


Preoperative Radiotherapy Is Associated With Significant Survival Benefits for Patients With Gastric Signet Ring Cell Carcinoma: A SEER-Based Approach

Technology in Cancer Research & Treatment
Volume 19: 1-6
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DOI: 10.1177/1533033820960746
journals.sagepub.com/home/tct


Hongyun Gong, MD¹, Yuxin Chu, MD¹ , Qinyong Hu, MD¹, and Qibin Song, MD¹

Abstract

Objective: To explore the clinical and pathological features of gastric signet ring cell carcinoma, and evaluate the survival impact of preoperative radiotherapy on these patients. **Methods:** The Surveillance, Epidemiology, and End Results database was used to extract eligible patients from 2004 to 2015. The patients were divided into those with and without preoperative radiotherapy. The categorical variables were described by chi-square tests. The patients' survival was compared between the 2 groups by Kaplan-Meier method with log-rank tests. Cox proportional hazard model was adopted to identify prognostic factors of cancer-specific survival. **Results:** Totally 4771 patients were recruited, of whom 218(4.6%) patients received preoperative radiotherapy, while 4553(95.4%) patients didn't receive this treatment. Survival analysis of the entire cohort demonstrated that preoperative radiotherapy improved both cancer-specific survival and overall survival ($p < 0.001$) of the patients. Cox proportional hazard models identified age >60 , tumor size >50 mm, TNM stage II-IV as independent risk factors for poor prognosis ($HR > 1$, $p < 0.05$). Notably, preoperative radiotherapy was identified as an independent protective factor for favorable prognosis ($HR < 1$, $p < 0.05$). Subgroup survival analysis showed that preoperative radiotherapy exerted significant survival benefits for the stages III and IV patients. **Conclusions:** In this population-based study, preoperative radiotherapy is associated with significant survival benefits for the patients with advanced gastric signet ring cell carcinoma. Hence preoperative radiotherapy is feasible for these patients.

Keywords

gastric signet ring cell carcinoma, preoperative radiotherapy, survival

Abbreviations

SRC, signet ring cell carcinoma; SEER, Surveillance, Epidemiology, and End Results; RT, radiotherapy; CSS, cancer-specific survival; OS, overall survival; AJCC, American Joint Committee on Cancer.

Received: May 6, 2020; Revised: August 20, 2020; Accepted: August 31, 2020.

Introduction

Gastric cancer (GC) is the third greatest cause of cancer-related death worldwide.¹ In America, about 11,140 deaths were estimated from this disease in 2019.² The median survival of GC is less than 12 months at advanced stages.³ Adenocarcinoma accounts for the vast majority of GC.⁴ Gastric signet ring cell carcinoma (SRC) is a unique subtype of gastric adenocarcinoma. In WHO classification, SRC was defined as tumor cell with central optically clear, globoid droplet of cytoplasmic mucin with an eccentrically placed nucleus.⁵ Recent studies have revealed that the incidence of gastric SRC has been

increasing constantly.⁶ Gastric SRC is also associated with aggressive tumor behavior and early metastasis, posing a major public health problem.⁷

¹ Department of Oncology I, Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China

Corresponding Author:

Yuxin Chu, Department of Oncology I, Cancer Center, Renmin Hospital of Wuhan University, Jiefang Road No. 238, Wuhan 430060, China.
Email: rm002346@whu.edu.cn



With respect to the treatment of GC, surgery remains the mainstay for localized GC.⁸ However, the survival still remains poor for surgery alone, the 5-year survival rate was only 20%-50%, leading to the efforts to improve the prognosis of these patients with adjuvant approaches.⁹ The INT0116 trial was a milestone study which reported significant survival benefits from adjuvant chemoradiotherapy for the GC patients after gastrectomy.¹⁰ Furthermore, the MAGIC trial also demonstrated superior survival of perioperative chemotherapy and surgery as compared to surgery alone for GC.¹¹ On the other hand, the ARTIST trial revealed that adjuvant radiotherapy (RT) combined with chemotherapy did not have a positive impact on the patients' survival.¹² The CRITICS trial also showed that in patients who received preoperative chemotherapy, postoperative chemoradiotherapy did not improve survival as compared to postoperative chemotherapy.¹³ With the growth of evidence, the benefits of neoadjuvant/adjuvant radiotherapy have become more controversial as therapeutic options. Preoperative chemoradiotherapy has been reported to show significant downstaging, facilitate radical tumor resection, and reduce local relapse for potentially resectable GC.¹⁴ However, this therapeutic modality is not the standard of care, with unpredictable outcomes. As a special subtype of GC, the survival impact of preoperative RT on patients with gastric SRC has not been clarified yet. This effect needs to be evaluated, so that clinicians can select more appropriate treatments for these patients.

Patients and Methods

Patient Selection

All the data were extracted from Surveillance, Epidemiology, and End Results (SEER) database (with additional treatment fields). The patients were selected by SEER*Stat version 8.3.5 software directly. The SEER data contain no identifiers and are publicly available, so ethical approval was exempt for our study. We designed the following inclusion criteria: (1) all patients were diagnosed from 2004 to 2015; (2) primary site was stomach; (3) primary gastric cancer was the first or only cancer diagnosis; (4) histological type was confined only to signet ring cell carcinoma (ICD-03, 8490/3); (5) surgery was performed; (6) chemotherapy recode was "yes". We excluded the patients with unknown information about table variables.

Data Collection

The extracted table variables were: age at diagnosis, gender, race, marital status, tumor size, grade, TNM stage, tumor depth, LN metastasis, radiation, histological type, survival months, SEER cause-specific death classification, and vital status recode. Cancer-specific survival (CSS) was defined as the time from cancer diagnosis to the date of death caused by gastric SRC specifically. Overall survival (OS) was defined as the duration from diagnosis to death from any cause. In this

study, the primary endpoint was CSS, and the secondary endpoint was OS.

Statistical Analysis

The eligible patients were divided into those with and without preoperative RT. The categorical variables were compared by chi-square tests. The survival differences between the 2 groups were evaluated by Kaplan-Meier method with log-rank tests. Cox proportional hazard models were utilized to identify prognostic factors associated with CSS. Factors with $p < 0.05$ in univariate Cox model were further adjusted by multivariate Cox analysis. The statistical analyses were completed by SPSS statistical software, version 25.0 (SPSS, Chicago, IL, USA). A two-tailed $p < 0.05$ was deemed statistically significant.

Results

Patient Characteristics

We recruited 4771 eligible patients with gastric SRC during the study period. In this cohort, 4553(95.4%) patients didn't receive preoperative RT, while 218 (4.6%) patients received preoperative RT. There were significant differences between the 2 groups in terms of gender, race, marital status, tumor size, TNM stage, tumor depth, LN metastasis ($p < 0.05$). Compared with the patients not radiated, those patients who received preoperative RT were more likely to be male (78.4% vs 51.6%), white race (89.0% vs 70.2%). The marital status also displayed significant difference between the 2 comparison groups, with married 68.8% in RT group versus 59.7% in no RT group ($p < 0.05$). As for tumor characteristics, the RT group showed more tumor size ≤ 50 mm, more patients with stage II/III, T2/T3, N1. The distributions of age and grade were comparable between the 2 groups ($p > 0.05$). Patient demographics and clinical features are summarized below (Table 1).

Survival Analysis

The survival outcomes of RT versus no RT groups were evaluated. The Kaplan-Meier plots demonstrated that the survival of RT group was significantly better than no RT group in both CSS and OS curves (Figure 1, $p < 0.001$). The median CSS of RT group was 25.0(20.8-29.2) months, while that of no RT group was 12.0(11.3-12.7) months (Table 2, $p < 0.001$). Likewise, the median OS of RT group was also superior to that of no RT group (Table 2, $p < 0.001$). These results indicated that preoperative RT exerted notable survival advantages for the patients with gastric SRC.

Identify Prognostic Factors

To identify prognostic factors associated with CSS, we constructed both uni- and multivariate Cox proportional hazard models within the cohort. In univariate analysis, the variables significantly associated with CSS were RT, age, race, marital status, tumor size, TNM stage, tumor depth, LN metastasis

($p < 0.05$). RT was found to be a significant prognostic factor (HR = 0.641, 95% CI = 0.541-0.759, $p < 0.001$). All these significant variables in univariate analysis were subsequently

Table 1. Baseline Characteristics of the Patients Dichotomized by Preoperative Radiotherapy.

Characteristics	No RT n = 4553 (95.4%)	RT n = 218 (4.6%)	Total n = 4771 (100%)	p value
Age (years)				0.435
≤60	2044(44.9%)	92(42.2%)	2136(44.8%)	
>60	2509(55.1%)	126(57.8%)	2635(55.2%)	
Gender				<0.001
Male	2351(51.6%)	171(78.4%)	2522(52.9%)	
Female	2202(48.4%)	47(21.6%)	2249(47.1%)	
Race				<0.001
White	3195(70.2%)	194(89.0%)	3389(71.0%)	
Black	541(11.9%)	10(4.6%)	551(11.5%)	
Others	817(17.9%)	14(6.4%)	831(17.4%)	
Marital status				0.007
Not married	1836(40.3%)	68(31.2%)	1904(39.9%)	
Married	2717(59.7%)	150(68.8%)	2867(60.1%)	
Tumor size (mm)				0.011
≤50	1622(35.6%)	96(44.0%)	1718(36.0%)	
>50	2931(64.4%)	122(56.0%)	3053(64.0%)	
Grade				0.743
I-II	129(2.8%)	7(3.2%)	136(2.9%)	
III-IV	4424(97.2%)	211(96.8%)	4635(97.1%)	
TNM stage				<0.001
I	1353(29.7%)	49(22.5%)	1402(29.4%)	
II	520(11.4%)	84(38.5%)	604(12.7%)	
III	619(13.6%)	58(26.6%)	677(14.2%)	
IV	2061(45.3%)	27(12.4%)	2088(43.8%)	
Tumor depth				<0.001
T1	1284(28.2%)	23(10.6%)	1307(27.4%)	
T2	1494(32.8%)	120(55.0%)	1614(33.8%)	
T3	907(19.9%)	62(28.4%)	969(20.3%)	
T4	868(19.1%)	13(6.0%)	881(18.5%)	
LN metastasis				<0.001
N0	2197(48.3%)	58(26.6%)	2255(47.3%)	
N1	1447(31.8%)	131(60.1%)	1578(33.1%)	
N2	561(12.3%)	21(9.6%)	582(12.2%)	
N3	348(7.6%)	8(3.7%)	356(7.5%)	

Abbreviations: TNM, tumor-node-metastasis; LN, lymph node; RT, radiotherapy.

recruited into the multivariate Cox regression model. After adjusting for other confounding factors, age >60, tumor size >50 mm, TNM stage II-IV were proved to be independent risk factors for poor prognosis (HR > 1, $p < 0.05$). Notably, pre-operative RT was still significantly associated with the patients' CSS (HR = 0.714, 95% CI = 0.599-0.850, $p < 0.001$). Hence preoperative RT was identified as an independent protective factor for favorable prognosis (HR < 1, $p < 0.05$). The detailed results are shown in Table 3.

Subgroup Survival Analysis

Given that TNM stage is also independently associated with the patients' CSS, we initiated a subgroup analysis to highlight the impact of preoperative RT on the prognosis of the patients. The Kaplan-Meier plots revealed that preoperative RT showed significant CSS advantages for patients with stages III and IV gastric SRC ($p < 0.05$). By contrast, no significant survival difference was found between the 2 groups in either stage I or stage II patients ($p > 0.05$). Thus, preoperative RT showed significant survival benefits for the patients with advanced gastric SRC. The survival curves of CSS stratified by TNM stage can be seen in Figure 2.

Discussion

Currently, the significance of preoperative RT for patients with gastric SRC has not been widely recognized. Based on a large population from the SEER database, we retrospectively analyzed the clinicopathological features of the patients with gastric SRC, highlighting the effect of preoperative RT on the

Table 2. Comparison of Median Survival of the Patients.

	Patients, No.	Median CSS, 95% CI, months	Median OS, 95% CI, months
No radiation	4553	12.0(11.3-12.7)	11.0(10.4-11.6)
Radiation	218	25.0(20.8-29.2)	24.0(20.2-27.8)
p value		<0.001	<0.001

Abbreviations: No., number; CSS, cancer-specific survival; OS, overall survival.

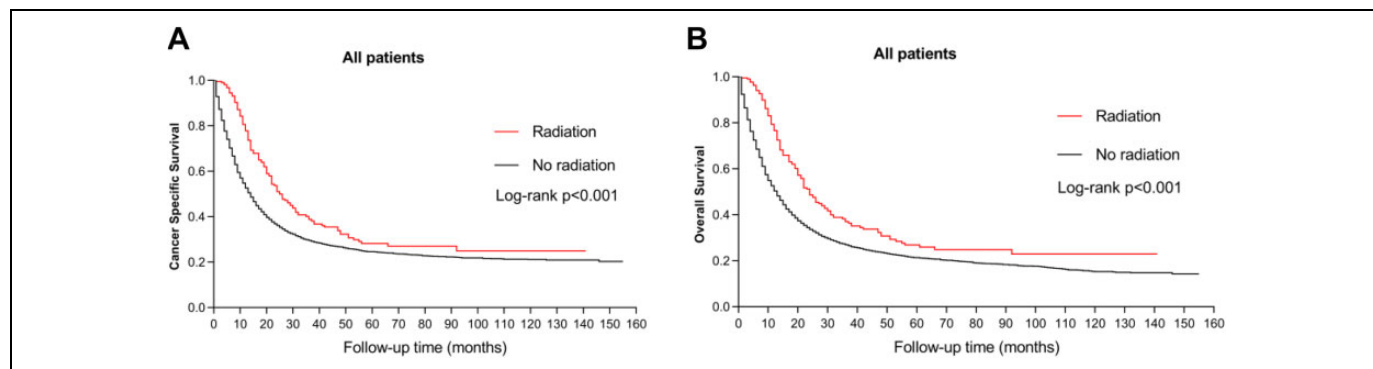


Figure 1. Kaplan-Meier survival curves. A, CSS ($p < 0.001$). B, OS ($p < 0.001$).

Table 3. Cox Regression Analysis of Cancer-Specific Survival.

Characteristics	Univariate Cox		Multivariate Cox	
	HR (95% CI)	p value	HR(95% CI)	p value
RT				
No	Reference		Reference	
Yes	0.641(0.541-0.759)	<0.001	0.714(0.599-0.850)	<0.001
Age (years)				
≤60	Reference		Reference	
>60	1.114(1.041-1.192)	0.002	1.370(1.278-1.468)	<0.001
Gender				
Male	Reference		NI	
Female	0.987(0.922-1.056)	0.694		
Race				
White	Reference		Reference	
Black	0.948(0.852-1.055)	0.326	0.968(0.869-1.079)	0.560
Others	0.723(0.657-0.796)	<0.001	0.830(0.754-0.914)	<0.001
Marital status				
Not married	Reference		Reference	
Married	0.832(0.776-0.891)	<0.001	0.810(0.755-0.868)	<0.001
Tumor size (mm)				
≤50	Reference		Reference	
>50	2.606(2.410-2.819)	<0.001	1.743(1.604-1.895)	<0.001
Grade				
I-II	Reference		NI	
III-IV	1.218(0.984-1.509)	0.071		
TNM Stage				
I	Reference		Reference	
II	1.831(1.610-2.083)	<0.001	1.928(1.645-2.260)	<0.001
III	2.827(2.509-3.186)	<0.001	2.973(2.526-3.500)	<0.001
IV	5.192(4.710-5.724)	<0.001	4.996(4.391-5.684)	<0.001
Tumor depth				
T1	Reference		Reference	
T2	1.485(1.349-1.634)	<0.001	0.985(0.882-1.101)	0.797
T3	2.029(1.829-2.251)	<0.001	0.932(0.817-1.063)	0.294
T4	3.281(2.953-3.646)	<0.001	1.049(0.928-1.187)	0.444
LN metastasis				
N0	Reference		Reference	
N1	1.513(1.400-1.635)	<0.001	0.881(0.807-0.963)	0.005
N2	1.604(1.443-1.782)	<0.001	0.807(0.714-0.911)	0.001
N3	2.006(1.772-2.271)	<0.001	0.700(0.610-0.803)	<0.001

Abbreviations: RT, radiotherapy; TNM, tumor-node-metastasis; LN, lymph node; HR, hazard ratio; NI, not included.

prognosis of such patients. The overall results indicated that preoperative RT was associated with significant survival benefits for the patients with gastric SRC.

The role of preoperative RT in treating GC patients has been reported by several relevant studies. A recent meta-analysis showed a statistically significant 5-year survival benefit with the addition of RT in patients with resectable GC.¹⁵ In another meta-analysis, GC patients could benefit from both preoperative and postoperative RT.¹⁶ However, it has not been clarified whether preoperative RT can benefit the survival of patients with gastric SRC likewise. A retrospective study demonstrated that neoadjuvant radiochemotherapy improved the survival of patients with locally advanced SRC in esophagogastric junction.¹⁷ Nevertheless, this study has not separately analyzed the survival impact of preoperative RT for gastric SRC. On the other hand, another study has found that gastric SRC was relatively chemoradiation resistant. A higher fraction of SRC was associated with higher resistance.¹⁸ Hence the previous studies concerning the prognostic impact of RT on patients with gastric

SRC are inconsistent. Comparatively, our study has investigated the influence of preoperative RT on the survival outcomes of patients with gastric SRC based on a large population analysis. Our results indicated the preoperative RT exerted notable survival advantages for these patients. Treatment-associated toxicity is a major contributing factor. A prospective, randomized trial has explored the toxicity and efficacy of surgery and preoperative radiotherapy for treating GC. The hematologic toxicity includes neutropenia, neutropenic fever, and anemia. Common complications were postoperative pancreatitis, anastomotic leakages, intestinal obstruction, and gastrointestinal bleeding. However, the incidence of these complications was relatively low. Preoperative radiotherapy was generally well tolerated, and resulted in a marked survival improvement.¹⁹ Therefore, preoperative RT seems applicable for the patients with gastric SRC.

With regard to the prognostic factors for gastric SRC, a recent study has comprehensively analyzed the clinicopathological characteristics and prognosis of such patients. When multivariate analysis with Cox regression was conducted, their results indicated that age, race, histological grade, AJCC stage were independent prognostic factors.²⁰ Based on the analysis of our cohort, we also identified age >60, tumor size >50 mm, TNM stage II-IV as independent risk factors for poor prognosis (HR > 1, p < 0.05). However, preoperative RT was still significantly associated with favorable CSS (HR < 1, p < 0.001). Thus preoperative RT was an independent protective factor for the patients with gastric SRC.

Tumor size is also an important prognostic factor for the GC patients, which is significantly associated with cancer progression, lymph node metastasis, and relapse. The patients with large tumors often indicated more aggressive features and worse prognosis than patients with small tumors. Tumor size could provide vital information for determining the width of surgical margin and the extent of lymph node dissection.²¹ A recent study also revealed that small GC was appropriate for radical surgery, while large GC with risk factors could not be surgically cured.²² In our study, we have also found that tumor size was an independent prognostic factor for the patients with gastric SRC. As for patients with large advanced tumors, preoperative radiotherapy may offer the potential advantages of reducing tumor size and allowing a R0 resection.²³

Based on analysis of the entire cohort, the survival benefits from preoperative RT have been confirmed for the patients with gastric SRC. For solid elucidation, we initiated a subgroup survival analysis by TNM stage. The stratified analysis showed that preoperative RT exerted significant CSS benefits for patients with stages III and IV gastric SRC. Preoperative RT has been reported to downstage the unresectable GC, some advanced patients might be converted into resectable ones.²⁴ The advantages of preoperative RT include intact tumor micro-environment, hence avoiding postoperative hypoxia that may compromise the treatment efficacy. Preoperative RT also has the advantages of clearer target delineation, smaller radiation volumes, and lower doses, which can improve the patients'

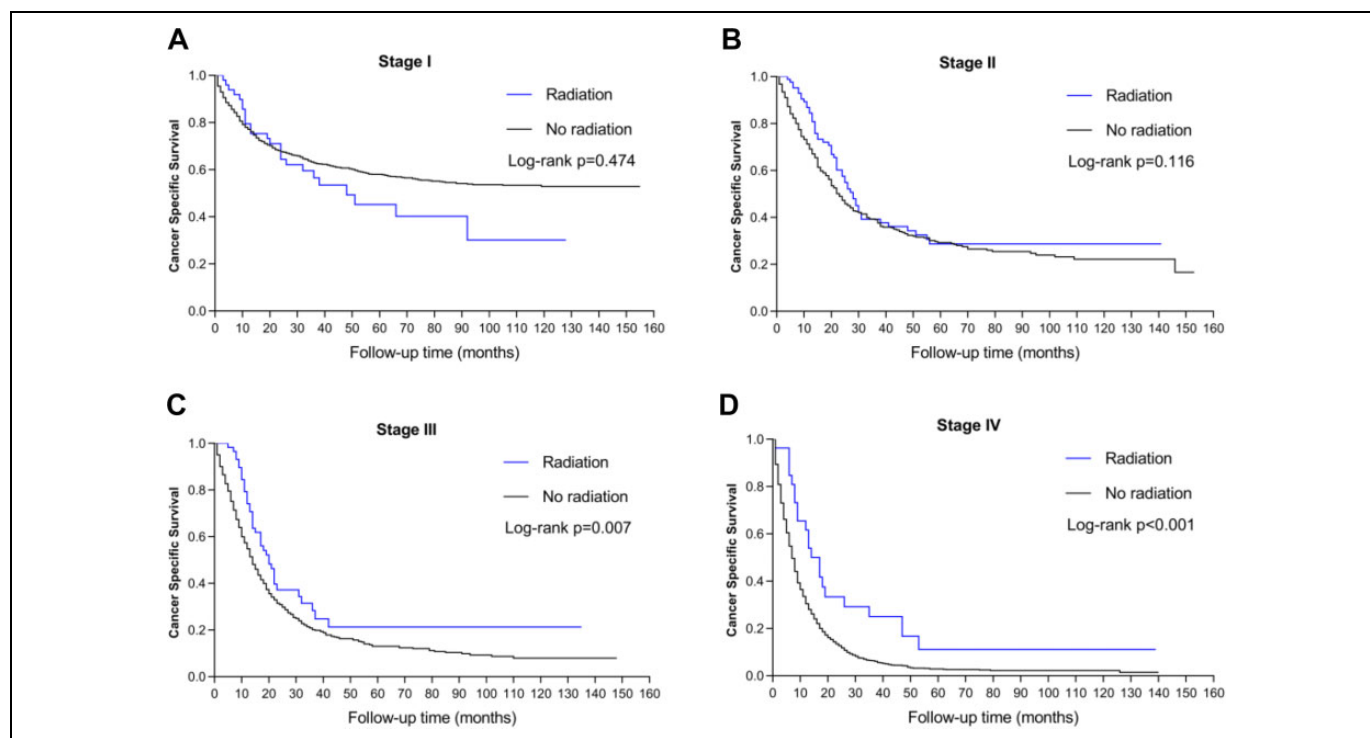


Figure 2. Kaplan-Meier survival curves stratified by TNM stage. A, Stage I ($p > 0.05$). B, Stage II ($p > 0.05$). C, Stage III ($p < 0.05$). D, Stage IV ($p < 0.05$).

survival.²⁴ Thus preoperative RT may be more appropriate for advanced gastric SRC.

There are several limitations of our study. First, this retrospective analysis has an inherent selection bias. The confounders in two cohorts may have an impact on the results. Second, the data are not available in the SEER database regarding radiation techniques and dose, which may have caused potential bias. Third, our findings can only be applied to the America rather than the global population, especially in endemic areas such as China.²⁵ Fourth, the sequences and specific chemotherapy regime are still not available in the SEER database, so the interaction of preoperative RT with distinct chemotherapy can't be accurately evaluated. To minimize the potential bias from multiple confounding factors, subgroup survival analysis was initiated to compensate the significant differences between the 2 comparison groups.²⁶ Given a large population that represents the real-world patients, our results are still considerably convincing.

Conclusion

Based on a large population from the SEER database, preoperative radiotherapy is associated with significant survival benefits for the patients with advanced gastric SRC. Hence preoperative radiotherapy is feasible for these patients. Our study will hopefully contribute to the future tailored treatment for the patients with gastric SRC.

Authors' Note

Our study does not require any ethical approval because we use publicly available SEER database. The SEER data contain no identifiers and are publicly available, so ethical approval was exempt for our study.

Acknowledgments

The authors acknowledge the Surveillance, Epidemiology, and End Results database for providing high quality clinical data for our study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the National Natural Science Foundation of China (81670123, 81670144).

ORCID iD

Yuxin Chu  <https://orcid.org/0000-0001-5526-997X>

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