surgically resected ESCC, and by comparing the areas under the AUC curve, SII was superior to NLR, PLR, and MLR in terms of prognostic ability. Undoubtedly, our results in ESCC patients undergoing radical radiotherapy were consistent with previous reports in ESCC patients undergoing curative esophagectomy. However, we found that in our study, the optimal cutoff value of SII was higher, and the OS was lower than that in previous studies. One possible reason was that the

patients undergoing radical radiotherapy had more advanced TNM stage than patients undergoing surgery. As previously mentioned, elevated SII was associated with advanced TNM stage [17], and TNM stage was one of prognostic factors for OS [20].

The mechanism of the correlation between SII and overall survival in patients with esophageal cancer remains unclear. Several potential theories may be used to explain the prognostic values of SII. Firstly, the cancer-mediated generation of bone marrow cells and various cytokines released during the generation may promote tumor angiogenesis, invasion and metastasis, shield cancer cells from immune destruction, and induce resistance to cytotoxic drugs [21]. Secondly, neutrophils can release cytokines leading to T cell activation disorders [22]. Platelets and neutrophils promote adhesion and implantation of distant organs by secreting vascular endothelial growth factor [23, 24]. Thirdly, lymphocytes display a significant antitumor role by inducing cytotoxic cell apoptosis and inhibiting tumor cell proliferation and migration, instituting the host's immune response to cancer.[25, 26] Therefore, inflammation deeply influences cancer microenvironment that supports cancer progression. Based on the above theories, SII should be an objective marker that reflects the balance between host inflammatory and immune response status, and a promising prognostic predictor for cancer patients.

There are several potential limitations in this study. First, this is a retrospective, single-institute study, and there may be selection bias during patients collection, although the PSM has been applied to imbalance the baseline characteristics. Second, some of our results were consistent with previous reports, but the optimal cutoff value of SII was different with previous similar studies. So it was not easy to verify our conclusions in another independent cohort. Therefore, larger prospective studies are required in the future to confirm these preliminary results.

In conclusion, the SII is a significant and independent predictor for survival of ESCC patients undergoing radical radiotherapy. SII displayed an exponential increase trend during radiotherapy. The change of SII was also associated with OS and PFS. Based on simple and inexpensive standard laboratory measurements, SII can be a promising marker for ESCC patients.

Abbreviations

SII: systemic immune-inflammation index; ESCC: esophageal squamous cell carcinoma ; PSM: propensity score matching; OS: overall survival; PFS: progression-free survival; PLR: platelet-lymphocyte ratio; NLR: neutrophil-lymphocyte ratio; MLR: monocyte-lymphocyte ratio; AJCC: American Joint Committee on cancer; GTV: gross tumor volume; ROC: receiver operating characteristics; HR: hazard ratio; CI: confidence interval; IFI: involved-field irradiation; ENI: elective node irradiation; RT: radiotherapy.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Fourth Affiliated Hospital of Hebei Medical University. Written informed consent was obtained from each participant by the institutional guidelines.

Consent for publication

Informed consent was obtained from all participants for publication.

Availability of data and materials

All data included in the present study were presented in the main manuscript.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YZ: data acquisition and manuscript writing, CYS and JRX: data acquisition and data analysis, SGL, WZD and JL: follow up and quality control of data, WBS: manuscript review, SCZ: study concept and design. All authors read and approved the final manuscript.

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Figures

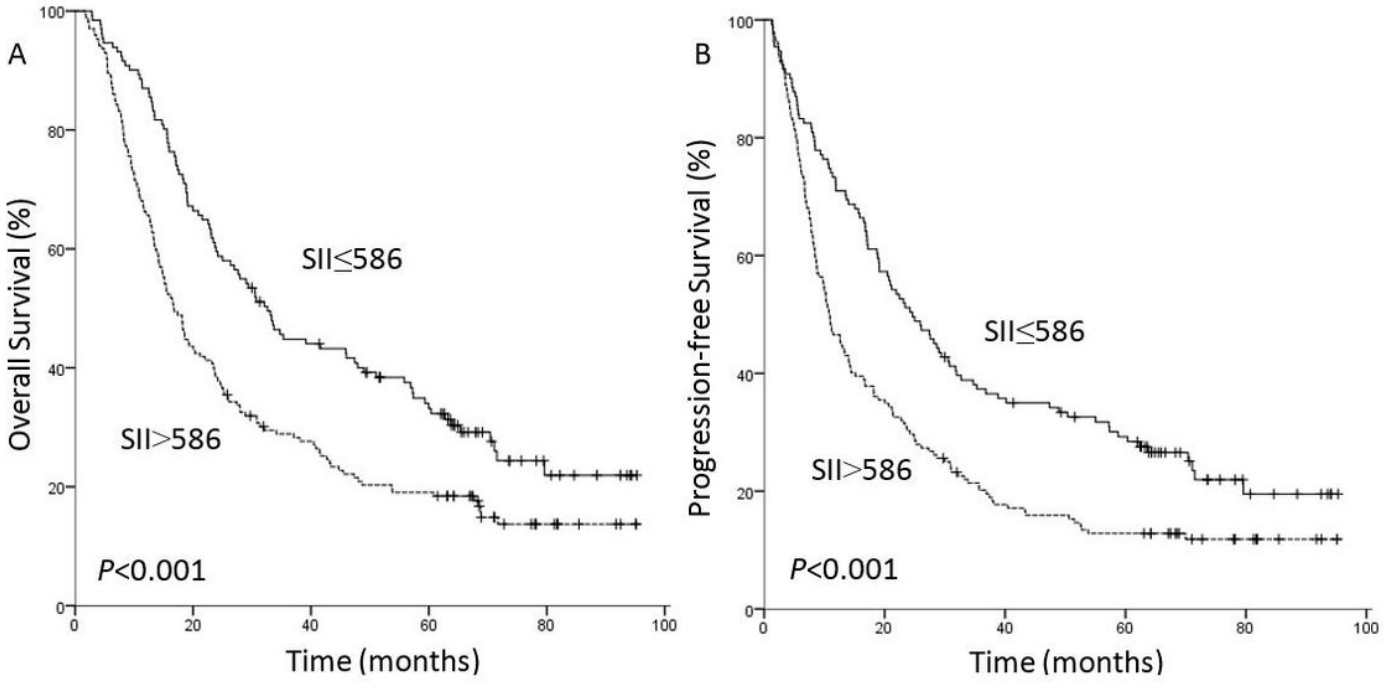
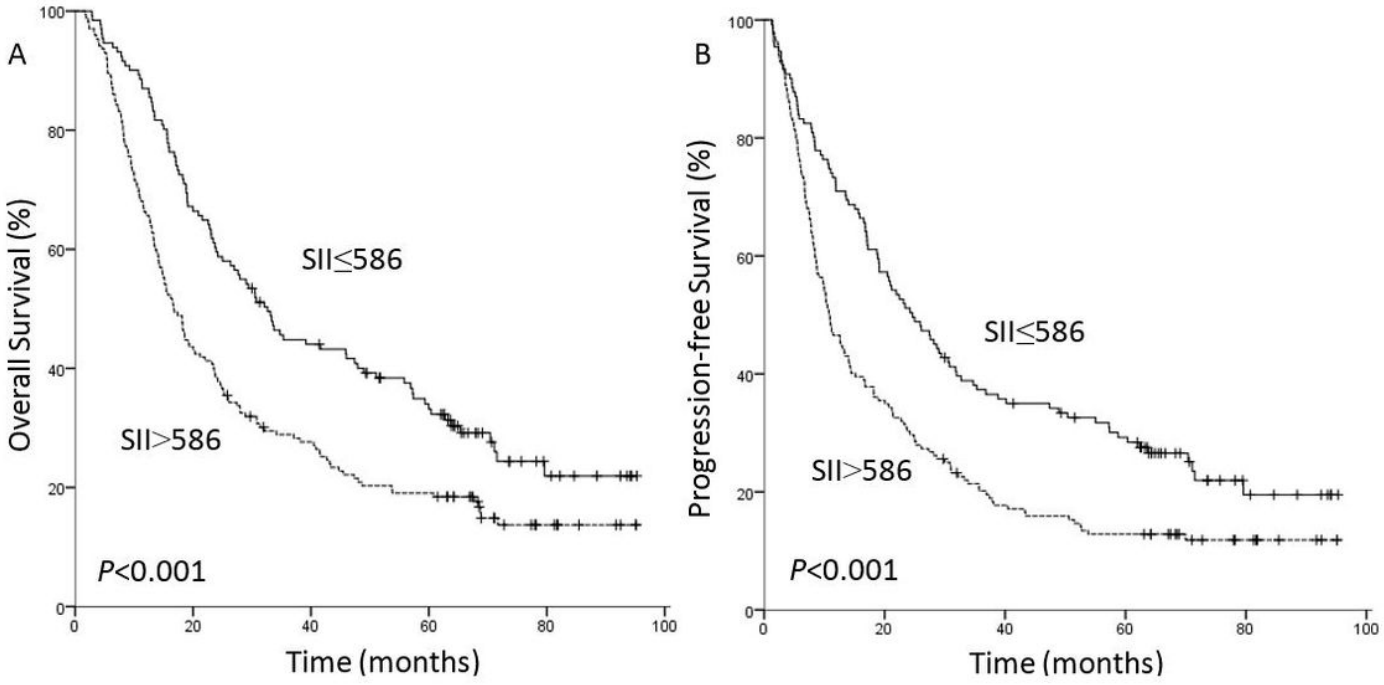


Figure 1

Kaplan-Meier curves of survival based on SII in 303 ESCC patients undergoing definitive radiotherapy. A: overall survival; B: progression-free survival.



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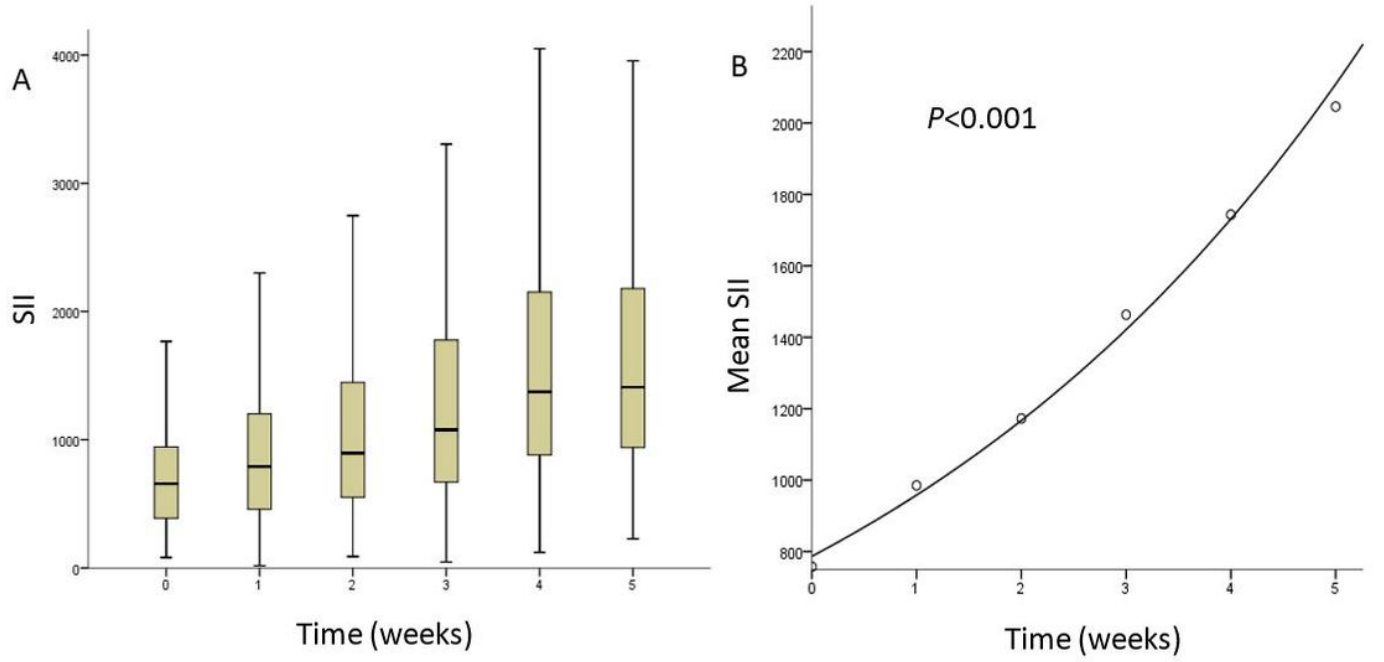
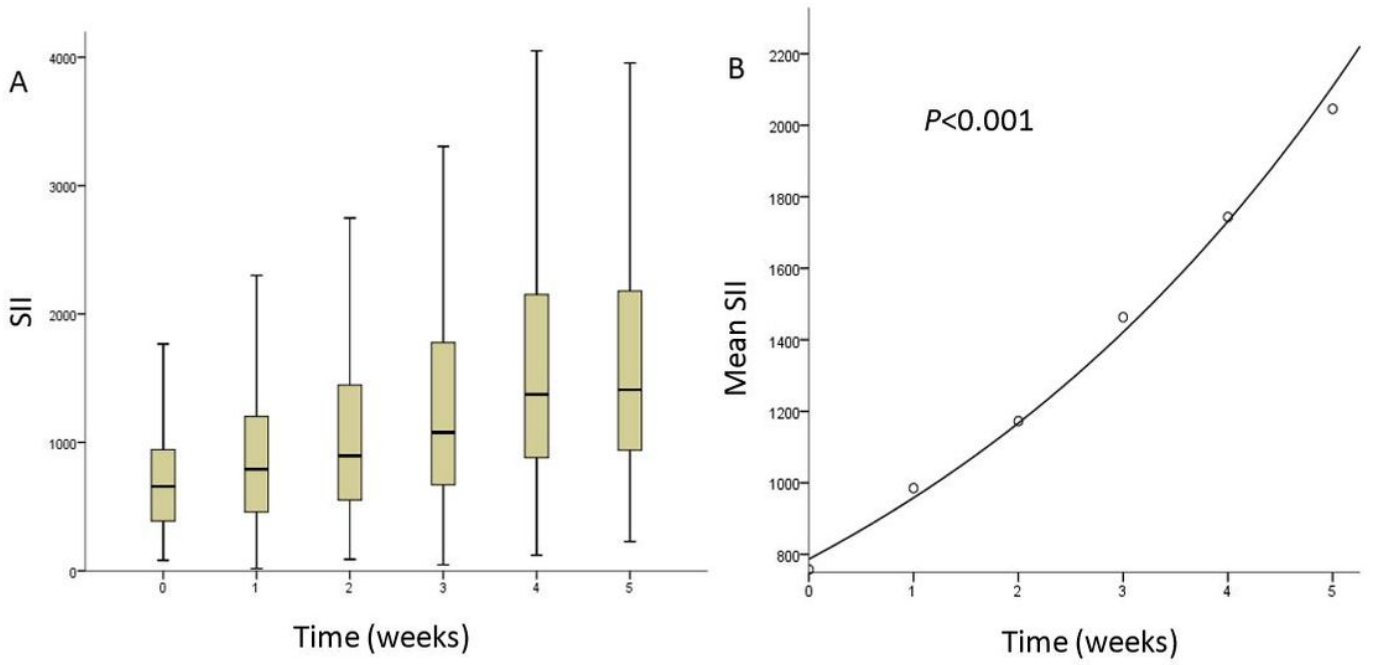


Figure 2

The change trend of SII during radiotherapy in 303 ESCC patients (A: the box plot of SII during radiotherapy; B: the change trend of mean SII)



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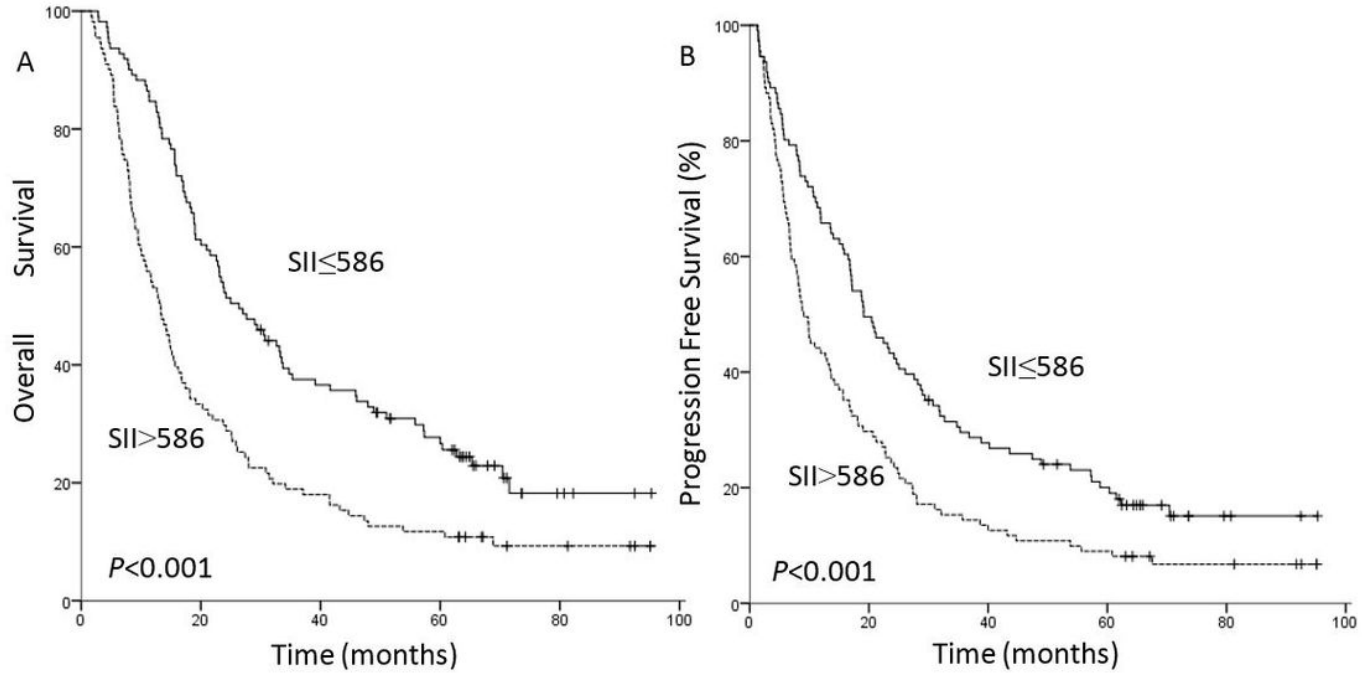
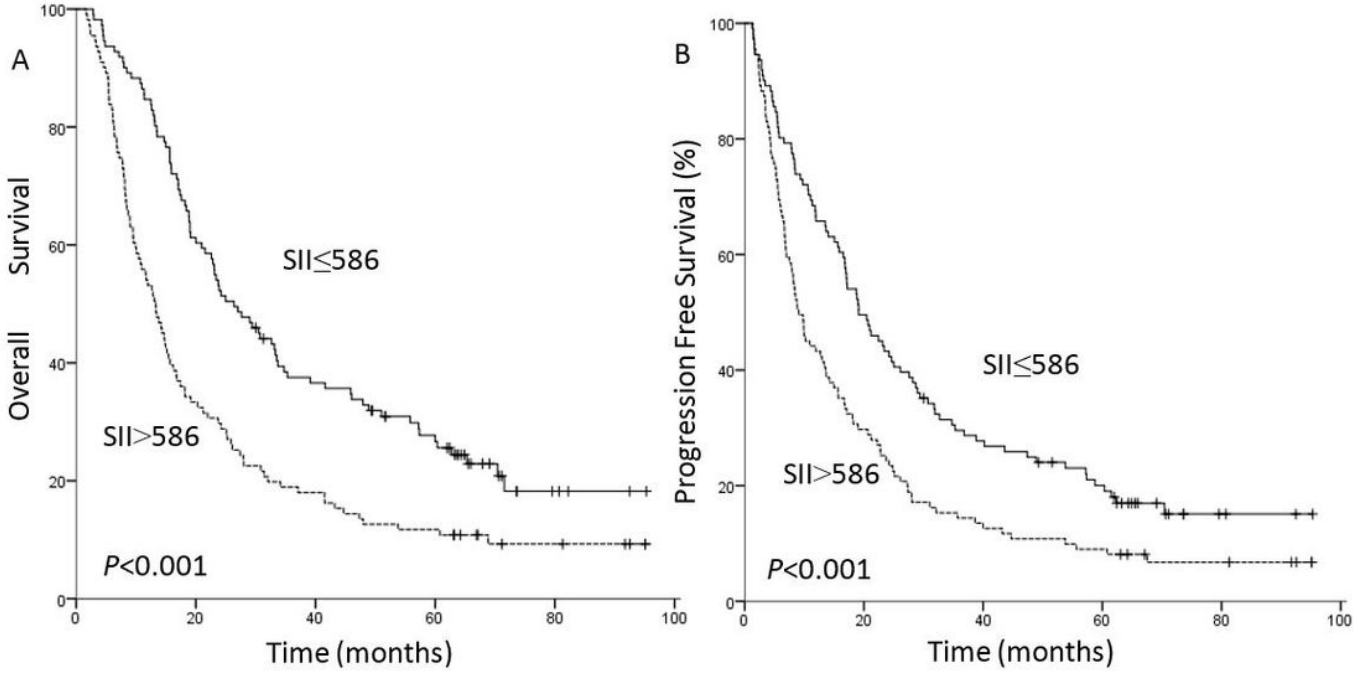


Figure 3

Kaplan-Meier curves of survival based on SII in propensity score matched 222 ESCC patients undergoing definitive radiotherapy. A: overall survival; B: progression-free survival.



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