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The value of predictive models in guiding clinical decisions for colorectal and pancreatic cancer

Dissertation

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Yuqiang Li
aus Hunan (China)

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1.1 The main contributor to the upswing of survival in locally advanced colorectal cancer: an analysis of the SEER database

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The main contributor to the upswing of survival in locally advanced colorectal cancer: an analysis of the SEER database

Yuqiang Li, Lilan Zhao, Cenap Güngör, Fengbo Tan, Zhongyi Zhou, Chenglong Li, Xiangping Song, Dan Wang, Qian Pei and Wenxue Liu

Abstract

Background: There is no conclusion about the most important contributor to the upswing of locally advanced colorectal cancer (LACRC) survival.

Methods: Data from the Surveillance, Epidemiology, and End Results (SEER) database was extracted to identify colorectal adenocarcinoma cancer patients at stage II and III diagnosed in the two periods 1989–1990 and 2009–2010. The statistical methods included Pearson's chi-squared test, log-rank test, Cox regression model and propensity score matching.

Results: The Cox regression model showed that hazard ratio (HR) of non-surgery dropped from 11.529 to 3.469 in right colon cancer (RCC), 5.214 to 2.652 in left colon cancer (LCC) and 3.275 to 3.269 in rectal cancer (RC) from 1989–1990 to 2009–2010. The 95% confidence intervals (CIs) for surgical resection in 2009–2010 were narrower than those in 1989–1990. HR became greater in LACRC without chemotherapy (from 1.337 to 1.779 in RCC, 1.269 to 2.017 in LCC, 1.317 to 1.811 in RC). There was no overlapping about the 95% CI of chemotherapy between the two groups. The progress of surgery was not linked to the improvement of overall survival (OS) of RCC ($p = 0.303$) and RC ($p = 0.660$). Chemotherapy had a significant association with OS of all colorectal cancer (CRC) patients ($p = 0.017$ in RCC; $p = 0.006$ in LCC; $p = 0.001$ in RC).

Conclusions: Advancements in chemotherapy regimen were the main contributor to the upswing of CRC survival. The improvements in surgery had a limited effect on improvements in CRC survival.

Keywords: adjuvant therapy, chemotherapy, locally advanced colorectal cancer, radiotherapy, surgery

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Correspondence to:
Qian Pei
Department of Gastrointestinal Surgery and National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, P.R. China
peiqian1221@hotmail.com

Wenxue Liu
Department of Cardiology and National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, P.R. China
liuwenxue25@yeah.net

Yuqiang Li
Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, China

Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Lilan Zhao
Cenap Güngör
Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Fengbo Tan
Zhongyi Zhou
Chenglong Li
Xiangping Song
Dan Wang
Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, China

National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, China

Introduction

Colorectal cancer (CRC) is the third most common adult cancer in the world, with an estimated 1.8 million cases and 881,000 deaths annually by the GLOBOCAN estimate in 2018.[1] With advances in treatment technology over the past few decades, the survival of patients with locally advanced colorectal cancer (LACRC) has improved significantly.

Treatment for locally advanced colorectal cancer includes surgical resection,[2] chemotherapy[3] and/or radiation therapy.[4] Advances in surgical resection techniques are attributed to updated surgical equipment and concepts. Total mesorectal excision (TME) and complete mesocolic excision (CME) have become the consensus of all colorectal surgeons.[5,6] In addition, application of laparoscopy and robot-assisted laparoscopy contribute to the refinement of CRC surgery.[7,8] Adjuvant chemotherapy for LACRC patients with high-risk stage II and III cancer has substantially evolved over the past decades, concomitant with progress in marketing of oxaliplatin, irinotecan, cetuximab

and bevacizumab, as well as the concept of neoadjuvant therapy.

The uptake of TME or CME combined with adjuvant oncological treatment for locally advanced rectal cancer has reduced local recurrence rates and improved long-term survival.[9] However, which is the most important contributor to the upswing in CRC survival? There is no final conclusion yet. Exploration of this issue can provide research directions relating to CRC, or even all tumors, in the future.

Therefore, the aim of this study was to explore the main contributor to the upswing of survival in LACRC.

Materials and methods

Patients

Data in this retrospective analysis were extracted from the Surveillance, Epidemiology, and End Results (SEER) linked database. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the USA that is updated annually. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the US population.[10] The target population was limited to patients with stage II and III colorectal adenocarcinoma diagnosed in the periods 1989–1990 and 2009–2010, which includes 40,470 patients in total. All patients were followed for more than 5 years. Exclusion criteria were: (1) appendix tumor, (2) diagnosed at autopsy or on the death certificate. The final study sample contained 40,184 patients.

We selected the period 1989–1990 as a baseline for comparison because the management of LACRC started to evolve rapidly from the 1990s;[9] we chose patients from the period 2009–2010 since these were the patients with the most recent with 5-year follow up. In 1989–1990 CRC was defined using the third edition AJCC staging. However, in 2009–2010 the sixth edition of the AJCC staging was adopted. Therefore, we re-staged the N stage according to the number of positive lymph nodes. We defined N1 as 1–3 lymph nodes positive and N2 as more than 4 lymph nodes positive.

Methods

Intergroup comparisons were analyzed using Pearson's chi-squared test. The log-rank test was used to compare overall survival (OS) between different groups. A hazard ratio (HR) and a 95% confidence interval (CI) were evaluated by a single factor and a multivariate Cox proportional hazards regression model. Univariate analysis of variables with significant differences was included in the Cox regression model for multivariate analysis. In order to eliminate the influence of other variables, we conducted propensity score matching (PSM). Statistical analyses were performed with IBM SPSS statistics trial v. 25.0 (IBM, Armonk, NY, USA). All reported p values lower than 0.05 were considered significant.

Results

Patient characteristics

This study enrolled 40,184 patients, including 10,604 (26.39%) cases in 1989–1990 and 29,580 (73.61%) cases in 2009–2010. We found marked differences between 1989–1990 and 2009–2010. The proportion of male LACRC increased from 49.72% to 51.21%. Elderly patients (more than 70 years old) with LACRC decreased from 53.54% to 45.30%. The ethnic composition was also different. In addition, T stage, N stage and histologic grade were significantly different between the two groups.

Importantly, there were significant differences in the rates of surgery, radiotherapy and chemotherapy between 1989–1990 and 2009–2010. The proportion of chemotherapy (from 21.64% to 45.58%) and radiotherapy (from 12.56% to 18.48%) increased significantly as the rate of surgery (from 99.56% to 96.73%) decreased from 1989–1990 to 2009–2010. The qualified number of regional nodes examined (RNE), an important indicator of the quality of surgery, soared from 35.00% to 77.29% (Table 1).

Survival analysis

The OS of patients with LACRC improved significantly due to advances in surgery combined with adjuvant therapy in the period between 1989–1990 and 2009–2010. The 5-year survival rate increased from 54.82% to 60.87% ($p < 0.001$, Figure 1(a)), 56.81% to 66.89% ($p < 0.001$,

Table 1. Characteristics of local advanced colorectal cancer.

Characteristics	1989–1990 ($n = 10,604$)	2009–2010 ($n = 29,580$)	p value
Gender			0.008
Male	5272 (49.72%)	15,148 (51.21%)	
Female	5332 (50.28%)	14,432 (48.79%)	
Age (years)			<0.001
⩽50	722 (6.81%)	3665 (12.39%)	
51–70	4205 (39.65%)	12,516 (42.31%)	
>70	5677 (53.54%)	13,399 (45.30%)	
Race			<0.001
White	9224 (86.99%)	23,586 (79.74%)	
Black	748 (7.05%)	3341 (11.29%)	
Other	630 (5.94%)	2572 (8.70%)	
Unknown	2 (0.02%)	81 (0.27%)	
Primary tumor location			0.209
Right colon	4451 (41.97%)	13,006 (43.97%)	
Left colon	3502 (33.03%)	8037 (27.17%)	
Rectum	2567 (24.21%)	8126 (27.47%)	
Unknown	84 (0.79%)	411 (1.39%)	
Histologic grade			<0.001
Well/moderately differentiated	7923 (74.72%)	22,590 (76.37%)	
Poor differentiated/undifferentiated	1829 (17.25%)	5965 (20.17%)	
Unknown	852 (8.03%)	1025 (3.47%)	
T staging			<0.001
T0–3	8553 (80.66%)	25,153 (85.03%)	
T4	2011 (18.96%)	4353 (14.72%)	
Unknown	40 (0.38%)	74 (0.25%)	
N staging			<0.001
N0	6065 (57.20%)	14,603 (49.37%)	
N1	2998 (28.27%)	10,106 (34.16%)	
N2	1207 (11.38%)	4871 (16.47%)	
Unknown	334 (3.15%)	0 (0.00%)	
Surgery			<0.001
Yes	10,557 (99.56%)	28,614 (96.73%)	
No	47 (0.04%)	889 (3.01%)	
Unknown	0 (0.00%)	77 (0.26%)	

(Continued)

Table 1. (Continued)

Characteristics	1989–1990 (n = 10,604)	2009–2010 (n = 29,580)	p value
Radiotherapy			<0.001
Yes	1332 (12.56%)	5467 (18.48%)	
No	9213 (86.88%)	24,051 (81.31%)	
Unknown	59 (0.56%)	62 (0.21%)	
Chemotherapy			<0.001
Yes	2295 (21.64%)	13,483 (45.58%)	
No	8309 (78.36%)	16,097 (54.42%)	
Regional nodes examined			<0.001
<12	6106 (57.58%)	6531 (22.08%)	
⩾12	3658 (35.00%)	22,863 (77.29%)	
Unknown	840 (7.92%)	186 (0.63%)	

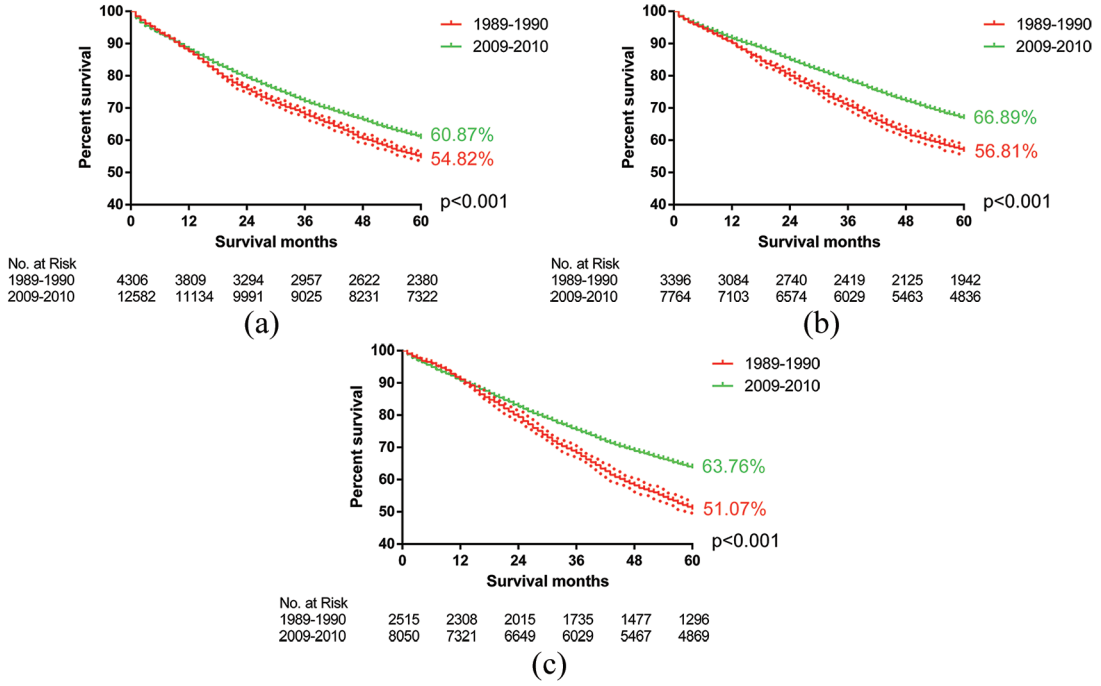


Figure 1. The log-rank test showed that the overall survival of patients with locally advanced colorectal cancer improved significantly due to the advances in surgery combined with adjuvant therapy. (a) The 5-year survival rate increased from 54.82% to 60.87% ($p < 0.001$) in right colon cancer; (b) the 5-year survival rate increased from 56.81% to 66.89% ($p < 0.001$) in left colon cancer; and (c) the 5-year survival rate increased from 51.07% to 63.76% ($p < 0.001$) in rectal cancer.

Figure 1(b)) and 51.07% to 63.76% ($p < 0.001$, Figure 1(c)) in right colon cancer (RCC), left colon cancer (LCC) and rectal cancer (RC) respectively. Meanwhile, LACRC patients undergoing chemotherapy increased by 14.52% (RCC, Figure 2(a)), 22.19% (LCC, Figure 2(b)) and 39.86% (RC, Figure 2(c)). Moreover, the proportion of radiotherapy grew from 37.39% to

58.40% in RC patients. There was also a significant increase in the number of RNE. The qualified ratio rose by 44.12% (RCC, Figure 2(a)), 50.74% (LCC, Figure 2(b)) and 31.32% (RC, Figure 2(c)).

Cox regression model

Age, pathological grade, T stage, N stage, surgery, chemotherapy and RNE were important prognostic factors in both LACRC of 1989–1990 and 2009–2010. Also, several new poor prognostic factors emerged in the cases of 2009–2010, including black people in RCC ($p < 0.001$), and men in LCC ($p < 0.001$) and RC ($p < 0.001$). Although used as a prognostic factor, radiotherapy was a risk factor in RCC patients in 2009–2010 (HR: 0.754, $p = 0.015$).

Interestingly, HR of non-surgery dropped from 11.529 to 3.469 in RCC, 5.214 to 2.652 in LCC and 3.275 to 3.269 in RC. Meanwhile, the 95% CIs for surgical resection in 2009–2010 were narrower than those in 1989–1990 (Figure 3(a)). Conversely, the HR became greater in LACRC without chemotherapy (from 1.337 to 1.779 in RCC, from 1.269 to 2.017 in LCC, from 1.317 to 1.811 in RC). There was no overlap about the 95% CI of chemotherapy between the two groups (Figure 3(b)) (Tables 2–4).

The impact of surgical advancement on survival

We screened patients who underwent surgery without adjuvant therapy. In order to eliminate the influence of the other variables, PSM was conducted for an analysis of variables, including age, gender, race, differentiation and T and N stage (Supplementary Tables 1–3). The number of regional nodes examined did not match between the two groups, which can reflect the quality of surgery. We found that the surgical advancement was associated with the qualified rate of regional nodes, which improved by 41.76%, 48.90% and 43.84% in RCC, LCC and RC respectively. The log-rank test showed that OS of LCC was significantly increased with the development of surgical techniques ($p = 0.015$) (Figure 4(b)). However, there was no significant effect of surgical advancement on the overall survival of RCC ($p = 0.303$, Figure 4(a)) and RC ($p = 0.660$, Figure 4(c)). Moreover, the 1-year survival rate of colorectal patients in 2009–2010 was lower than that in 1989–1990 (RCC, 88.19% *versus* 84.24%; LCC, 89.85% *versus* 87.77%; RC, 90.33% *versus* 82.25%).

The impact of advancement of adjuvant therapy on survival

Patients treated with both surgery and chemotherapy were selected for PSM. The variables for PSM consisted of age, gender, race, differentiation, T stage, N stage, radiotherapy and the number of RNE (Supplementary Tables 4–6). A higher likelihood of improved OS occurred in all colorectal cancers after completion of updated adjuvant therapy compared to the patients with the old version of adjuvant therapy ($p = 0.017$ in RCC, Figure 5(a); $p = 0.006$ in LCC, Figure 5(b); $p = 0.001$ in RC, Figure 5(c)).

For exploration of the impact of radiotherapy on the survival of RC patients, those receiving radiotherapy were the target population. The variables for PSM were age, gender, race, differentiation, T stage, N stage, chemotherapy, surgery and the number of RNE (Supplementary Table 7). Adjuvant radiotherapy was associated with an increased OS from 57.54% to 67.36% ($p = 0.001$, Figure 6).

Discussion

To the best of our knowledge, this study was the first to look into the main reason for the improvement of survival in LACRC. We selected patients with LACRC in the periods 1989–1990 and 2009–2010, explored the relative importance of prognostic factors by a Cox regression model, and compared the effects of surgery and adjuvant therapy on survival after PSM. We believe that research on the progress of treatment can be fundamental to guiding the improvement of current treatment options. Also, successful experience in CRC treatment can be regarded as a reference for other tumors.

Although decreasing, the HR of non-surgical treatment was still the highest among various treatment methods. Therefore, it is still undoubted that surgery is the first-choice treatment for CRC. Colorectal surgery had also seen tremendous developments in the two decades. The qualified number of RNE reached 77.29% in 2009–2010. Moreover, a narrow range of 95% CI in 2009–2010 suggested that colorectal surgeons reached some consensus on the methods and scope of

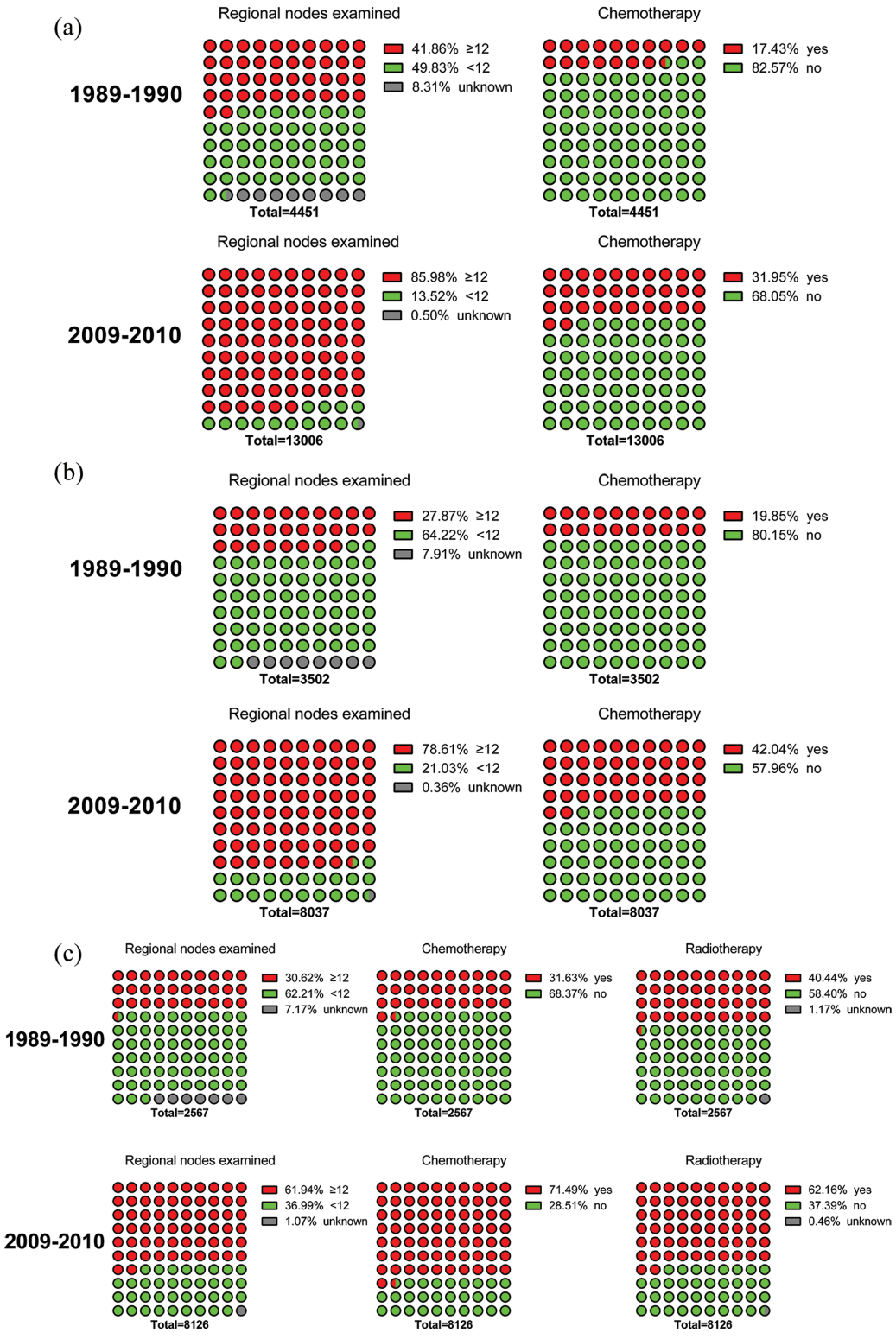


Figure 2. The ratio of chemotherapy (radiotherapy) and qualified regional nodes examined (RNE) in colorectal cancer patients. (a) Patients undergoing chemotherapy increased by 14.52% and the ratio of qualified RNE, which was ⩾12, increased by 44.12% in right colon cancer. (b) Patients undergoing chemotherapy increased by 22.19% and the ratio of qualified RNE increased by 50.74% in left colon cancer. (C) Patients undergoing chemotherapy increased by 39.86%, the proportion of radiotherapy increased by 21.72% and the ratio of qualified RNE increased by 31.32% in rectal cancer.

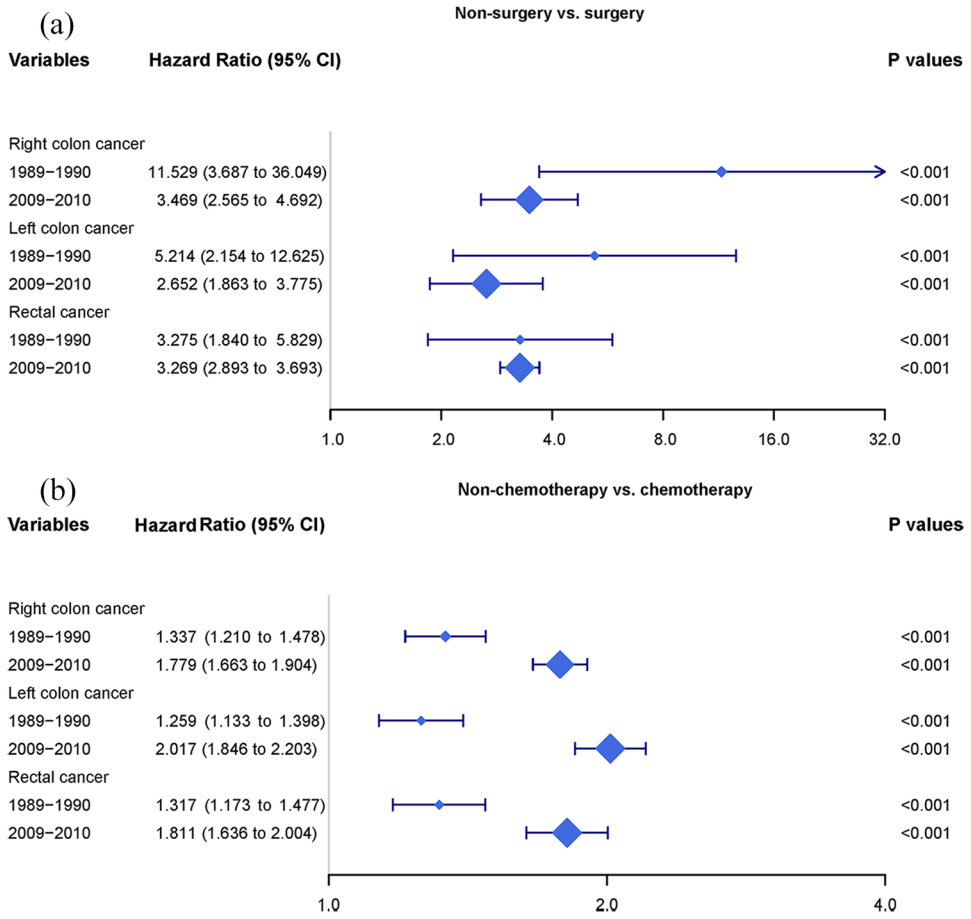


Figure 3. Forest plots for the Cox regression model. (a) Non-surgery *versus* surgery. Hazard ratio (HR) of non-surgery dropped from 11.529 to 3.469 in right colon cancer; 5.214 to 2.652 in left colon cancer; and 3.275 to 3.269 in rectal cancer. (B) Non-chemotherapy *versus* chemotherapy. The HR became greater in locally advanced colorectal cancer without chemotherapy (from 1.337 to 1.779 in right colon cancer, from 1.269 to 2.017 in left colon cancer, from 1.317 to 1.811 in rectal cancer).

surgical resection, like TME and CME. Unfortunately, patient survival of RCC and RC did not improve significantly with advances in surgery, while LCC patients may benefit from CME and/or advanced equipment. Although many researchers reported that laparoscopic colectomy, which was widely used in the field of colorectal surgery in 2009–2010, significantly improves the short-term outcomes of patients,[11–14] the short-term survival rate in 2009–2010 was lower than that in 1989–1990. Therefore, surgeons need to pay more attention to the short-term survival rate after surgery in future research, especially for patients who need surgery only, even though the scope of surgical resection can be considered to be appropriately restricted.

TME was proposed by Heald and colleagues in 1982[15] and has become the standard for surgery of RC after more than 20 years of practice.[16] Owing to the successful experience of TME, CME was quickly recognized by colorectal surgeons, and was initially introduced in 2009.[17,18] Therefore, both colon and rectal cancer can benefit from advances in surgical equipment, but the revolutionary concept was only proposed for the treatment of colon cancer between 1989–1990 and 2009–2010. The values of HR and 95% CI for RC surgery varied minimally in our Cox regression model from 1989–1990 to 2009–2010; on the contrary, the change was huge in colon cancer. Therefore, we considered that advances in surgical equipment may be beneficial to the

Table 2. Multivariate analysis of survival months in right colon cancer patients.

Variables	1989–1990		2009–2010	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)		<0.001		<0.001
51–70 *versus* ⩽50	2.834 (2.280–3.524)	<0.001	1.396 (1.208–1.614)	<0.001
>70 *versus* ⩽50	7.015 (5.639–8.727)	<0.001	2.991 (2.599–3.442)	<0.001
51–70 *versus* >70	0.404 (0.373–0.438)	<0.001	0.466 (0.437–0.496)	<0.001
Race		0.050		<0.001
Black *versus* white	1.141 (1.002–1.300)	0.047	1.152 (1.060–1.252)	0.001
Other *versus* white	0.900 (0.767–1.056)	0.196	0.832 (0.742–0.933)	0.002
Black *versus* other	1.268 (1.039–1.548)	0.020	1.363 (1.193–1.557)	<0.001
Histologic grade				
Poor/undifferentiated *versus* well/moderately differentiated	1.111 (1.027–1.203)	0.009	1.218 (1.150–1.291)	<0.001
T staging				
T4 *versus* T0–3	1.142 (1.050–1.242)	<0.001	1.816 (1.701–1.938)	<0.001
N staging		<0.001		<0.001
N1 *versus* N0	1.311 (1.210–1.421)	<0.001	1.592 (1.492–1.699)	<0.001
N2 *versus* N0	2.258 (2.021–2.522)	<0.001	2.823 (2.619–3.042)	<0.001
N1 *versus* N2	0.581 (0.517–0.652)	<0.001	0.555 (0.516–0.597)	<0.001
Surgery				
No *versus* Yes	11.529 (3.687–36.049)	<0.001	3.469 (2.565–4.692)	<0.001
Chemotherapy				
No *versus* Yes	1.337 (1.210–1.478)	<0.001	1.779 (1.663–1.904)	<0.001
Radiotherapy				
No *versus* Yes	NA	NA	0.754 (0.593–0.959)	0.015
Regional nodes examined				
<12 *versus* ⩾12	1.341 (1.252–1.437)	<0.001	1.524 (1.420–1.637)	<0.001

NA, not applicable.

stability of operations, but the revolutionary surgical concept was the real engine for surgical progress.

More and more attention to adjuvant therapy is paid in modern medicine. The proportion of LACRC patients receiving chemotherapy and/or

Table 3. Multivariate analysis of survival months in left colon cancer patients.

Variables	1989–1990		2009–2010	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years)		<0.001		<0.001
51–70 *versus* ⩽50	1.762 (1.456–2.134)	<0.001	1.296 (1.126–1.492)	<0.001
>70 *versus* s50	4.180 (3.445–5.073)	<0.001	2.903 (2.529–3.333)	<0.001
51–70 *versus* >70	0.404 (0.373–0.438)	<0.001	0.446 (0.412–0.484)	<0.001
Gender				
Male *versus* female	NA	NA	1.182 (1.100–1.271)	<0.001
Race		0.204		
Black *versus* white	1.040 (0.895–1.209)	0.609	NA	NA
Other *versus* white	0.875 (0.748–1.024)	0.096	NA	NA
Black *versus* other	1.188 (0.964–1.465)	0.106	NA	NA
Histologic grade				
Poor/undifferentiated *versus* well/moderately differentiated	1.170 (1.039–1.316)	0.009	1.270 (1.157–1.393)	<0.001
T staging				
T4 *versus* T0–3	1.142 (1.050–1.242)	<0.001	1.953 (1.788–2.134)	<0.001
N staging		<0.001		<0.001
N1 *versus* N0	1.271 (1.163–1.389)	<0.001	1.406 (1.289–1.533)	<0.001
N2 *versus* N0	1.731 (1.513–1.981)	<0.001	2.495 (2.254–2.762)	<0.001
N1 *versus* N2	0.734 (0.639–0.843)	<0.001	0.563 (0.510–0.623)	<0.001
Surgery				
No *versus* Yes	5.214 (2.154–12.625)	<0.001	2.652 (1.863–3.775)	<0.001
Chemotherapy				
No *versus* Yes	1.259 (1.133–1.398)	<0.001	2.017 (1.846–2.203)	<0.001
Regional nodes examined				
<12 *versus* ⩾12	1.162 (1.068–1.264)	<0.001	1.536 (1.415–1.669)	<0.001

NA, not applicable.

radiotherapy in 2009–2010 was almost double that in 1989–1990. Advancements in chemotherapy regimen had a significant association with OS of CRC patients. The main chemotherapy regimen for CRC was 5-FU/leucovorin in the 1990s.[19] FOLFOX (oxaliplatin/5-FU/leucovorin) has become the first-line treatment for CRC in the 21st century.[20] We found that there was no intersection about the 95% CIs of chemotherapy between the two groups. Meanwhile, OS of LACRC patients

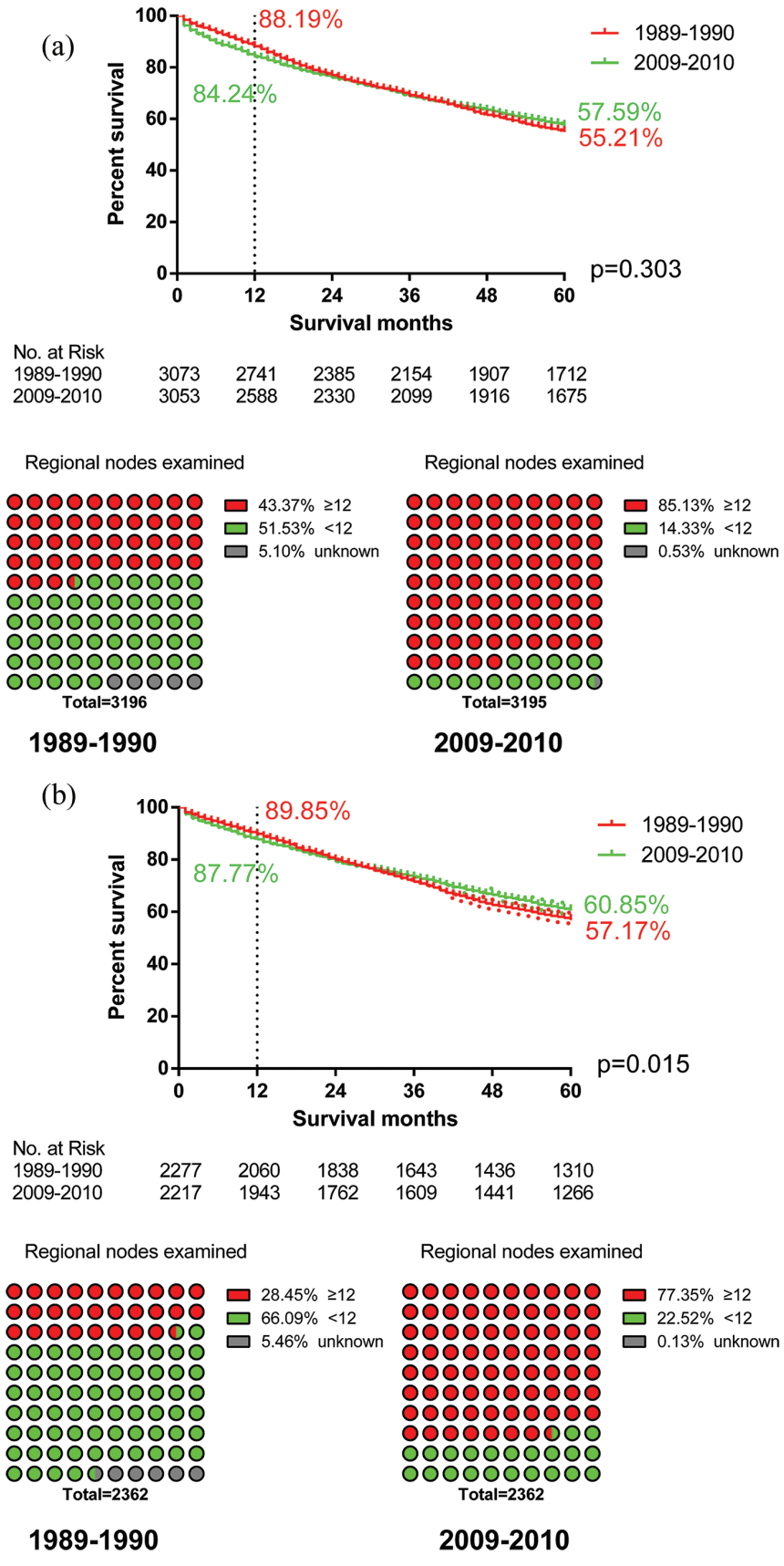
Table 4. Multivariate analysis of survival months in rectal cancer patients.

Variables	1989–1990		2009–2010	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age(years)		<0.001		<0.001
51–70 *versus* ⩽50	2.047 (1.683–2.489)	<0.001	1.397 (1.231–1.585)	<0.001
>70 *versus* ⩽50	4.251 (3.473–5.203)	<0.001	2.874 (2.530–3.265)	<0.001
51–70 *versus* >70	0.482 (0.437–0.531)	<0.001	0.486 (0.448–0.527)	<0.001
Gender				
Male *versus* female	NA	NA	1.150 (1.067–1.240)	<0.001
Histologic grade				
Poor/undifferentiated *versus* well/moderately differentiated	1.166 (1.035–1.313)	0.012	1.399(1.275–1.535)	<0.001
T staging				
T4 *versus* T0–3	1.364 (1.202–1.548)	<0.001	1.992 (1.806–2.196)	<0.001
N staging		<0.001		<0.001
N1 *versus* N0	1.266 (1.142–1.403)	<0.001	1.308 (1.201–1.424)	<0.001
N2 *versus* N0	1.792 (1.561–2.057)	<0.001	2.067 (1.868–2.288)	<0.001
N1 *versus* N2	0.706 (0.613–0.814)	<0.001	0.633 (0.572–0.700)	<0.001
Surgery				
No *versus* Yes	3.275 (1.840–5.829)	<0.001	3.269 (2.893–3.693)	<0.001
Chemotherapy				
No *versus* Yes	1.317 (1.173–1.477)	<0.001	1.811 (1.636–2.004)	<0.001
Radiotherapy				
No *versus* Yes	1.008 (0.907–1.121)	0.878	0.935 (0.847–1.032)	0.184
Regional nodes examined				
<12 *versus* ⩾12	1.192 (1.082–1.312)	<0.001	1.328 (1.219–1.448)	<0.001

NA, not applicable.

who underwent surgery with chemotherapy improved significantly ($p = 0.017$ in RCC; $p = 0.006$ in LCC; $p = 0.001$ in RC) after PSM, suggesting that the advancements in chemotherapy regimen are the root cause of the improvement in CRC survival.

Further investigations to explore the effects of radiotherapy on survival of CRC are needed. Although the OS of patients with RC who received radiotherapy in 2009–2010 was better than that in 1989–1990, the effects of chemotherapy cannot be ruled out. And radiotherapy cannot serve as a good prognostic factor in the Cox regression model. Specifically, patients who underwent radiotherapy had worse survival than those who did not undergo radiotherapy in RCC. Therefore, we tend to believe



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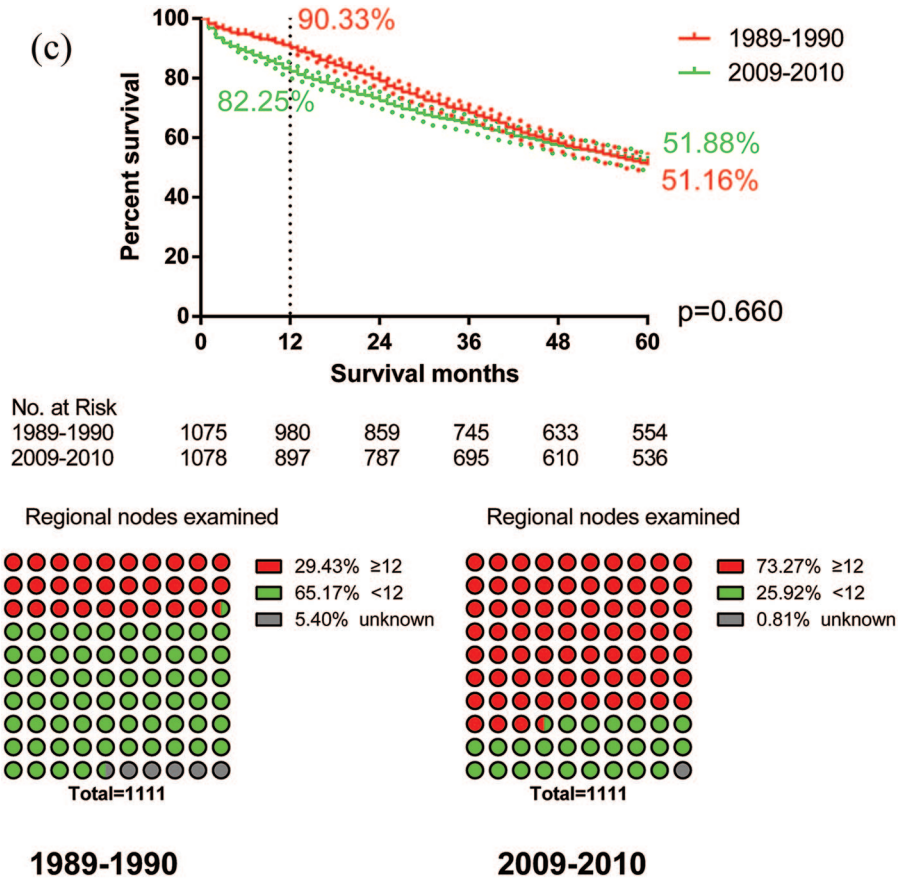

Figure 4. The impact of surgical advancement on survival. (a) The overall survival of right colon cancer patients did not improve significantly ($p = 0.303$). The 1-year survival rate of right colon cancer patients dropped from 88.19% to 84.24%. The rate of qualified RNE increased by 41.76% in right colon cancer. (b) OS of left colon cancer patients was significantly increased ($p = 0.015$). The 1-year survival rate of left colon cancer patients dropped from 89.85% to 87.77%. The rate of qualified RNE increased by 48.90% in left colon cancer. (c) The overall survival of rectal cancer did not improve significantly ($p = 0.660$). The 1-year survival rate of rectal cancer patients dropped from 90.33% to 82.25%. The rate of qualified RNE increased by 43.84% in rectal cancer.

that radiotherapy alone cannot improve the RC survival. But we also cannot ignore the effect of radiotherapy on sphincter preservation in low rectal cancer.

The interesting findings of this study include: (1) although advancements in surgical treatment had not significantly prolonged the survival of CRC, surgeons should explore a more appropriate area of surgical resection and improve short-term outcomes without affecting the long-term survival of LACRC; (2) effective drugs are the key to cancer treatment since chemotherapy is the main contributor to the progress in treatment of CRC; (3) oncologists should consider whether the administration of radiotherapy can be abandoned for patients with mid/low rectal cancer if radiotherapy does not affect sphincter preservation. Access to only retrospective data was the main limitation of this study.

Conclusion

Advancements of chemotherapy regimen were the main contributor to the upswing in CRC survival. The improvements in surgery had a limited effect on improvements in CRC survival. The short-term survival of LACRC patients in 2009–2010 was even lower than that in 1989–1990.

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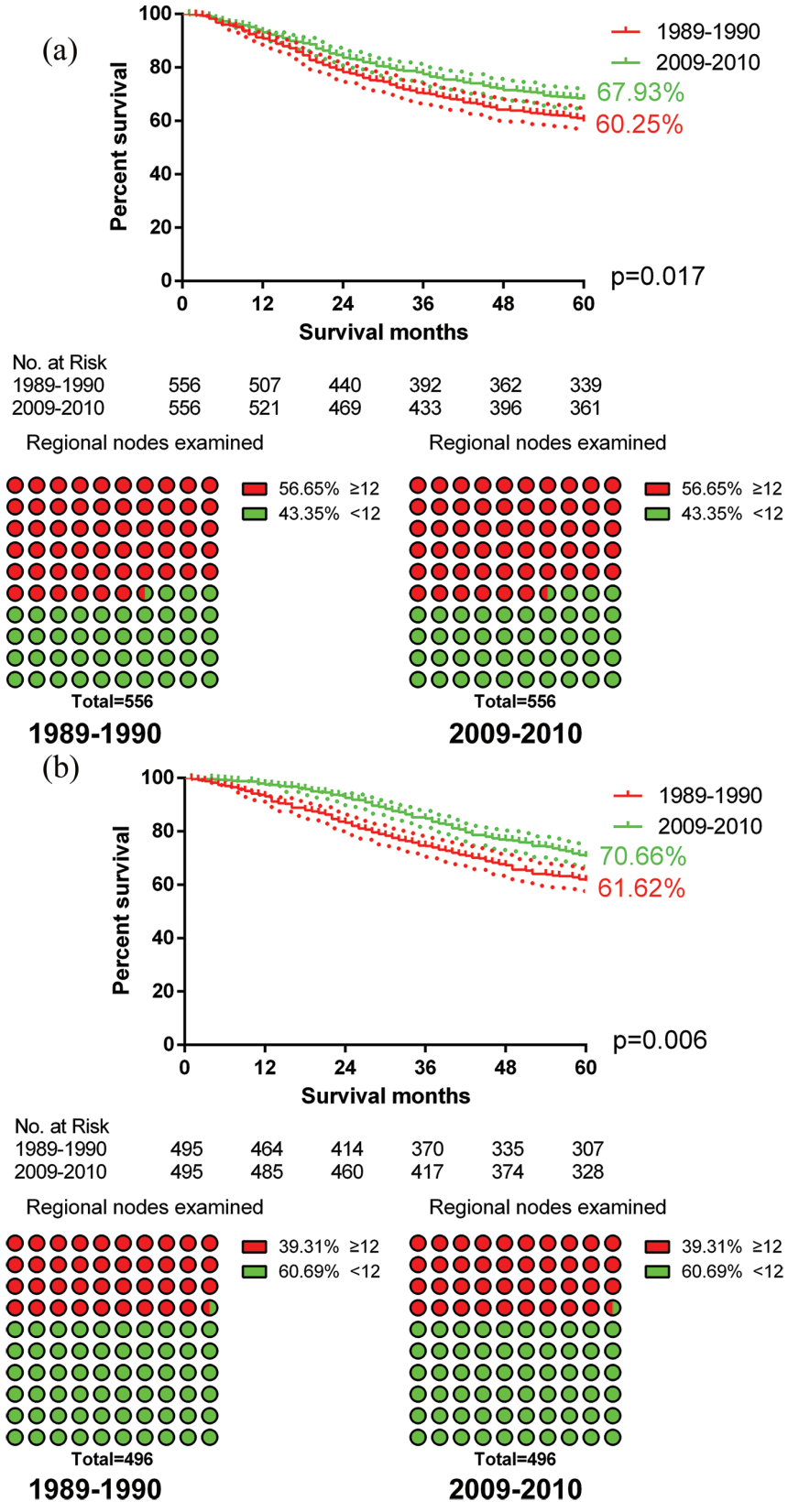

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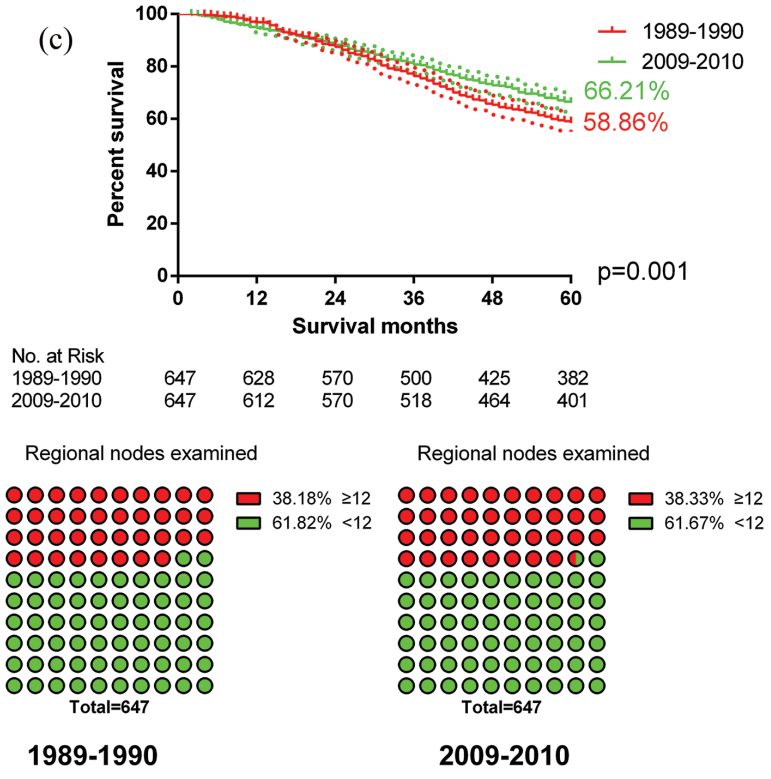

Figure 5. The impact of chemotherapy advancements on survival. (a) Overall survival (OS) of right colon cancer patients increased from 60.25% to 67.93% ($p = 0.017$); (b) OS of left colon cancer patients increased from 61.62% to 70.66% ($p = 0.006$); and (c) OS of rectal cancer patients increased from 58.86% to 66.21% ($p = 0.001$).

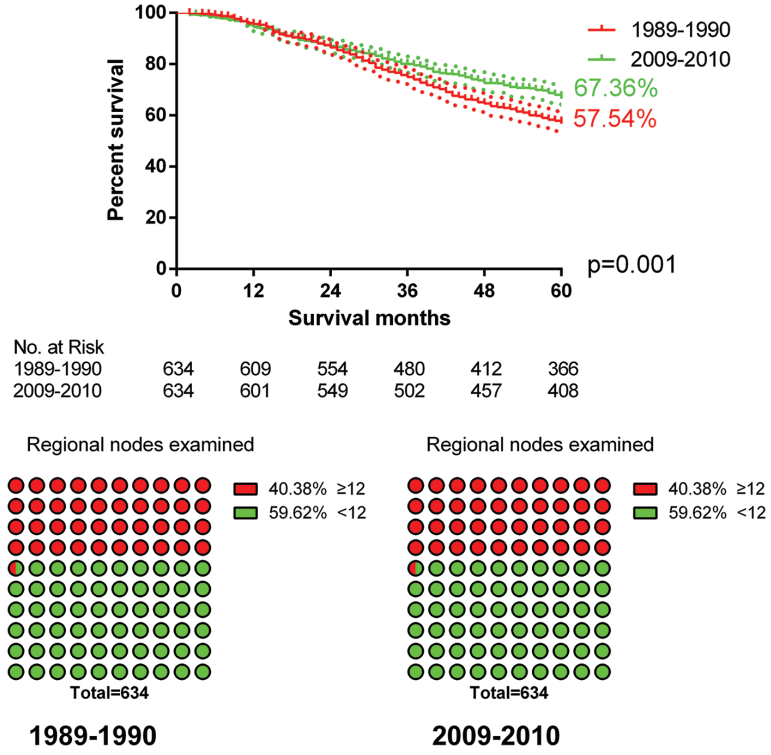

Figure 6. The impact of radiotherapy advancements on survival. Overall survival increased from 57.54% to 67.34% ($p = 0.001$).

(SEER) Program tumor registries in the creation of the SEER database. The interpretation and reporting of these data are the sole responsibility of the authors.

Author contributions

The first author, Yuqiang Li, contributed mainly to this article.

Ethics statement

This retrospective study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University with Approval No. 201903130. Patients' informed consent was waived because of the retrospective nature of the study design.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

ORCID iD

Yuqiang Li https://orcid.org/0000-0003-1517-3687

Supplemental material

Supplemental material for this article is available online.

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Supplementary table 1 Characteristics of local advanced right colon cancer after PSM

Characteristics	1989-1990(n=3195)	2009-2010(n=3195)	P value
Gender			1.000
Male	1378(43.13%)	1378(43.13%)	
Female	1817 (56.87%)	1817(56.87%)	
Age(years)			1.000
≤50	120(3.76%)	120(3.76%)	
51-70	921(28.83%)	921(28.83%)	
＞70	2154(67.42%)	2154(67.42%)	
Race			0.916
White	2809 (87.92%)	2808(87.89%)	
Black	250 (7.82%)	248(7.76%)	
Other	136 (4.26%)	139(4.35%)	
Histologic grade			0.904
Well/ Moderately differentiated	2482(77.68%)	2478(77.56%)	
Poor differentiated/Undifferentiated	713(22.32%)	717(22.44%)	
T staging			0.899
T0-3	2587(80.97%)	2583(80.85%)	
T4	608(19.03%)	612(19.15%)	
N staging			0.939
N0	2174(68.04%)	2172(67.98%)	
N1	729(22.82%)	729(22.92%)	
N2	292(9.14%)	294(9.20%)	

Supplementary table 2 Characteristics of local advanced left colon cancer after PSM

Characteristics	1989-1990(n=2362)	2009-2010(n=2362)	P value
Gender			1.000
Male	1150(48.69%)	1150(48.69%)	
Female	1212 (51.31%）	1212 (51.31%）	
Age(years)			1.000
⩽50	106 (4.49%)	106 (4.49%)	
51-70	894(37.85%)	894(37.85%)	
＞70	1362(57.66%)	1362(57.66%)	
Race			1.000
White	2042 (86.45%)	2042 (86.45%)	
Black	163 (6.90%)	163 (6.90%)	
Other	157 (6.65%)	157 (6.65%)	
Histologic grade			1.000
Well/ Moderately differentiated	2097(88.78%)	2097(88.78%)	
Poor differentiated/Undifferentiated	265(11.22%)	265(11.22%)	
T staging			1.000
T0-3	1977(83.70%)	1977(83.70%)	
T4	385(16.30%)	385(16.30%)	
N staging			1.000
N0	1601(67.78%)	1601(67.78%)	
N1	590 (24.98%)	590 (24.98%)	
N2	171(7.24%)	171(7.24%)	

Supplementary table 3 Characteristics of local advanced rectal cancer after PSM

Characteristics	1989-1990(n=1111)	2009-2010(n=1111)	P value
Gender			1.000
Male	602(54.19%)	602(54.19%)	
Female	509 (45.81%）	509 (45.81%）	
Age(years)			1.000
⩽50	40 (3.60%)	40 (3.60%)	
51-70	398(35.82%)	398(35.82%)	
＞70	673(60.58%)	673(60.58%)	
Race			1.000
White	985 (88.66%)	985 (88.66%)	
Black	67 (6.03%)	67 (6.03%)	
Other	59 (5.31%)	59 (5.31%)	
Histologic grade			1.000
Well/ Moderately differentiated	955(85.96%)	955(85.96%)	
Poor differentiated/Undifferentiated	156(14.04%)	156(14.04%)	
T staging			1.000
T0-3	1002(90.19%)	1002(90.19%)	
T4	109(9.82%)	109(9.82%)	
N staging			1.000
N0	739(66.52%)	739(66.52%)	
N1	276(24.84%)	276(24.84%)	
N2	96(8.64%)	96(8.64%)	

Supplementary table 4 Characteristics of local advanced right colon cancer after PSM

Characteristics	1989-1990(n=556)	2009-2010(n=556)	P value
Gender			0.208
Male	280(50.36%)	301(54.14%)	
Female	276(49.64%)	255(45.86%)	
Age(years)			0.408
≤50	71(12.77%)	78(14.03%)	
51-70	296(53.24%)	300 (53.96%)	
>70	189(33.99%)	178(32.01%)	
Race			0.249
White	480 (86.33%)	457(82.19%)	
Black	28 (5.04%)	51(9.17%)	
Other	48 (8.63%)	48(8.63%)	
Histologic grade			0.687
Well/ Moderately differentiated	407(73.20%)	401(72.12%)	
Poor differentiated/Undifferentiated	149(26.80%)	155(27.88%)	
T staging			0.594
T0-3	453(81.47%)	446(80.22%)	
T4	103(18.53%)	110(19.78%)	
N staging			0.618
N0	148(26.61%)	154(27.70%)	
N1	267 (48.02%)	267(48.02%)	
N2	141(25.36%)	135(24.28%)	
Radiotherapy			1.000
Yes	12(2.16%)	12(2.16%)	
No	544(97.84%)	544(97.84%)	
Regional nodes examined			1.000
<12	241(43.35%)	241(43.35%)	
≥12	315(56.65%)	315(56.65%)	

Supplementary table 5 Characteristics of local advanced left colon cancer after PSM

Characteristics	1989-1990(n=496)	2009-2010(n=496)	P value
Gender			0.482
Male	272(54.84%)	283 (57.06%)	
Female	224(45.16%)	213(42.94%)	
Age(years)			0.604
≤50	72(14.52%)	67(13.51%)	
51-70	305(61.49%)	305(61.49%)	
>70	119(23.99%)	124(25.00%)	
Race			0.612
White	430(86.69%)	422(85.08%)	
Black	30(6.05%)	37(7.46%)	
Other	36(7.26%)	37(7.46%)	
Histologic grade			0.705
Well/ Moderately differentiated	430(86.69%)	434(87.50%)	
Poor differentiated/Undifferentiated	66(13.31%)	62(12.50%)	
T staging			0.743
T0-3	407(82.06%)	403(81.25%)	
T4	89(17.94%)	93(18.75%)	
N staging			0.512
N0	147(29.64%)	140(28.23%)	
N1	256(51.61%)	256(51.61%)	
N2	93(18.75%)	100(20.16%)	
Radiotherapy			1.000
Yes	52(10.48%)	52(10.48%)	
No	444(89.52%)	444(89.52%)	
Regional nodes examined			1.000
<12	301(60.69%)	301(60.69%)	
≥12	195 (39.31%)	195 (39.31%)	

Supplementary table 6 Characteristics of local advanced rectal cancer after PSM

Characteristics	1989-1990(n=647)	2009-2010(n=647)	P value
Gender			0.954
Male	416(64.30%)	417(64.45%)	
Female	231(35.70%)	230(35.55%)	
Age(years)			0.624
≤50	102(15.77%)	99(15.30%)	
51-70	394(60.90%)	389(60.12%)	
>70	151(23.34%)	159(24.57%)	
Race			0.350
White	572(88.41%)	563(87.02%)	
Black	29(4.48%)	28(4.33%)	
Other	46(7.11%)	56(8.66%)	
Histologic grade			0.519
Well/ Moderately differentiated	532(82.23%)	523(80.83%)	
Poor differentiated/Undifferentiated	115(17.77%)	124(19.17%)	
T staging			1.000
T0-3	567(87.64%)	567(87.64%)	
T4	80(12.36%)	80(12.36%)	
N staging			0.939
N0	200(30.91%)	199(30.76%)	
N1	305(47.14%)	305(47.14%)	
N2	142(21.95%)	143(22.10%)	
Radiotherapy			0.948
Yes	497(76.82%)	496(76.66%)	
No	150(23.18%)	151(23.34%)	
Regional nodes examined			0.954
<12	400(61.82%)	399(61.67%)	
≥12	247(38.18%)	248 (38.33%)	

Supplementary table 7 Characteristics of local advanced rectal cancer after PSM

Characteristics	1989-1990(n=634)	2009-2010(n=634)	P value
Gender			0.953
Male	407(64.20%)	406(64.04%)	
Female	227(35.80%)	228(35.96%)	
Age(years)			0.930
≤50	97(15.30%)	96(15.14%)	
51-70	364(57.41%)	364(57.41%)	
>70	173(27.29%)	174(27.44%)	
Race			1.000
White	561(88.49%)	561(88.49%)	
Black	34(5.36%)	34(5.36%)	
Other	39(6.15%)	39(6.15%)	
Histologic grade			1.000
Well/ Moderately differentiated	530(83.60%)	530(83.60%)	
Poor differentiated/Undifferentiated	104(16.40%)	104(16.40%)	
T staging			0.871
T0-3	547(86.28%)	545(85.96%)	
T4	87(13.72%)	89(14.03%)	
N staging			1.000
N0	246(38.80%)	245(38.64%)	
N1	262(41.32%)	264(41.64%)	
N2	126(19.87%)	125(19.72%)	
Chemotherapy			0.945
Yes	501(79.02%)	500(78.86%)	
No	133(20.98%)	134(21.14%)	
Surgery			0.795
Yes	627(98.90%)	626(98.74%)	
No	7(1.10%)	8(1.26%)	
Regional nodes examined			1.000
<12	378(59.62%)	378(59.62%)	
≥12	256(40.38%)	256(40.38%)	

1.2 The Main Bottleneck for Non-Metastatic Pancreatic Adenocarcinoma in Past Decades: A Population-Based Analysis

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The Main Bottleneck for Non-Metastatic Pancreatic Adenocarcinoma in Past Decades: A Population-Based Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Yuqiang Li
CDEF 2 Wenxue Liu
ABD 3 Lilan Zhao
CDE 1 Yang Xu
DEF 4 Tingyu Yan
BCF 5 Qionghui Yang
ACF 6 Qian Pei
ABCDEF 1 Cenap Güngör

1 Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
2 Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, P.R. China
3 Department of Thoracic Surgery, Fujian Provincial Hospital, Fuzhou, Fujian, P.R. China
4 Department of Ophthalmology, The Fourth Affiliated Hospital of China Medical University, Shenyang, Liaoning, P.R. China
5 Department of Pediatrics, Yueqing Third People's Hospital, Yueqing, Zhejiang, P.R. China
6 Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, Hunan, P.R. China

Corresponding Authors: Cenap Güngör, e-mail: c.guengoer@uke.de, Yuqiang Li, e-mail: liyuqiang22@yeah.net
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Background: Despite recent advancements in surgical techniques, chemotherapy, and radiotherapy, the 5-year survival rate of patients with pancreatic ductal adenocarcinoma (PDAC) remains an unsatisfactory ~8%.

Material/Methods: Data were extracted to identify patients with non-metastatic pancreatic adenocarcinoma diagnosed in the periods 1988–1996 and 2010–2014 in the Surveillance, Epidemiology, and End Results (SEER) database. The statistical analyses were performed with the log-rank test, Pearson's chi-square test, propensity score matching, and Cox regression model.

Results: The hazard ratio (HR) of surgery was reduced from 0.454 to 0.302 in Cox regression modeling, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. The HR values of radiotherapy, which were new prognostic factor for resectable PDAC in 2010–2014, were reduced in both the resectable and unresectable groups. The upgraded chemotherapy regimen reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC. The log-rank test results showed that advances in surgery significantly improved the median survival from 13 months to 32 months. Radiotherapeutic and chemotherapeutic advancements extended median survival by 12 months and 11 months, respectively, in resectable PDAC. The median survivals were extended by 3 months for both of radiotherapy and chemotherapy in unresectable PDAC.

Conclusions: The development of chemotherapy and radiotherapy has been slow, especially for unresectable PDAC. Although advances in surgery contributed significantly to improved survival for resectable PDAC, lack of early diagnostic tools, which lead to low resection rates, remain a barrier for all PDAC patients.

MeSH Keywords: Carcinoma, Pancreatic Ductal • Chemotherapy, Adjuvant • General Surgery • Radiotherapy

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Background

Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms worldwide [1]. The main histological type of pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC), which accounts for about 85% of cases [2,3]. Early locoregional metastasis, unusual aggressiveness, and distant spread of pancreatic cancer cells are the basis of the urgent need for new therapeutic options for patients with PDAC, as its incidence is still nearly equal to its mortality in Western countries [4].

Treatment for PDAC involves surgical resection, chemotherapy, and/or radiotherapy. The development of surgical resection has involved perfection of surgical concepts and equipment. Several techniques, including total mesopancreatic excision (TMpE) and accurate assessment of the resection margins, which have been learned from experience treating colorectal cancer, are used by pancreatic surgeons [5,6]. Additionally, application of robot-assisted laparoscopy contributes to the refinement of surgery [7]. Adjuvant chemotherapy for patients with PDAC was converted from 5-FU-based regimens in the early 1990s to gemcitabine-based regimens in the 2000s [8,9] and FOLFIRINOX in the 2010s. Intensity-modulated radiation therapy (IMRT), which can not only adjust the dose of radiotherapy and increase the radiation dose of tumor but also reduce the radiation damage of normal tissues, emerged due to the development of CT technology and three-dimensional conformal radiotherapy (3D-CRT) [10,11].

Despite recent advances in surgical techniques, chemotherapy, and radiation therapy, the 5-year survival rate of patients with PDAC remains a dismal 8.2% [12]. The present study explored whether improved surgical resection, chemotherapy, and radiotherapy regimens have helped patients with PDAC obtain a longer survival, as well as to identify the main barriers to improved survival in non-metastatic PDAC, in recent decades. Thus, the purpose of the present study was to determine the impact of therapeutic advancements by comparing the overall survival (OS) of patients with PDAC between the periods 1988–1996 and 2010–2014.

Material and Methods

Materials

Patient data were extracted from the Surveillance, Epidemiology, and End Results (SEER) linked database in this retrospective analysis. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States (U.S.) that is updated annually. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximate 34.6% of the U.S. population. according to SEER historic stage A (localized PDAC is limited to the pancreas; regional PDAC is confined to nearby lymph nodes or other organs and distant disease involves systemic metastasis). The target population in our study was limited to patients with localized and regional pancreatic adenocarcinoma diagnosed in the periods of 1988–1996 and 2010–2014, with a total of 20 589 patients. Follow-up times of all patients were more than 2 years. We excluded patients with missing data regarding race, tumor size, extension, lymph nodes, regional nodes examined, and treatment programs. The final study sample embodied consisted of 15 077 patients.

We chose the period 1988–1996 as a baseline because partial data, which included tumor size, regional nodes examined, and lymph nodes, were available since 1988 and gemcitabine was recommended as first-line chemotherapy for pancreatic cancer in 1997. We chose patients from the period 2010–2014, which was the latest for the 2-year follow-up, since the FOLFIRINOX regimen emerged as a new treatment options for metastatic pancreatic cancer in 2010 [13,14]. According to the code of CS extension and EOD 10-extent, we classified patients who were equivalent to the T0-2 staging in the seventh edition of AJCC as mild extension, and those who matched with T3-4 staging as grievous extension. The codes of negative node were 0 in CS lymph nodes (2004–2015) and EOD 10 – nodes (1988–2003). The codes of positive nodes were 100, 110, 200, 210, 250, and 800 in CS lymph nodes (2004–2015) and 1 and 8 in EOD 10-nodes (1988–2003). Patients with codes of 10–90 in RX Summ – Surg Prim Site (1998+) and Site-specific surgery (1973–1997, with varying details by year and site) were classified to the resectable group.

Methods

Pearson's chi-square test was applied for intergroup comparisons and the log-rank test was applied to compare overall survival (OS) between different cohorts. We evaluated 95% confidence interval (CI) and hazard ratio (HR) by multivariate Cox proportional hazards regression models. Propensity score matching (PSM) was conducted to eliminate the influence of other variables. The nearest neighbor matching with a caliper width of 0.0001 was employed. Statistical analyses were performed with IBM SPSS statistics trial ver. 25.0 (IBM, Armonk, NY, USA). All reported p-values lower than 0.05 were considered significant.

Results

Patient Characteristics

This study enrolled 15 077 patients, involving 2144 (14.22%) cases in 1988–1996 and 12 933 (85.78%) cases in 2010–2014.

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Patients with resectable pancreatic cancer accounted for 49.86% (1069/2144) in 1988–1996 and 38.34% (4958/12933) in 2010–2014. The ratio of qualified regional nodes examined (RNE), which was RNE more than 15, an available indicator that reflects the quality of surgery in SEER database [15], increased by 8.50%. The proportion of patients receiving chemotherapy increased significantly by 14.36%, whereas radiotherapy regimens decreased by 14.12%. In addition, differences in sex, age, primary tumor location, histologic grade, lymph nodes, tumor size, and extension were also compared between the 2 periods (Table 1).

Survival improvement of PDAC

Patients with non-metastatic PDAC had longer overall survival due to therapeutic advancements, including surgery and adjuvant therapy, during 1988–1996 and 2010–2014. Median survival improved from 10 months to 14 months in all patients ($p<0.001$, Figure 1A). Median survival significantly increased by 23 months in the resectable patients ($p<0.001$, Figure 1B). The proportion of resectable PDAC patients receiving chemotherapy increased from 34.89% (373/1069) to 50.18% (2488/4958), and those receiving radiotherapy decreased from 37.61% (402/1069) to 25.47% (1263/4958). Furthermore, the proportion of qualified RNE significantly improved from 16.28% (174/1069) to 43.49% (2156/4958).

However, median survival only slightly improved, from 7 months to 9 months, in the unresectable PDAC ($p<0.001$, Figure 1C). There were also significant differences in the ratio of radiotherapy (44.19%, 475/1075 *vs.* 27.72%, 2211/7975) and chemotherapy (42.70% 459/1075 *vs.* 55.15% 4398/7975) between the 2 periods.

Cox regression model

We used Cox regression modeling to analyze prognostic factors in all, unresectable, and resectable patients (Table 2). Age, histologic grade, tumor size, extension, and lymph nodes were always prognostic factors in all groups. Importantly, surgery was associated with survival in the 2 periods. Moreover, the hazard ratio (HR) of surgery decreased from 0.454 to 0.302, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. In addition, although not for all PDAC patients, RNE can be used as a prognostic factor for resectable pancreatic cancer.

The HR values of radiotherapy, which was a new prognostic factor for resectable PDAC in 2010–2014, were reduced in both the resectable and unresectable groups. Advances in radiotherapeutic technology not only made radiotherapy a prognostic factor, but also reduced HR values for all PDAC patients. In addition, the 95% CIs of radiotherapy in 1988–1996 were wider than those in 2010–2014.

Use of the upgraded chemotherapy regimen reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC, but it did not improve the survival of resectable patients in 2010–2014 ($p=0.366$). Similarly, the 95% CIs of chemotherapy in 1988–1996 were wider than those in 2010–2014, except for the resectable group (Figure 2).

The impact of therapeutic advancement on survival

We conducted a propensity score matching (PSM) to eliminate the influence of the other variables such as sex, race, age, and grade, which better show the effects of therapeutic advances on the survival of PDAC patients. First, we screened resectable PDAC patients without adjuvant therapy (Supplementary Table 1). The number of RNEs, an available indicator that reports the quality of surgery in the SEER database, did not match between the 2 groups. Log-rank testing showed that advances in surgery significantly improved the median survival, from 13 months to 32 months ($p<0.001$, Figure 3A). Radiotherapeutic and chemotherapeutic advances extended median survival by 12 months ($p<0.001$, Figure 3B) and 11 months, respectively ($p<0.001$, Figure 3C), after PSM (Supplementary Tables 2, 3) in resectable PDAC.

PSM then was performed to explore the impact of radiotherapeutic and chemotherapeutic advancements in the unresectable group (Supplementary Tables 4, 5). Log-rank testing showed that the median survivals were extended by 3 months for radiotherapy ($p=0.005$, Figure 4A) and chemotherapy ($p= 0.003$, Figure 4B). Finally, we performed PSM for those who missed all treatments in the unresectable group (Supplementary Table 6). The log-rank test indicated that selective bias was effectively eliminated by PSM ($p=0.875$, Figure 4C).

Discussion

To the best of our knowledge, this is the first study to assess barriers to improvement of survival in patients with PDAC in recent decades. We selected PDAC patients from the periods 1988–1996 and 2010–2014, determined the influences of prognostic factors by HR value and 95% CI in Cox regression modeling, and explored the significance of therapeutic advances involving surgery and adjuvant therapy for survival following PSM. Researches focusing on the progress of treatment can be a basis for guiding improvement of current therapeutic modalities.

The cornerstones for treating pancreatic cancer undoubtedly include surgery, chemotherapy, and radiotherapy, which prolonged the survival of PDAC patients in the past few decades. Among them, surgery was always the preferred choice of treatment for PDAC, since HRs of surgery had the smallest value in

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Table 1. Characteristics of non-metastatic PDAC.

Characteristics	1988–1996 (n=2144)		2010–2014 (n=12933)		P value
Gender					0.014
Male	1013	(47.25%)	6481	(50.11%)	
Female	1131	(52.75%)	6452	(49.89%)	
Age (years)					<0.001
≤50	214	(9.98%)	979	(7.57%)	
51–70	1080	(50.37%)	6096	(47.14%)	
>70	850	(39.65%)	5858	(45.29%)	
Race					0.052
White	1768	(82.46%)	10413	(80.51%)	
Black	217	(10.12%)	1461	(11.30%)	
Other	159	(7.42%)	1059	(8.19%)	
Primary tumor location					<0.001
Head	1692	(78.92%)	8666	(67.01%)	
Body or tail	243	(11.33%)	2334	(18.05%)	
Other	209	(9.75%)	1933	(14.94%)	
Histologic grade					<0.001
I/II	942	(43.94%)	4295	(33.21%)	
III/IV	558	(26.02%)	1885	(14.57%)	
Unknown	644	(30.04%)	6753	(52.22%)	
Resectable					<0.001
No	1075	(50.14%)	7975	(61.66%)	
Yes	1069	(49.86%)	4958	(38.34%)	
Radiotherapy					<0.001
No	1265	(59.00%)	9457	(73.12%)	
Yes	879	(41.00%)	3476	(26.88%)	
Chemotherapy					<0.001
No	1310	(61.10%)	6045	(46.74%)	
Yes	834	(38.90%)	6888	(53.26%)	
Regional nodes examined					<0.001
<15	1968	(91.79%)	10772	(83.29%)	
≥15	176	(8.21%)	2161	(16.71%)	
Lymph nodes					<0.001
Negative	1224	(57.09%)	8751	(67.66%)	
Positive	920	(42.91%)	4182	(32.34%)	
Tumor size (cm)					<0.001
≤2	291	(13.57%)	2185	(16.89%)	
2–4	1006	(46.92%)	7091	(54.83%)	
>4	847	(39.51%)	3657	(28.28%)	
Extension					<0.001
Mild	665	(31.02%)	4253	(32.88%)	
Grievous	1479	(68.98%)	8680	(67.12%)	

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Table 2. Multivariate analysis of survival months in non-metastatic pancreatic adenocarcinoma.

Variables	Whole				Resectable				Unresectable			
	1988–1996		2010–2014		1988–1996		2010–2014		1988–1996		2010–2014	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Gender												
Male	Reference		Reference		Reference		Reference		Reference		Reference	
Female	0.989 (0.907–1.079)	0.802	0.961 (0.924–1.000)	0.051	1.010 (0.892–1.144)	0.873	0.949 (0.880–1.024)	0.179	0.994 (0.878–1.125)	0.922	0.967 (0.924–1.013)	0.160
Age(years)												
≤50	Reference		Reference		Reference		Reference		Reference		Reference	
51–70	1.490 (1.272–1.746)	<0.001	1.527 (1.388–1.679)	<0.001	1.358 (1.103–1.673)	0.004	1.650 (1.408–1.934)	<0.001	1.442 (1.121–1.856)	0.004	1.315 (1.167–1.481)	<0.001
>70	1.844 (1.564–2.174)	<0.001	2.197 (1.997–2.418)	<0.001	1.647 (1.315–2.062)	<0.001	2.369 (2.012–2.789)	<0.001	1.722 (1.334–2.224)	<0.001	1.804 (1.603–2.031)	<0.001
Race												
White	Reference		Reference		Reference		Reference		Reference		Reference	
Black	1.134 (0.982–1.310)	0.086	1.013 (0.952–1.079)	0.677	1.140 (0.926–1.404)	0.218	1.157 (1.016–1.317)	0.027	1.050 (0.857–1.287)	0.637	0.975 (0.908–1.047)	0.484
Other	1.137 (0.962–1.343)	0.131	0.949 (0.881–1.022)	0.165	1.113 (0.878–1.411)	0.377	0.946 (0.814–1.099)	0.466	1.186 (0.937–1.502)	0.157	0.954 (0.875–1.039)	0.277
Primary tumor location												
Head	Reference		Reference		Reference		Reference		Reference		Reference	
Body or tail	0.751 (0.648–0.870)	<0.001	0.623 (0.585–0.663)	<0.001	0.675 (0.544–0.839)	<0.001	0.532 (0.460–0.615)	<0.001	1.075 (0.876–1.318)	0.489	0.709 (0.661–0.760)	<0.001
Other	0.912 (0.786–1.057)	0.221	0.799 (0.755–0.846)	<0.001	0.869 (0.683–1.106)	0.253	0.793 (0.699–0.900)	<0.001	1.052 (0.868–1.276)	0.604	0.847 (0.794–0.904)	<0.001
Histologic grade												
I/II	Reference		Reference		Reference		Reference		Reference		Reference	
III/IV	1.370 (1.232–1.524)	<0.001	1.821 (1.707–1.944)	<0.001	1.305 (1.135–1.501)	<0.001	1.700 (1.560–1.853)	<0.001	1.465 (1.237–1.735)	<0.001	1.648 (1.490–1.823)	<0.001
Unknown	0.909 (0.817–1.013)	0.083	1.352 (1.277–1.432)	<0.001	0.579 (0.466–0.721)	<0.001	1.164 (1.028–1.319)	0.017	1.169 (1.017–1.344)	0.028	1.335 (1.245–1.432)	<0.001
Surgery												
No	Reference		Reference		NA		NA		NA		NA	
Yes	0.454 (0.409–0.503)	<0.001	0.302 (0.282–0.324)	<0.001	NA		NA		NA		NA	
Radiotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.937 (0.826–1.063)	0.313	0.852 (0.812–0.893)	<0.001	0.933 (0.755–1.153)	0.521	0.886 (0.809–0.971)	0.009	0.843 (0.720–0.988)	0.035	0.813 (0.769–0.860)	<0.001
Chemotherapy												
No	Reference		Reference		Reference		Reference		Reference		Reference	
Yes	0.738 (0.649–0.838)	<0.001	0.689 (0.657–0.722)	<0.001	0.800 (0.647–0.990)	0.040	1.047 (0.948–1.155)	0.366	0.656 (0.558–0.771)	<0.001	0.588 (0.557–0.621)	<0.001

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Table 2 continued. Multivariate analysis of survival months in non-metastatic pancreatic adenocarcinoma.

Variables	Whole				Resectable				Unresectable			
	1988–1996		2010–2014		1988–1996		2010–2014		1988–1996		2010–2014	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Regional nodes examined												
<15	Reference		Reference		Reference		Reference		Reference		Reference	
≥15	0.846 (0.716–1.001)	0.051	1.000 (0.926–1.080)	0.998	0.777 (0.656–0.922)	0.004	0.832 (0.768–0.901)	<0.001	0.395 (0.055–2.833)	0.355	1.066 (0.399–2.845)	0.899
Lymph nodes												
Negative	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	1.218 (1.114–1.332)	<0.001	1.243 (1.188–1.301)	<0.001	1.390 (1.221–1.584)	<0.001	1.558 (1.423–1.706)	<0.001	1.060 (0.931–1.206)	0.379	1.093 (1.035–1.154)	0.001
Tumor size (cm)												
≤2	Reference		Reference		Reference		Reference		Reference		Reference	
2–4	1.229 (1.073–1.407)	0.003	1.661 (1.550–1.781)	<0.001	1.241 (1.058–1.456)	0.008	1.470 (1.313–1.645)	<0.001	1.353 (1.033–1.771)	0.028	1.754 (1.606–1.914)	<0.001
>4	1.311 (1.136–1.512)	<0.001	1.883 (1.748–2.028)	<0.001	1.288 (1.072–1.547)	0.007	1.670 (1.471–1.896)	<0.001	1.542 (1.175–2.022)	0.002	2.032 (1.852–2.229)	<0.001
Extension												
Mild	Reference		Reference		Reference		Reference		Reference		Reference	
Grievous	1.213 (1.102–1.336)	<0.001	1.538 (1.463–1.618)	<0.001	1.439 (1.246–1.661)	<0.001	2.005 (1.787–2.250)	<0.001	0.999 (0.876–1.139)	0.982	1.394 (1.318–1.475)	<0.001

NA – not available.

Cox regression model of the 2 analyzed periods. Advancements in surgery were demonstrated by the increasing rate of qualified RNE and non-intersecting 95% CIs in Cox regression modeling between the 2 periods. Moreover, the maximum median survival extension proved that advances in surgery are the main contributor to improved survival in resectable PDAC patients. In fact, advances in pancreatic surgery involved refined equipment and new concepts. Although they contributed to the refinement of surgery, laparoscopic and robotic surgery have not improved the survival of patients with PDAC [16]. Several concepts may be used as milestones in the treatment of pancreatic cancers, including total mesopancreatic excision (TMpE) and accurate assessment of the resection margins, which have been learned from clinical experiences in colorectal cancer. The presence of mesopancreas and the feasibility and clinical value of TMpE are important topics among surgeons. Pancreatic surgeons were committed to the development of TMpE after the concept of "mesopancreas" was first proposed by Gockel et al. in 2007 [17]. Adham et al. reported a significant increase in the R0 resection rate of pancreatic cancer with TMpE compared with conventional pancreatic cancer radical surgery in 2012 [5]. In the same year, Kawabata et al. retrospectively compared TMpE with standard pancreatic cancer surgery, showing that the TMpE group had more lymph node dissections (26 *vs.* 18, p=0.027) and a higher R0 resection rate (93% *vs.* 60%, p=0.019) [18]. Due to almost symptomless progression, PDAC is still often diagnosed in advanced stages, at which point the best opportunity for surgical resection has been missed [4]. The surgical resection rate of pancreatic cancer was only 38.34% in 2010–2014 in the present study.

The surgical advancements were accompanied by an increase in RNE. This study selected 15 as the cutoff value of RNE because Schwarz et al. found that the number of lymph nodes detected had an important effect on lymph node ratio (LNR) and prognosis by retrospectively analyzing the SEER database [19]. The proportion of eligible RNE, which was refined as RNE ≥15 for PDAC in this study, increased from 16.28% to 43.49% in resectable PDAC patients. Meanwhile, qualified RNE was beneficial for the survival of resectable PDAC (p=0.004 in 1988–1996; p<0.001 in 2010–2014). Other retrospective database analyses also found that PDAC patients had a better prognosis with an increasing number of examined lymph nodes [20].

Additionally, this study showed some evidence that the chemotherapy regimens for PDAC in 2010–2014 were superior to that in 1988–1996. The median survival increased in PDAC patients with chemotherapy in 2010–2014. The HR value of chemotherapy

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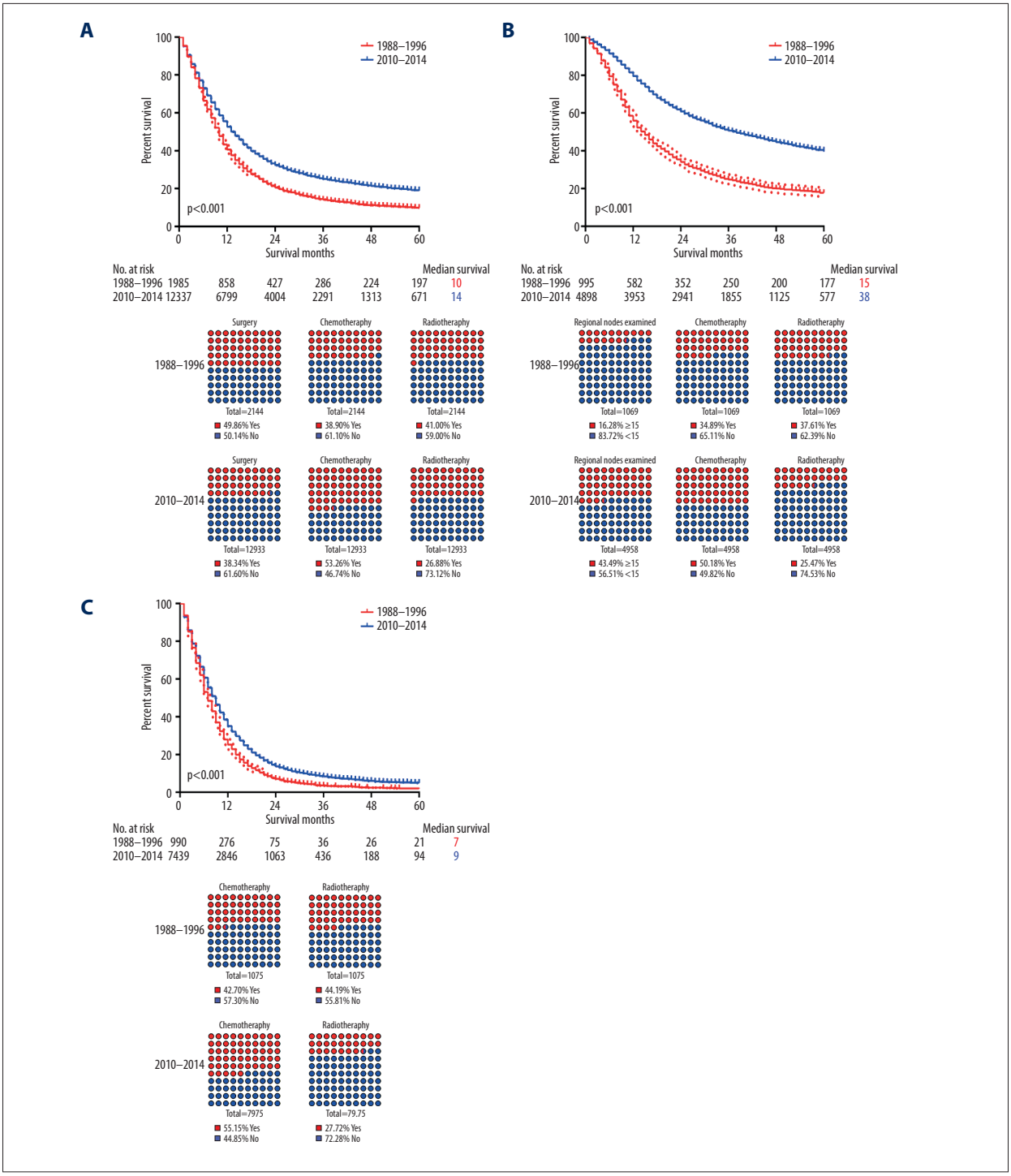

Figure 1. Log-rank test showed that PDAC patients had longer overall survival due to therapeutic advances. (**A**) Median survival improved from 10 months to 14 months in all patients with PDAC (p<0.001). The proportion of chemotherapy increased by 14.36% while the ratio of patients receiving radiotherapy and surgery decreased by 14.12% and 11.52%, respectively. (**B**) Median survival improved from 15 months to 38 months in patients with resectable PDAC (p<0.001). The ratio of qualified RNE, which was ≥15, and patients receiving chemotherapy, increased by 27.21% and 15.29%, respectively, while the proportion of radiotherapy decreased by 12.14%. (**C**) Median survival improved from 7 months to 9 months in patients with irresectable PDAC (p<0.001). The ratio of patients receiving chemotherapy increased by 12.45%, while the proportion of patients receiving radiotherapy decreased by 16.47%.

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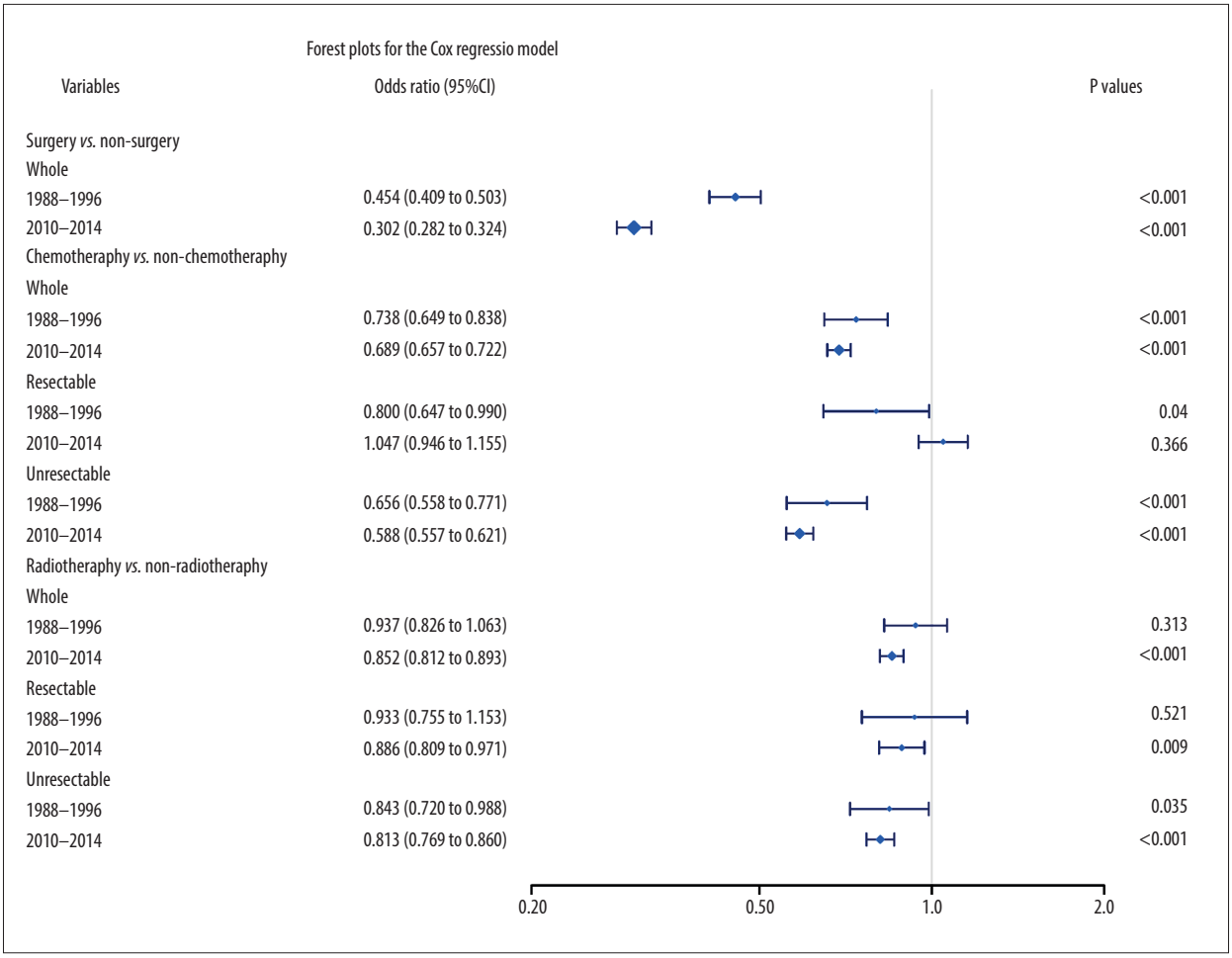

Figure 2. Forest plots for Cox regression model. The hazard ratio (HR) of surgery fell from 0.454 to 0.302, and there was no overlapping about the 95% confidence intervals (CI) of surgery between the 2 periods. The HR values of radiotherapy were reduced in both the resectable and unresectable groups. Meanwhile, the 95% CIs for radiotherapy in 2010–2014 were narrower than those in 1988–1996. The improvement in chemotherapy regimens reduced the HR values from 0.738 to 0.689 in all PADC patients, and from 0.656 to 0.588 in unresectable PDAC. However, there was no improved survival of resectable patients in 2010–2014 (p=0.366). Similarly, the 95% CIs for chemotherapy in 2010–2014 were narrower than those in 1988–1996, except for the resectable group.

was reduced from 1988–1996 to 2010–2014. However, the development of chemotherapy has been slow. In particular, the median survival of unresectable patients with updated chemotherapy was only extended by 3 months. Another study also reported that gemcitabine, which was the most important chemotherapy drug for PDAC in 2010–2014, provides clinical benefit and a modest survival advantage over treatment with bolus 5-FU, which was the main chemotherapy drug used in 1988–1996 [8]. Promising chemotherapy regimens, including nab-paclitaxel plus gemcitabine and FOLFIRINOX, also demonstrated superiority [21–23], but advances in chemotherapy regimens seemed to be unable to keep up with the pace of surgery, which cannot be used as a prognostic factor for resectable PDAC in 2010–2014. In addition, the updated chemotherapy regimen did not improve survival as much as surgical advancements after PSM.

The 95% CIs for radiotherapy in 1988–1996 nearly covered the Cox regression model of regional PDAC analyzed for 2010–2014, showing the accuracy and reliability of current radiotherapy technology. Precise radiotherapy can improve margin-negative resection, sterilize vessel margins, and/or improve local control [24]. Landry et al. reported a significant reduction in radiation dose to the small intestine during IMRT [25]. Ben-Josef and Milano also found that the efficacy of IMRT was satisfactory, with low secondary damage [10,26]. Regrettably, this study reported that advanced radiotherapy, which was similar to chemotherapy, slightly improved the median survival of PDAC patients. In fact, chemotherapy drugs could be used as sensitizers for radiotherapy. Therefore, the update of chemotherapy regimens may improve the effect of radiotherapy for pancreatic cancer. Moreover, advanced chemoradiotherapy can

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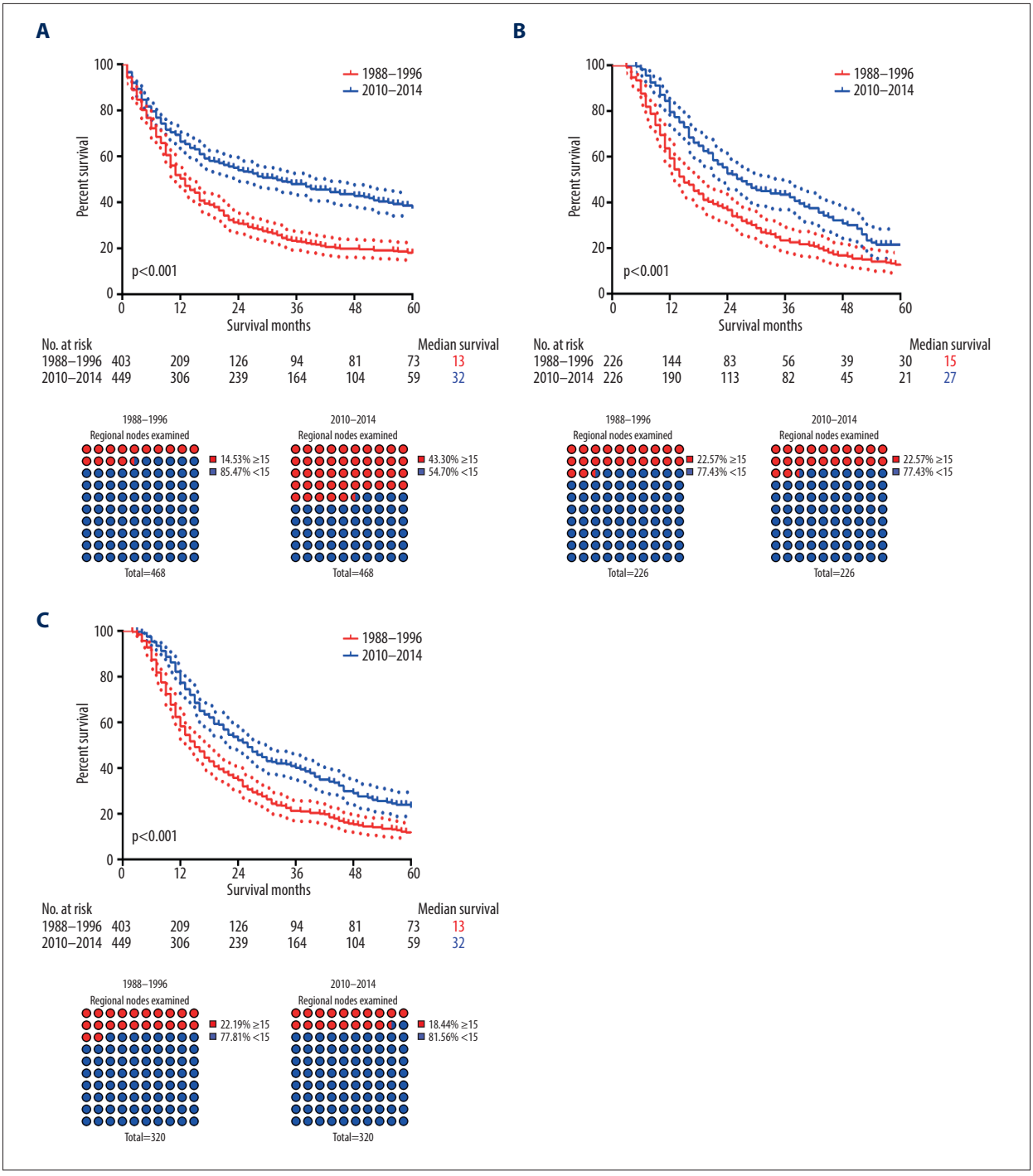

Figure 3. The impact of therapeutic advancement on survival of resectable PDAC. (**A**) Advances in surgery extended the median survival by 19 months and increased the qualified RNE rate by 30.77% in resectable PDAC patients (p<0.001). (**B**) Median survival increased by 12 months in resectable PDAC patients with radiotherapeutic advances (p<0.001). (**C**) Median survival increased by 11 months in resectable PDAC patients with chemotherapeutic advances (p<0.001).

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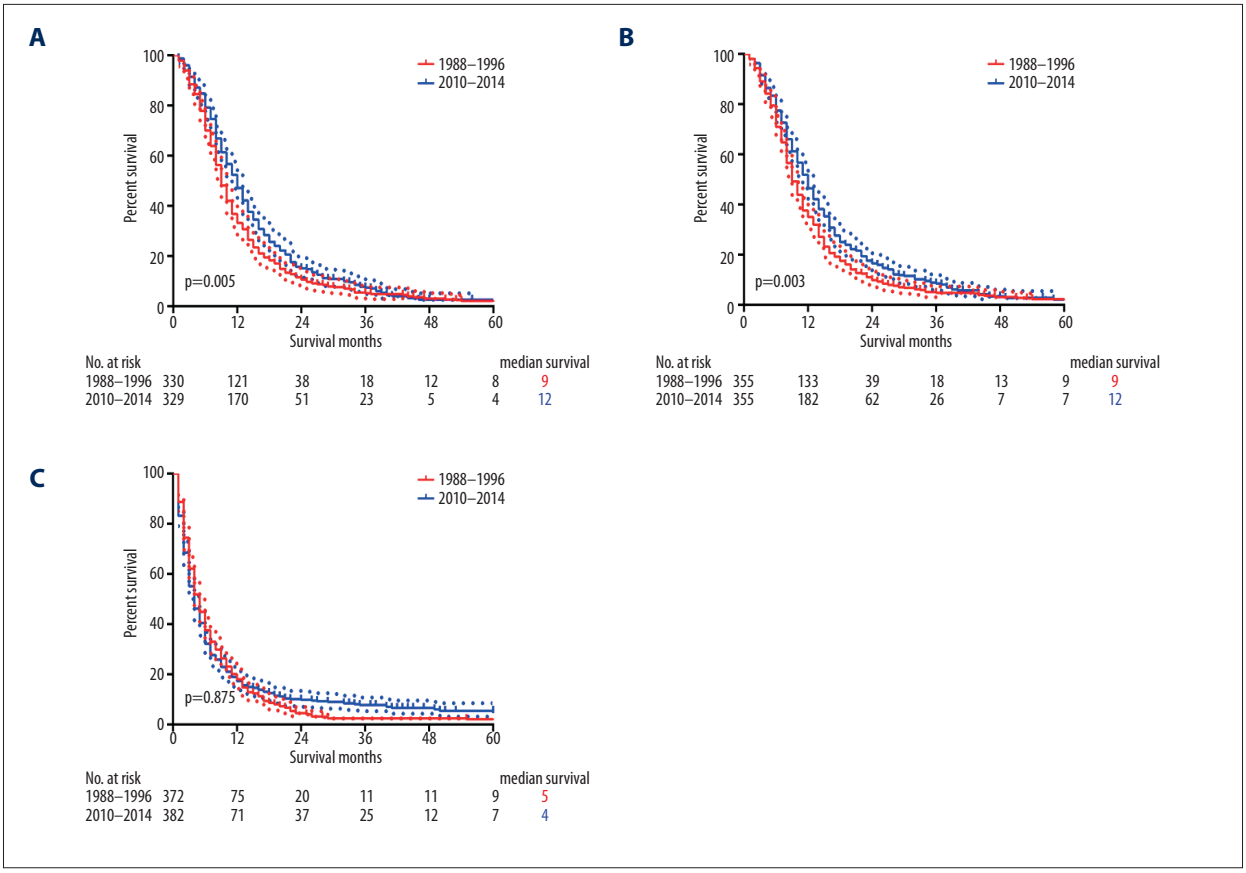

Figure 4. The impact of therapeutic advances on survival of irresectable PDAC patients. (**A**) Median survival increased by 3 months in irresectable PDAC patients with radiotherapeutic advances (p=0.005). (**B**) Median survival also increased by 3 months in irresectable PDAC patients with chemotherapeutic advances (p=0.003). (**C**) There was no difference in irresectable PDAC patients without adjuvant therapy (p=0.875).

promote surgical resection rates for locally advanced and borderline resectable PDAC, which may extend survival for those patients. However, this study cannot draw clear conclusions due to the limited information in the SEER database.

Advances in adjuvant therapy contributed markedly to the increased survival for locally advanced rectal cancer (LARC) after the emergence of total mesorectal excision (TME) [15]. However, disappointing adjuvant therapy limited the conversion therapy and survival improvement in patients with PDAC. Although it provided survival benefits for advanced pancreatic cancer [21], FOLFIRINOX cannot be recommended for all PDAC patients, especially those with poor performance status, due to its highly toxic combination and serious adverse effects [27]. Another promising regimen for PDAC, Nab-paclitaxel plus gemcitabine, has similar problems. It is believed that current chemotherapy and/or radiotherapy are still far from perfect for PDAC. Therefore, we still have a long and challenging journey ahead of us to establish a satisfactorily chemotherapy program.

The significance of this study was to find barriers to treating pancreatic cancer, which are the low rate of surgical resection and poor adjuvant therapy. This is why researchers are eagerly looking for new therapy targets and improving early diagnostic tools for pancreatic cancer, which could help to improve the outcome of PDAC in combination with surgery. Limitations of this study include: (1) the use of retrospective data; (2) detailed treatment information for included patients was not recorded in the SEER cohort, and we could not investigate specific options, including R0 or not, preoperative or postoperative chemotherapy in the survival of PDAC patients; (3) Cases in 1988–1996 lacked TNM staging data.

Conclusions

Development of chemotherapy and radiotherapy has been slow, especially for unresectable pancreatic cancer. Although advances in surgery were major contributors to the improvement of survival in resectable patients, lack of early diagnostic tools, which resulted in low resection rates, was still an obstacle for all PDAC patients.

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Conflict of interests

None.

Supplementary Data

Supplementary Table 1. Characteristics of localized PDAC patients underwent surgery without adjuvant therapy after PSM.

Characteristics	1992–1996 (n=86)	2010–2014 (n=86)	P value
Gender			0.879
Male	46 (53.49%)	45 (52.33%)	
Female	40 (46.51%)	41 (47.67%)	
Age (years)			1.000
≤50	7 (8.14%)	7 (8.14%)	
51–70	46 (53.49%)	46 (53.49%)	
>70	33 (38.37%)	33 (38.37%)	
Race			0.583
White	76 (88.37%)	72 (83.72%)	
Black	4 (4.65%)	8 (9.30%)	
Other	6 (6.98%)	6 (6.98%)	
Primary tumor location			0.824
Head	60 (69.77%)	59 (68.60%)	
Body or tail	17 (19.77%)	17 (19.77%)	
Other	9 (10.47%)	10 (11.63%)	
Histologic grade			0.923
Well/moderately differentiated	55 (63.95%)	56 (65.12%)	
Poor differentiated/uindifferentiated	15 (17.44%)	14 (16.28%)	
Unknown	16 (18.60%)	16 (18.60%)	
Regional nodes positive			0.532
Negative	74 (86.05%)	71 (82.56%)	
Not checked	12 (13.95%)	15 (17.44%)	
Tumor size (cm)			0.807
≤2	32 (37.21%)	31 (36.05%)	
2–4	34 (39.53%)	34 (39.53%)	
>4	13 (15.12%)	13 (15.12%)	
Unknown	7 (8.14%)	8 (9.30%)	

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Supplementary Table 2. Characteristics of regional PDAC patients underwent surgery without adjuvant therapy after PSM.

Characteristics	1992–1996 (n=283)	2010–2014 (n=283)	P value
Gender			0.801
Male	143 (50.53%)	146 (51.59%)	
Female	140 (49.47%)	137 (48.41%)	
Age (years)			0.776
≤50	15 (5.30%)	18 (6.36%)	
51–70	147 (51.94%)	145 (51.24%)	
>70	121 (42.76%)	120 (42.40%)	
Race			0.936
White	239 (84.45%)	240 (84.81%)	
Black	30 (10.60%)	27 (9.54%)	
Other	14 (4.95%)	16 (5.65%)	
Primary tumor location			0.937
Head	252 (89.05%)	252 (89.05%)	
Body or tail	12 (4.24%)	11 (3.89%)	
Other	19 (6.71%)	20 (7.07%)	
Histologic grade			0.890
Well/moderately differentiated	174 (61.48%)	175 (61.84%)	
Poor differentiated/undifferentiated	91 (32.16%)	91 (32.16%)	
Unknown	18 (6.36%)	17 (6.01%)	
Regional nodes positive			0.874
Negative	111 (39.22%)	112 (39.58%)	
Positive	165 (58.30%)	165 (58.30%)	
Not checked	7 (2.47%)	6 (2.12%)	
Tumor size (cm)			0.906
≤2	49 (17.31%)	47 (16.61%)	
2–4	160 (56.54%)	161 (56.89%)	
>4	65 (22.97%)	67 (23.67%)	
Unknown	9 (3.18%)	8 (2.83%)	
Extension			1.000
Mild	23 (8.13%)	23 (8.13%)	
Grievous	260 (91.87%)	260 (91.87%)	

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Supplementary Table 3. Characteristics of localized PDAC patients with chemotherapy after PSM.

Characteristics	1992–1996 (n=82)	2010–2014 (n=82)	P value
Gender			1.000
Male	46 (56.10%)	46 (56.10%)	
Female	36 (43.90%)	36 (43.90%)	
Age (years)			0.752
≤50	0 (0.00%)	0 (0.00%)	
51–70	32 (39.02%)	34 (41.46%)	
>70	50 (60.98%)	48 (58.54%)	
Race			0.860
White	70 (85.37%)	69 (84.15%)	
Black	10 (12.20%)	11 (13.41%)	
Other	2 (2.44%)	2 (2.44%)	
Primary tumor location			0.834
Head	59 (71.95%)	60 (73.17%)	
Body or tail	10 (12.20%)	10 (12.20%)	
Other	13 (15.85%)	12 (14.63%)	
Histologic grade			0.794
Well/moderately differentiated	25 (30.49%)	26 (31.71%)	
Poor differentiated/undifferentiated	13 (15.85%)	14 (17.07%)	
Unknown	44 (53.66%)	42 (51.22%)	
Surgery			0.823
Yes	11 (13.41%)	12 (14.63%)	
No	71 (86.59%)	70 (85.37%)	
Radiotherapy			1.000
Yes	56 (68.29%)	56 (68.29%)	
No	26 (31.71%)	26 (31.71%)	
Regional nodes examined			1.000
<15	81 (98.78%)	81 (98.78%)	
≥15	1 (1.22%)	1 (1.22%)	
Regional nodes positive			0.809
Negative	9 (10.98%)	10 (12.20%)	
Not checked	73 (89.02%)	72 (87.80%)	
Tumor size (cm)			0.864
≤2	6 (7.32%)	7 (8.54%)	
2–4	33 (40.24%)	33 (40.24%)	
>4	25 (30.49%)	24 (29.27%)	
Unknown	18 (21.95%)	18 (21.95%)	

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Supplementary Table 4. Characteristics of regional PDAC patients with chemotherapy after PSM.

Characteristics	1992–1996 (n=538)	2010–2014 (n=538)	P value
Gender			0.808
Male	270 (50.19%)	266 (49.44%)	
Female	268 (49.81%)	272 (50.56%)	
Age (years)			0.526
≤50	37 (6.88%)	46 (8.55%)	
51–70	334 (62.08%)	328 (60.97%)	
>70	167 (31.04%)	164 (30.48%)	
Race			0.413
White	472 (87.73%)	463 (86.06%)	
Black	44 (8.18%)	49 (9.11%)	
Other	22 (4.09%)	26 (4.83%)	
Primary tumor location			0.318
Head	428 (79.55%)	416 (77.32%)	
Body or tail	44 (8.18%)	45 (8.36%)	
Other	66 (12.27%)	77 (14.31%)	
Histologic grade			0.512
Well/moderately differentiated	207 (38.48%)	222 (41.26%)	
Poor differentiated/undifferentiated	125 (23.23%)	114 (21.19%)	
Unknown	206 (38.29%)	202 (37.55%)	
Surgery			0.608
Yes	182 (33.83%)	190 (35.32%)	
No	356 (66.17%)	348 (64.68%)	
Radiotherapy			0.823
Yes	426 (79.18%)	423 (78.62%)	
No	112 (20.82%)	115 (21.38%)	
Regional nodes examined			0.152
<15	492 (91.45%)	478 (88.85%)	
≥15	46 (8.55%)	60 (11.15%)	
Regional nodes positive			0.966
Negative	66 (12.27%)	67 (12.45%)	
Positive	152 (28.25%)	151 (28.07%)	
Not checked	320 (59.48%)	320 (59.48%)	
Tumor size (cm)			0.475
≤2	39 (7.25%)	30 (5.58%)	
2–4	217 (40.33%)	211 (39.22%)	
>4	179 (33.27%)	198 (36.80%)	
Unknown	103 (19.14%)	99 (18.40%)	
Extension			1.000
Mild	35 (6.51%)	35 (6.51%)	
Grievous	503 (93.49%)	503 (93.49%)	

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Supplementary Table 5. Characteristics of localized PDAC patients with radiotherapy after PSM.

Characteristics	1992–1996 (n=78)	2010–2014 (n=78)	P value
Gender			0.874
Male	39 (50.00%)	38 (48.72%)	
Female	39 (50.00%)	40 (51.28%)	
Age (years)			0.741
≤50	0 (0.00%)	0 (0.00%)	
51–70	29 (37.18%)	27 (34.62%)	
>70	49 (62.82%)	51 (65.38%)	
Race			0.849
White	68 (87.18%)	66 (84.62%)	
Black	8 (10.26%)	11 (14.10%)	
Other	2 (2.56%)	61 (1.28%)	
Primary tumor location			0.904
Head	62 (79.49%)	62 (79.49%)	
Body or tail	7 (8.97%)	8 (10.26%)	
Other	9 (11.54%)	8 (10.26%)	
Histologic grade			0.789
Well/moderately differentiated	23 (29.49%)	25 (32.05%)	
Poor differentiated/undifferentiated	13 (16.67%)	12 (15.38%)	
Unknown	42 (53.85%)	41 (52.56%)	
Surgery			1.000
Yes	10 (12.82%)	10 (12.82%)	
No	68 (87.18%)	68 (87.18%)	
Chemotherapy			0.852
Yes	59 (75.64%)	60 (76.92%)	
No	19 (24.36%)	18 (23.08%)	
Regional nodes examined			1.000
<15	77 (98.72%)	77 (98.72%)	
≥15	1 (1.28%)	1 (1.28%)	
Regional nodes positive			1.000
Negative	8 (10.26%)	8 (10.26%)	
Not checked	70 (89.74%)	70 (89.74%)	
Tumor size (cm)			0.856
≤2	8 (10.26%)	6 (7.69%)	
2–4	39 (50.00%)	43 (55.13%)	
>4	17 (21.79%)	17 (21.79%)	
Unknown	14 (17.95%)	12 (15.38%)	

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Supplementary Table 6. Characteristics of regional PDAC patients with radiotherapy after PSM.

Characteristics	1992–1996 (n=466)	2010–2014 (n=466)	P value
Gender			0.432
Male	225 (48.28%)	237 (50.86%)	
Female	241 (51.72%)	229 (49.14%)	
Age (years)			1.000
≤50	32 (6.87%)	30 (6.44%)	
51–70	288 (61.80%)	292 (62.66%)	
>70	146 (31.33%)	144 (30.90%)	
Race			0.203
White	416 (89.27%)	403 (86.48%)	
Black	34 (7.30%)	42 (9.01%)	
Other	16 (3.43%)	21 (4.51%)	
Primary tumor location			0.961
Head	372 (79.83%)	372 (79.83%)	
Body or tail	41 (8.80%)	40 (8.58%)	
Other	53 (11.37%)	54 (11.59%)	
Histologic grade			0.797
Well/moderately differentiated	179 (38.41%)	187 (40.13%)	
Poor differentiated/undifferentiated	103 (22.10%)	94 (20.17%)	
Unknown	184 (39.48%)	185 (39.70%)	
Surgery			0.891
Yes	162 (34.76%)	160 (34.33%)	
No	304 (65.24%)	306 (65.67%)	
Chemotherapy			0.306
Yes	419 (93.95%)	428 (91.85%)	
No	47 (6.05%)	38 (8.15%)	
Regional nodes examined			0.817
<15	424 (90.99%)	426 (91.42%)	
≥15	42 (9.01%)	40 (8.58%)	
Regional nodes positive			0.817
Negative	58 (12.45%)	59 (12.66%)	
Positive	136 (29.18%)	129 (27.68%)	
Not checked	272 (58.37%)	278 (59.66%)	
Tumor size (cm)			0.761
≤2	33 (7.08%)	31 (6.65%)	
2–4	192 (41.20%)	188 (40.34%)	
>4	154 (33.04%)	160 (34.33%)	
Unknown	87 (18.67%)	87 (18.67%)	
Extension			0.772
Mild	26 (5.58%)	24 (5.15%)	
Grievous	440 (94.42%)	442 (94.85%)	

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1.3 Nomograms predicting Overall Survival and Cancer-specific Survival for Synchronous Colorectal Liver-limited Metastasis

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Research Paper

Nomograms predicting Overall Survival and Cancer-specific Survival for Synchronous Colorectal Liver-limited Metastasis

Yuqiang Li[1,2*], Wenxue Liu[3,4], Lilan Zhao[5], Cenap Güngör[2], Yang Xu[2], Xiangping Song[1], Dan Wang[1,2], Zhongyi Zhou[1], Yuan Zhou[1], Chenglong Li[1], Qian Pei[1], Fengbo Tan[1]✉ and Haiping Pei[1]✉

1. Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, China.
2. Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
3. Department of Cardiology, Xiangya Hospital, Central South University, Changsha, China.
4. Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.
5. Department of Thoracic surgery, Fujian Provincial Hospital, Fuzhou, China.

*This author contributed mainly to this article as a first author.

✉ Corresponding authors: Haiping Pei, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, P.R. China; E-mail: peihaiping1966@hotmail.com; Fengbo Tan, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, P.R. China; E-mail: fengbotan@hotmail.com.

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Abstract

Background: Colorectal cancer (CRC) ranks as the third most frequent cancer type and the second leading cause of cancer-related death worldwide. The liver is the most common metastatic site of CRC with 20%-34% of patients suffering synchronous liver metastasis. Patients with colorectal liver-limited metastasis account for one-third of deaths from colorectal cancer. Moreover, some evidence indicated that CRC patients with synchronous liver disease encounter a worse prognosis and more disseminated disease state comparing with metastatic liver disease that develops metachronously.

Methods: Data in this retrospective analysis were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Nomograms were constructed with basis from a multivariate Cox regression analysis. The prognostic nomograms were validated by C-index, time-dependent receiver operating characteristic (ROC) curve, decision curve analysis (DCA) and calibration curves.

Results: A total of 9,958 CRC patients with synchronous liver-limited metastasis were extracted from the SEER database during 2010-2016. Both overall survival (OS) and cancer-specific survival (CSS) were significantly correlated with age, marital status, race, tumor location, pathological grade, histologic type, T stage, N stage, surgery for primary tumor, surgery for liver metastasis, chemotherapy and CEA. All of the significant variables were used to create the nomograms predicting OS and CSS. C-index values, time-dependent ROC curves, DCA curves and calibration curves, proved the superiority of the nomograms.

Conclusions: Our research investigated a national cohort of almost 10,000 patients to create and verify nomograms based on pathological, therapeutic and demographic features to predict OS and CSS for synchronous colorectal liver-limited metastasis (SCLLM). The nomograms may act as an excellent tool to integrate clinical characteristics to guide the therapeutic choice for SCLLM patients.

Key words: Nomogram; colorectal cancer; liver metastasis; overall survival; cancer-specific survival

Introduction

Colorectal cancer (CRC) ranks as the third most frequent cancer type and the second leading cause of cancer-related death worldwide [1]. The liver is the most common metastatic site of CRC with 20%-34% of patients suffering synchronous liver metastasis [2, 3]. Meanwhile, hepatic metastasis is now the leading

cause of death in CRC patients [4]. Patients with colorectal liver-limited metastasis account for one-third of deaths from colorectal cancer [5]. Moreover, some evidence indicated that CRC patients with synchronous liver disease encountered a worse prognosis and more disseminated disease state comparing with metastatic liver disease that develops metachronously [6]. Accordingly, this study focused on synchronous colorectal liver-limited metastasis (SCLLM).

Notwithstanding that technologies and therapeutic strategies have progressed over the last several decades, the survival of CRC patients with synchronous liver-limited metastasis still remains unsatisfactory. It is urgent to identify prognostic factors for patients with SCLLM. A nomogram, a simple graphical representation combining and quantifying all independent prognostic factors [7], plays an increasingly important role in medical research and clinical practice. Large public databases, like the Surveillance, Epidemiology, and End Results (SEER) database provide available, authentic and reliable data to explore clinical issues.

The purpose of this study was to construct nomograms predicting overall survival (OS) and cancer-specific survival (CSS) for patients with SCLLM based on the SEER database.

Materials and Methods

Patients

Data in this retrospective analysis were extracted from the SEER database. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States (U.S.) that is updated annually. The definition of SCLLM is colorectal cancer with liver-limited metastases at the time of diagnosis. Therefore, colorectal adenocarcinoma patients (ICD-O-3: 8140, 8144, 8145, 8201, 8210, 8211, 8213, 8253, 8255, 8260, 8261, 8262, 8263, 8310, 8323, 8480, 8481, 8490) with liver metastasis were collected from the period 2010-2016, resulting in 32,353 patients in total. Exclusion criteria: diagnosed at autopsy or death certificate (n=26); survival months is 0 (n=3289); lack of positive histology (n=489); status of lung, bone and brain is yes, unknown or N/A (n=8488); T0, T4NOS, Tx, N1NOS, N2NOS, M1b, M1 and blank(s) in AJCC stage (n=10103). The final study sample contained 9,958 patients.

For each patient, the following data was acquired: age at diagnosis, marital status, insurance, gender, race, grade, histological type, T stage, N stage, regional nodes examined (RNE), CEA, surgery for primary tumor, surgery for hepatic metastasis, perineural invasion (PNI), radiotherapy and chemotherapy. We defined colectomy with RNE ≥12 as standard colectomy and colectomy with RNE <12/NOS as simplified colectomy. All patients were randomly separated into two groups (training group, n = 6639 and validation group, n = 3319).

Follow-up and outcome

The follow-up cutoff was December 31, 2016. The endpoint of this study was OS and CSS. OS was computed from the time of diagnosis to the time of death due to any cause or the time of last follow-up with the patient still alive. CSS was computed from the time of diagnosis to the time of death attributed to colorectal cancer or still alive at last follow-up censored. The OS and CSS curves were evaluated using the Kaplan-Meier method and compared using the log-rank test.

Statistical Analysis

An odds ratio (OR) and a 95% confidence interval (CI) were evaluated by univariable and multivariate Cox regression model. Variables with significant differences in univariate analysis were included in the Cox regression model for multivariate analysis. Nomograms were constructed with basis from the multivariate analysis results, using R 3.6.1 software (Institute for Statistics and Mathematics, Vienna, Austria; http://www.r-project.org/). The prognostic nomograms were validated by a C-index, time-dependent receiver operating characteristic (ROC) curve, decision curve analysis (DCA) and calibration curves. Statistical analyses were performed with IBM SPSS statistics trial ver. 22.0 (IBM, Armonk, NY, USA). All reported *p*-values lower than 0.05 were considered significant.

Results

Patient Characteristics

A total of 9,958 CRC patients with synchronous liver-limited metastasis were extracted from the SEER database for the period from 2010-2016. Characteristics of the target population were summarized in **Table 1.** A total 6,639 patients were divided into a training cohort and 3,319 into a validation cohort. Insurance covered 94.45% of SCLLM patients. The majority of patients were elderly (≥60 years), married, and white. The right colon (41.33%) was the most common tumor location in SCLLM. Interestingly, patients with T3 accounted for 57.41%, which was more than the ratio of T4 (28.67%). In addition, positive lymph nodes (68.77%) and CEA (58.24%) were detected in most patients. The median OS and CSS were 17-month and 18-month respectively.

Table 1. Characteristics of patients with SCLLM in the training and validation group

Characteristics	Total (n=9958)		Training group (n=6639)		Validation group (n=3319)	
	N	%	N	%	N	%
Gender						
Female	4239	42.57%	2828	42.60%	1411	42.51%
Male	5719	57.43%	3811	57.40%	1908	57.49%
Age (years)						
≤50	1734	17.41%	1178	17.74%	556	16.75%
51-60	2398	24.08%	1580	23.80%	818	24.65%
61-70	2692	27.03%	1816	27.35%	876	26.39%
71-80	1899	19.07%	1243	18.72%	656	19.76%
>80	1235	12.40%	822	12.38%	413	12.44%
Marital status						
Married	5351	53.74%	3598	54.19%	1753	52.82%
Single	1794	18.02%	1188	17.89%	606	18.26%
Divorced/Separated	1129	11.34%	729	10.98%	400	12.05%
Widowed	1198	12.03%	796	11.99%	402	12.11%
NOS	486	4.88%	328	4.94%	158	4.76%
Insurance						
Yes	9405	94.45%	6273	94.49%	3132	94.37%
No/unknown	553	5.55%	366	5.51%	187	5.63%
Race						
White	7556	75.88%	5040	75.92%	2516	75.81%
Black	1531	15.37%	1010	15.21%	521	15.70%
Other/NOS	871	8.75%	589	8.87%	282	8.50%
Tumor location						
Right colon	4116	41.33%	2777	41.83%	1339	40.34%
Left colon	3367	33.81%	2199	33.12%	1168	35.19%
Rectum†	2294	23.04%	1549	23.33%	745	22.45%
NOS	181	1.82%	114	1.72%	67	2.02%
Pathological grade						
I	377	3.79%	259	3.90%	118	3.56%
II	6637	66.65%	4426	66.67%	2211	66.62%
III	1750	17.57%	1181	17.79%	569	17.14%
IV	378	3.80%	240	3.62%	138	4.16%
Unknown	816	8.19%	533	8.03%	283	8.53%
Histological type						
Adenocarcinomas	9397	94.37%	6259	94.28%	3138	94.55%
MCC/SRCC	561	5.63%	380	5.72%	181	5.45%
T stage						
T1	996	10.00%	670	10.09%	326	9.82%
T2	390	3.92%	266	4.01%	124	3.74%
T3	5717	57.41%	3786	57.03%	1931	58.18%
T4a	1800	18.08%	1218	18.35%	582	17.54%
T4b	1055	10.59%	699	10.53%	356	10.73%
N stage						
N0	3110	31.23%	2081	31.35%	1029	31.00%
N1a	1264	12.69%	855	12.88%	409	12.32%
N1b	1805	18.13%	1215	18.30%	590	17.78%
N1c	224	2.25%	151	2.27%	73	2.20%
N2a	1660	16.67%	1104	16.63%	556	16.75%
N2b	1895	19.03%	1233	18.57%	662	19.95%
Colectomy						
Standard colectomy	6866	68.95%	4567	68.79%	2299	69.27%
Simplified colectomy	1413	14.19%	946	14.25%	467	14.07%
Non-colectomy/NOS	1679	16.86%	1126	16.96%	553	16.66%
Hepatic surgery						
Yes	1941	19.49%	1285	19.36%	656	19.76%
No/unknown	8017	80.51%	5354	80.64%	2663	80.24%
Radiotherapy						
Yes	963	9.67%	638	9.61%	325	9.79%
No/Unknown	8995	90.33%	6001	90.39%	2994	90.21%
Chemotherapy						
Yes	7426	74.57%	4958	74.68%	2468	74.36%
No/Unknown	2532	25.43%	1681	25.32%	851	25.64%
CEA						
Negative	1351	13.57%	886	13.35%	465	14.01%
Positive	5800	58.24%	3899	58.73%	1901	57.28%
NOS	2807	28.19%	1854	27.93%	953	28.71%
PNI						
Negative	5971	59.96%	3977	59.90%	1994	60.08%
Positive	2188	21.97%	1493	22.49%	695	20.94%
NOS	1799	18.07%	1169	17.61%	630	18.98%
OS (months)	17 (7-31)		17 (7-31)		18 (8-32)	
CSS (months)	18 (8-32)		18 (8-31)		18 (8-32)	

MCC: mucinous cell carcinoma; SRCC: signet ring cell carcinoma; RNE: regional nodes examined; PNI: perineural invasion; NOS: not otherwise specified.
†: Rectum includes Rectosigmoid junction.

Most SCLLM patients underwent the surgery for primary tumor, including 68.95% of cases that received the colectomy with an RNE of more than 12 and 14.19% of patients accepted simplified colectomy. Meanwhile, hepatic surgery was performed for only 19.49% of SCLLM patients. Lastly, 2,532 (25.43%) patients missed chemotherapy in this study.

Independent prognostic factors for OS and CSS

Independent predictors were identified by univariable and multivariable Cox regression analyses. The multivariate Cox regression model was further applied to analyze the qualified variables in univariable one. As shown in **Table 2 and 3**, both of OS and CSS were significantly correlated with age, marital status, race, tumor location, pathological grade, histologic type, T stage, N stage, surgery for primary tumor, surgery for liver metastasis, chemotherapy and CEA.

All of the significant variables were used to create the nomograms for OS and CSS. The prognostic nomogram for 1-, 2-, and 3-year OS was shown in **Figure 1A.** The prognostic nomogram for 1-, 2-, and 3-year CSS was shown in **Figure 1B.** By adding up the scores related to each variable and projecting total scores to the bottom scales, we were easily able to calculate the estimated 1-, 2-, and 3-year OS and CSS probabilities.

Calibration and Validation of Prognostic Nomograms

Various methods, including C-index values, time-dependent ROC curves, decision curve analysis (DCA) and calibration curves, were utilized to evaluate the discriminating superiority of nomograms. The C-indexes proved that the nomograms provided favorable predictive accuracy. The nomogram predicting OS obtained 0.744 (95%CI: 0.736-0.752) and 0.749 (95%CI: 0.738-0.760) regarding the C-index in the training and validation group, respectively. While the C-index values of the nomogram predicting CSS were 0.741 (95%CI:

0.732-0.750) and 0.753 (95%CI: 0.741-0.766) in the training and validation group, respectively (**Table 4**). Besides, the calibration curves were able to visually illustrate the relationship between actual probability and predicted probability. As shown in **Figure 2**, the calibration curves, without obvious deviations from the reference line, illustrated the optimal agreement between model prediction and actual observations for 1-, 2-, 3-year OS and CSS.

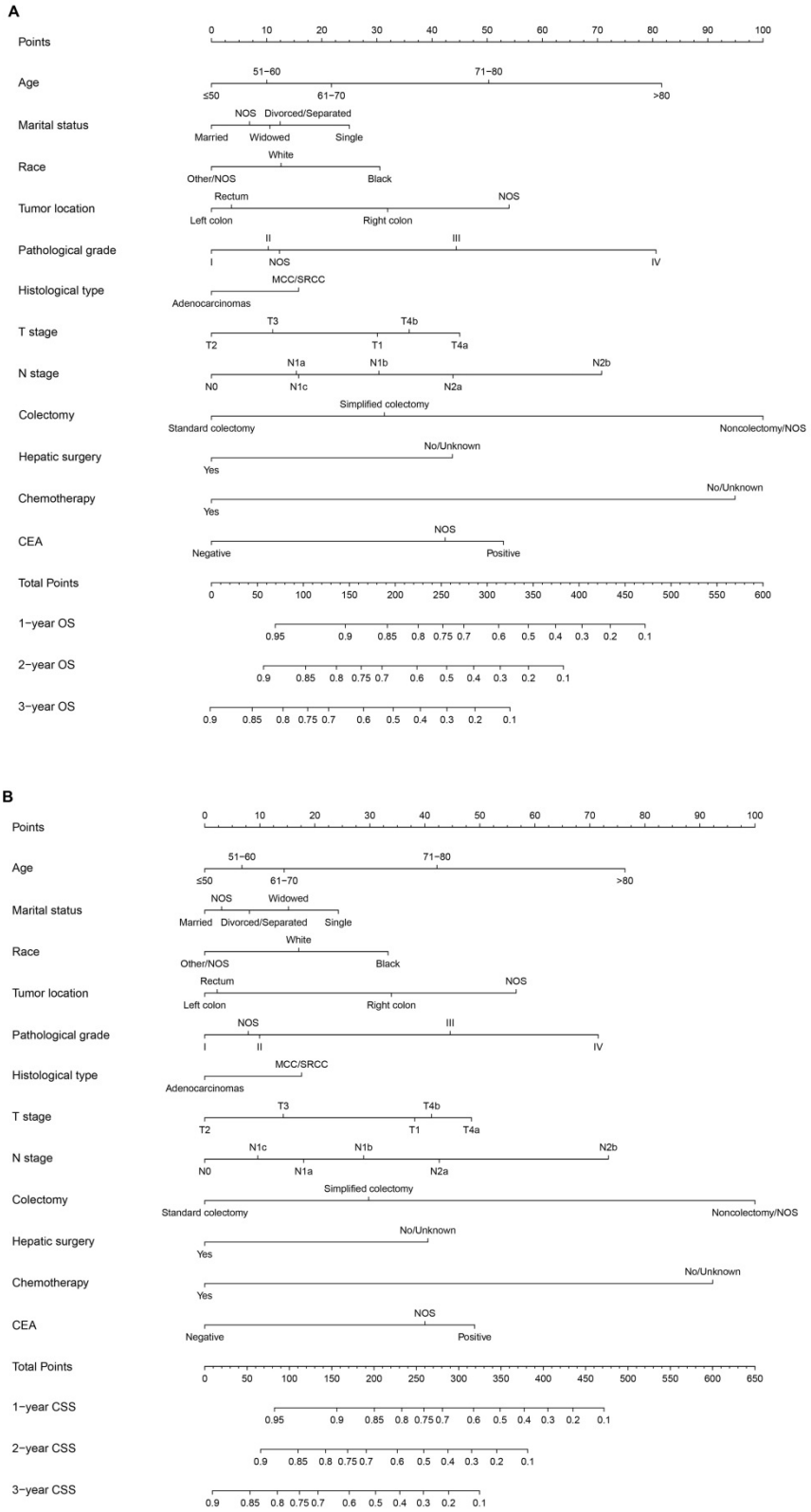

Figure 1. A. Nomogram of predicting OS for patients with SCLLM; **B.** Nomogram of predicting CSS for patients with SCLLM.

Table 2. Univariable and multivariable Cox regression model analyses of OS for nomogram

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	*p*-value	OR	95% CI lower	95% CI upper	*p*-value
Gender				0.118				
Female		Reference				NA		
Male	0.952	0.895	1.013	0.118				
Age (years)				<0.001				<0.001
≤50		Reference				Reference		
51-60	1.137	1.027	1.260	0.014	1.095	0.987	1.214	0.086
61-70	1.311	1.188	1.447	<0.001	1.225	1.108	1.355	<0.001
71-80	1.846	1.666	2.045	<0.001	1.597	1.434	1.778	<0.001
>80	3.294	2.951	3.677	<0.001	2.124	1.874	2.408	<0.001
Marital status				<0.001				<0.001
Married		Reference				Reference		
Single	1.238	1.139	1.345	<0.001	1.259	1.155	1.372	<0.001
Divorced/Separated	1.150	1.041	1.271	0.006	1.123	1.015	1.243	0.024
Widowed	1.887	1.722	2.067	<0.001	1.102	0.998	1.218	0.056
NOS	1.141	0.989	1.316	0.071	1.065	0.923	1.230	0.389
Insurance				0.405				
Yes		Reference				NA		
No/unknown	0.944	0.825	1.081	0.405				
Race				<0.001				<0.001
White		Reference				Reference		
Black	1.215	1.119	1.320	<0.001	1.179	1.082	1.285	<0.001
Other/NOS	0.890	0.795	0.996	0.042	0.892	0.797	1.000	0.049
Tumor location				<0.001				<0.001
Right colon		Reference				Reference		
Left colon	0.645	0.600	0.692	<0.001	0.743	0.689	0.800	<0.001
Rectum†	0.682	0.630	0.738	<0.001	0.787	0.719	0.862	<0.001
NOS	1.372	1.104	1.705	0.004	1.227	0.985	1.527	0.068
Pathological grade				<0.001				<0.001
I		Reference				Reference		
II	0.942	0.801	1.108	0.471	1.097	0.931	1.292	0.269
III	1.418	1.195	1.683	<0.001	1.498	1.257	1.785	<0.001
IV	1.903	1.539	2.353	<0.001	2.066	1.661	2.568	<0.001
Unknown	1.325	1.097	1.599	0.003	1.122	0.925	1.360	0.243
Histological type				<0.001				0.018
Adenocarcinomas		Reference				Reference		
MCC/SRCC	1.329	1.175	1.504	<0.001	1.165	1.027	1.322	0.018
T stage				<0.001				<0.001
T1		Reference				Reference		
T2	0.436	0.358	0.531	<0.001	0.771	0.623	0.953	0.016
T3	0.559	0.507	0.616	<0.001	0.850	0.746	0.969	0.015
T4a	0.822	0.735	0.918	0.001	1.158	1.002	1.339	0.048
T4b	0.808	0.712	0.916	0.001	1.066	0.922	1.232	0.387
N stage				<0.001				<0.001
N0		Reference				Reference		
N1a	0.805	0.724	0.894	<0.001	1.150	1.026	1.289	0.017
N1b	0.934	0.853	1.023	0.140	1.319	1.188	1.465	<0.001
N1c	0.863	0.680	1.094	0.223	1.147	.900	1.463	0.267
N2a	1.024	0.934	1.123	0.608	1.487	1.336	1.656	<0.001
N2b	1.327	1.218	1.445	<0.001	1.905	1.715	2.116	<0.001
Colectomy				<0.001				<0.001
Standard colectomy		Reference				Reference		
Simplified colectomy	1.245	1.142	1.358	<0.001	1.343	1.229	1.469	<0.001
Non-colectomy/NOS	1.964	1.817	2.123	<0.001	2.599	2.288	2.953	<0.001
Hepatic surgery				<0.001				<0.001
Yes		Reference				Reference		
No/unknown	1.971	1.807	2.150	<0.001	1.502	1.373	1.643	<0.001
Radiotherapy				<0.001				.100
Yes		Reference				Reference		
No/Unknown	1.476	1.319	1.651	<0.001	1.110	0.980	1.256	0.100
Chemotherapy				<0.001				<0.001
Yes		Reference				Reference		
No/Unknown	2.850	2.669	3.044	<0.001	2.387	2.223	2.563	<0.001
CEA				<0.001				<0.001
Negative		Reference				Reference		
Positive	1.697	1.532	1.880	<0.001	1.624	1.465	1.801	<0.001
NOS	1.666	1.492	1.860	<0.001	1.476	1.321	1.649	<0.001

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	*p*-value	OR	95% CI lower	95% CI upper	*p*-value
PNI				<0.001				0.412
Negative		Reference				Reference		
Positive	1.091	1.011	1.178	0.025	1.043	0.964	1.129	0.293
NOS	1.403	1.297	1.518	<0.001	0.970	0.885	1.064	0.521

MCC: mucinous cell carcinoma; SRCC: signet ring cell carcinoma; RNE: regional nodes examined; PNI: perineural invasion; NOS: not otherwise specified; NA: Unavailable.
†: Rectum includes Rectosigmoid junction.

Table 3. Univariable and multivariable Cox regression model analyses of CSS for nomogram

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	*p*-value	OR	95% CI lower	95% CI upper	*p*-value
Gender				0.060				
Female		Reference				NA		
Male	0.935	0.872	1.003	0.060				
Age (years)				<0.001				<0.001
≤50		Reference				Reference		
51-60	1.111	0.997	1.238	0.057	1.065	0.954	1.189	0.259
61-70	1.242	1.117	1.382	<0.001	1.151	1.032	1.283	0.011
71-80	1.777	1.585	1.992	<0.001	1.503	1.333	1.695	<0.001
>80	3.221	2.835	3.660	<0.001	2.070	1.790	2.395	<0.001
Marital status				<0.001				<0.001
Married		Reference				Reference		
Single	1.261	1.150	1.383	<0.001	1.262	1.147	1.388	<0.001
Divorced/Separated	1.142	1.018	1.281	0.024	1.083	0.964	1.217	0.181
Widowed	1.949	1.749	2.171	<0.001	1.159	1.030	1.304	0.015
NOS	1.127	0.959	1.326	0.147	1.030	.875	1.213	0.722
Insurance				0.857				
Yes		Reference				NA		
No/unknown	0.987	0.852	1.142	0.857				
Race				<0.001				<0.001
White		Reference				Reference		
Black	1.257	1.146	1.378	<0.001	1.166	1.059	1.283	0.002
Other/NOS	0.902	0.795	1.023	0.109	0.852	0.750	0.968	0.014
Tumor location				<0.001				<0.001
Right colon		Reference				Reference		
Left colon	0.621	0.572	0.673	<0.001	0.719	0.660	0.782	<0.001
Rectum†	0.674	0.616	0.737	<0.001	0.751	0.677	0.833	<0.001
NOS	1.408	1.096	1.810	0.007	1.244	0.965	1.604	0.092
Pathological grade				<0.001				<0.001
I		Reference				Reference		
II	0.937	0.780	1.124	0.482	1.101	0.915	1.324	0.310
III	1.434	1.182	1.740	<0.001	1.527	1.253	1.861	<0.001
IV	1.899	1.493	2.415	<0.001	1.942	1.517	2.485	<0.001
Unknown	1.274	1.028	1.579	.027	1.089	0.873	1.359	0.451
Histological type				<0.001				0.017
Adenocarcinomas		Reference				Reference		
MCC/SRCC	1.315	1.142	1.514	<0.001	1.193	1.033	1.378	0.017
T stage				<0.001				<0.001
T1		Reference				Reference		
T2	0.412	0.325	0.522	<0.001	0.702	0.544	0.905	0.006
T3	0.548	0.489	0.613	<0.001	0.799	0.685	0.931	0.004
T4a	0.810	0.713	0.921	0.001	1.100	0.927	1.304	0.275
T4b	0.786	0.680	0.909	0.001	1.032	0.874	1.218	0.711
N stage				<0.001				<0.001
N0		Reference				Reference		
N1a	0.822	0.728	0.927	0.001	1.183	1.038	1.348	0.012
N1b	0.943	0.850	1.047	0.270	1.309	1.160	1.477	<0.001
N1c	0.871	0.665	1.140	0.315	1.083	0.821	1.428	0.572
N2a	1.034	0.930	1.149	0.538	1.485	1.314	1.679	<0.001
N2b	1.391	1.263	1.532	<0.001	1.989	1.765	2.241	<0.001
Colectomy				<0.001				<0.001
Standard colectomy		Reference				Reference		
Simplified colectomy	1.222	1.106	1.350	<0.001	1.338	1.207	1.484	<0.001
Non-colectomy/NOS	1.984	1.814	2.170	<0.001	2.714	2.349	3.136	<0.001
Hepatic surgery				<0.001				<0.001
Yes		Reference				Reference		

Characteristics	Univariable analysis				Multivariable analysis			
	OR	95% CI lower	95% CI upper	*p*-value	OR	95% CI lower	95% CI upper	*p*-value
No/unknown	1.960	1.776	2.162	<0.001	1.479	1.336	1.637	<0.001
Radiotherapy				<0.001				0.235
Yes		Reference				Reference		
No/Unknown	0.666	0.586	0.757	<0.001	1.090	0.945	1.258	0.235
Chemotherapy				<0.001				<0.001
Yes		Reference				Reference		
No/Unknown	2.843	2.635	3.068	<0.001	2.412	2.221	2.620	<0.001
CEA				<0.001				<0.001
Negative		Reference				Reference		
Positive	1.722	1.534	1.934	<0.001	1.593	1.417	1.791	<0.001
NOS	1.702	1.502	1.929	<0.001	1.466	1.292	1.663	<0.001
PNI				<0.001				0.099
Negative		Reference				Reference		
Positive	1.102	1.011	1.202	0.027	1.082	0.990	1.184	0.084
NOS	1.367	1.248	1.496	<0.001	0.948	0.854	1.054	0.325

MCC: mucinous cell carcinoma; SRCC: signet ring cell carcinoma; RNE: regional nodes examined; PNI: perineural invasion; NOS: not otherwise specified; NA: Unavailable.
†: Rectum includes Rectosigmoid junction.

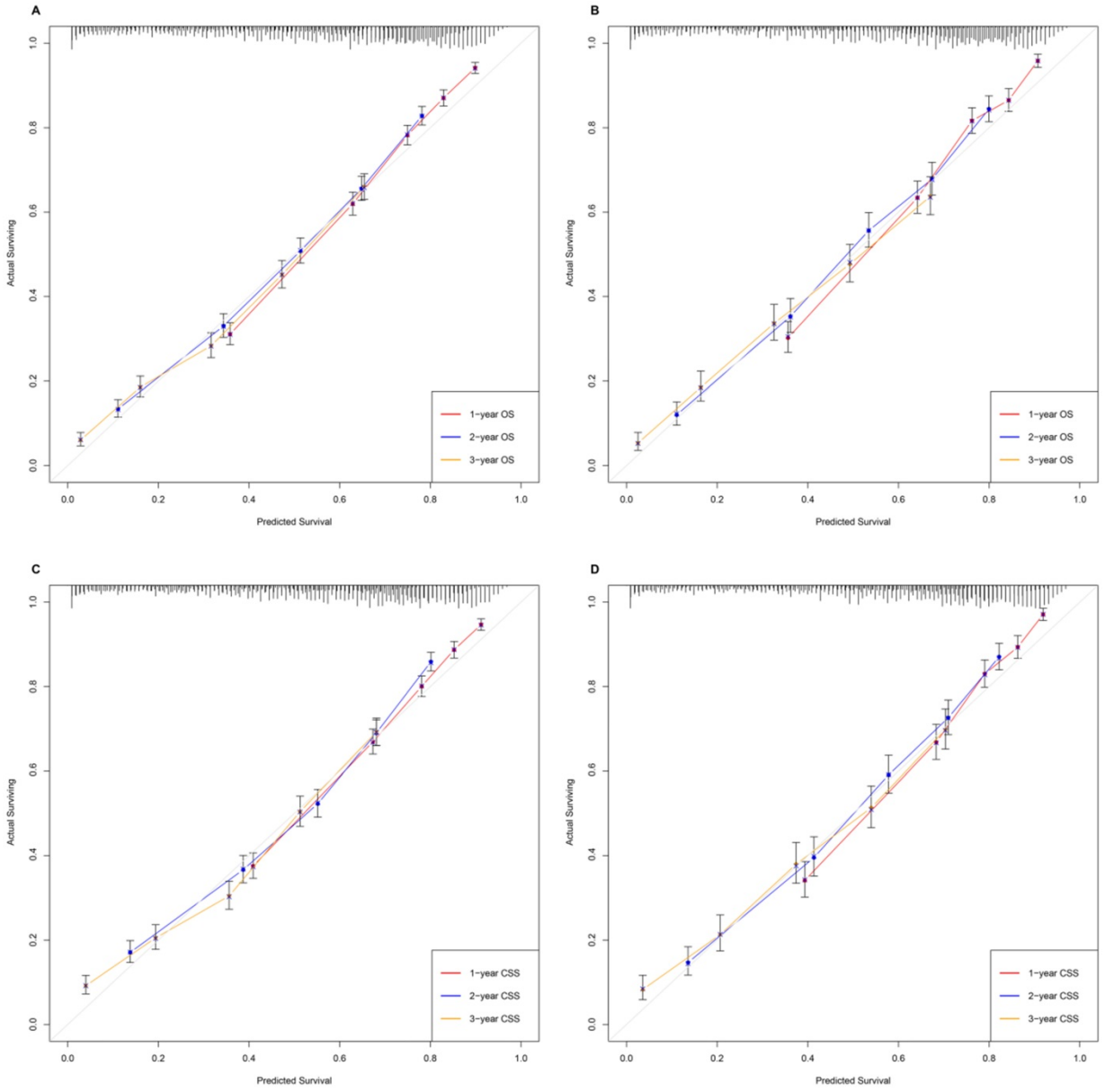

Figure 2. The calibration curves, without obviously deviations from the reference line, illustrated optimal agreement between model prediction and actual observations for 1-, 2-, 3-year OS and CSS. **A.** Predicting patients' OS at 1-year, 2-year, 3-year in the training group. **B.** Predicting patients' OS at 1-year, 2-year, 3-year in the validation group. **C.** Predicting patients' CSS at 1-year, 2-year, 3-year in the training group. **D.** Predicting patients' CSS at 1-year, 2-year, 3-year in the validation group.

Table 4. The C-indices for predictions of overall survival and cancer-specific survival

	OS		CSS	
	C-index	95% CI	C-index	95% CI
Training group	0.744	0.736-0.752	0.741	0.732-0.750
Validation group	0.749	0.738-0.760	0.753	0.741-0.766

Abbreviations: OS, overall survival; CSS, cancer-specific survival; C-index, index of concordance; CI, confidence interval.

The time-dependent receiver operating characteristic (ROC) has been used widely to display sensitivity and specificity in predictive models. The area under the curve (AUC) values of ROC were 81.65%, 79.45% and 77.92% regarding for nomograms predicting 1-, 2- and 3- year OS, respectively, in the training cohort. While the 1-, 2-, and 3-year AUC values of the nomogram for OS were 82.87%, 79.88% and 77.04%, respectively, in the validation cohort. Similarly, the nomogram of CSS obtained the outstanding AUC values in training (AUC=81.03% for 1-year CSS; AUC=79.18% for 2-year CSS and AUC=77.69% for 3-year CSS) and the validation group (AUC=83.56% for 1-year CSS; AUC=80.42% for 2-year CSS and AUC=77.00% for 3-year CSS) (**Figure 3**).

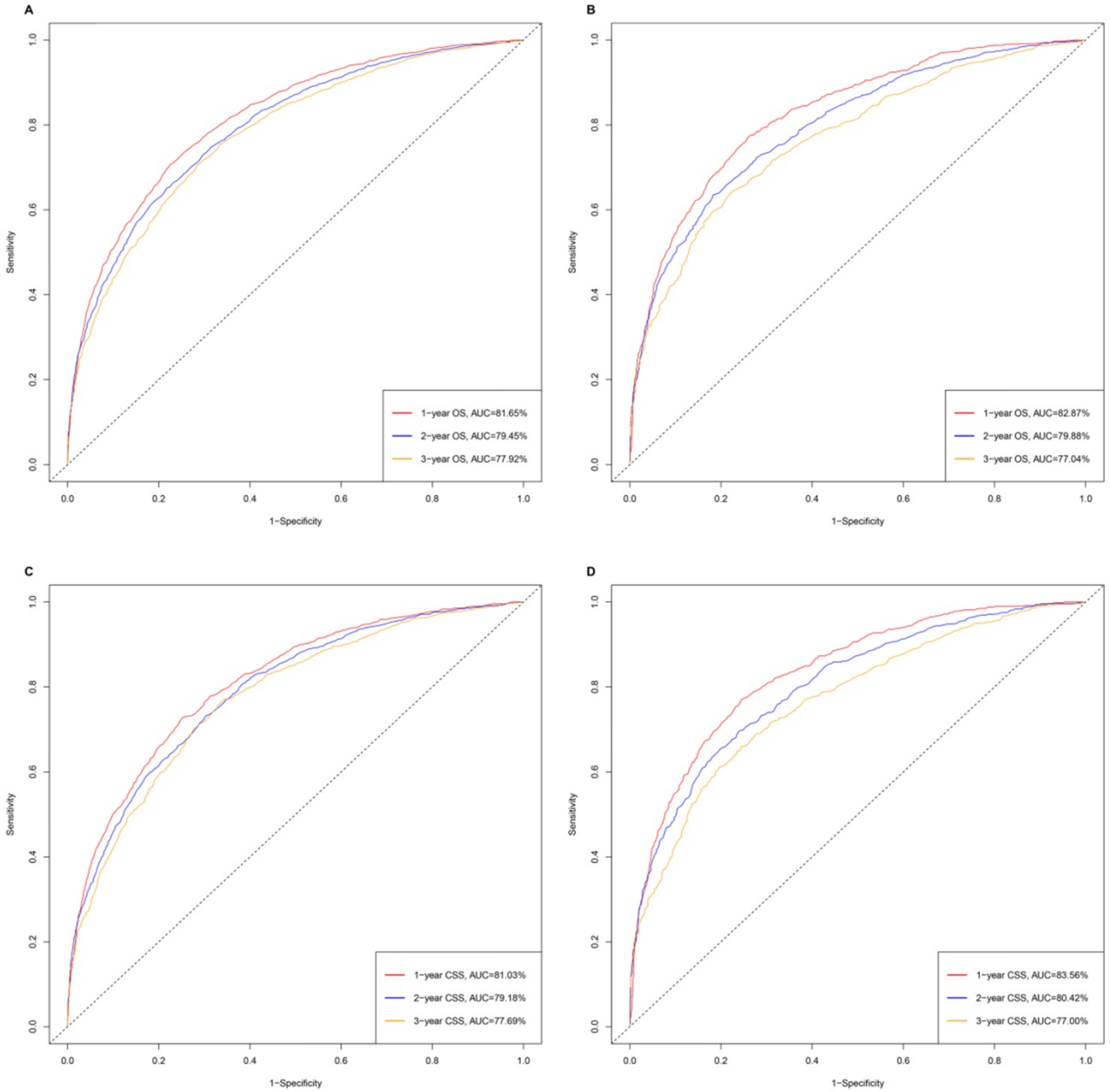

Figure 3. The time-dependent ROC curves of nomograms. **A.** The AUC values of ROC were 81.65%, 79.45% and 77.92% regarding nomograms predicting 1-, 2- and 3- year OS in training cohort. **B.** The 1-, 2-, and 3-year AUC values of the nomogram for OS were 82.87%, 79.88% and 77.04% in validation cohort. **C.** The AUC values of ROC were 81.03%, 79.18% and 77.69% regarding nomograms predicting 1-, 2- and 3- year CSS in training cohort. **D.** The 1-, 2-, and 3-year AUC values of the nomogram for CSS were 83.56%, 80.42% and 77.00% in validation cohort.

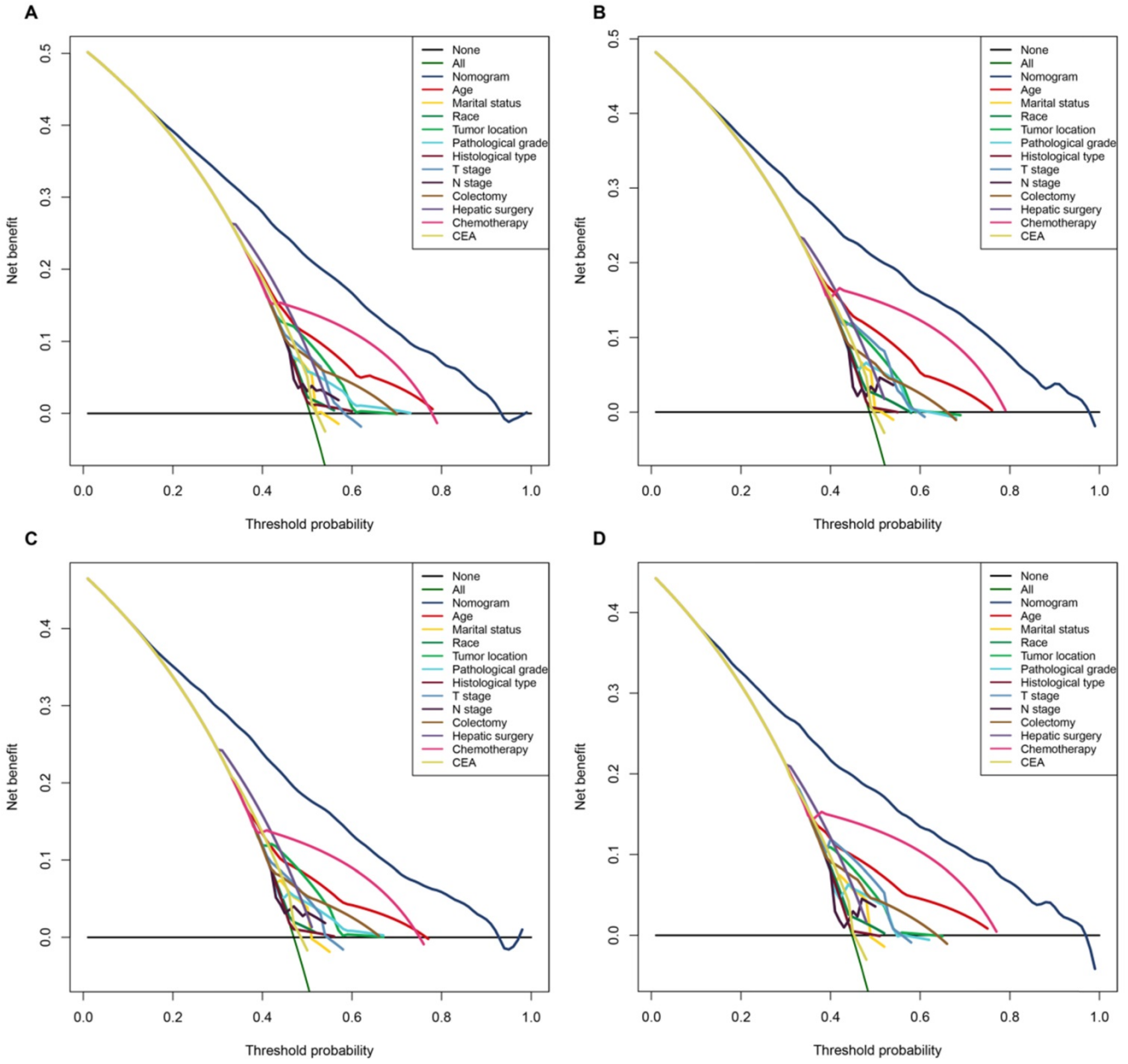

Figure 4. The decision curve analysis (DCA) demonstrated that the nomograms owned excellent net benefits and was superior to the any single prognostic factors across the wider range of reasonable threshold probabilities in OS and CSS. **A.** The DCA of the nomogram and all prognostic factors for OS in the training cohort. **B.** The DCA of the nomogram and all prognostic factors for OS in the validation cohort. **C.** DCA of the nomogram and all prognostic factors for CSS in the training cohort. **D.** The DCA of the nomogram and all prognostic factors for CSS in the validation cohort.

Moreover, in terms of clinical utility, DCA demonstrated that the nomograms, provided excellent net benefits and were superior to the any single prognostic factors across the wider range of reasonable threshold probabilities in OS and CSS (**Figure 4**).

Performance of the Nomograms in Stratifying on the Basis of Risk Scores

The prognostic scores of all independent predictors were assigned on the basis of the established nomogram, and optimal cut-off values were calculated by using X-tile based on the total scores of patients in the training cohort [8]. According to the cut-off values of the nomogram for OS, SCLLM were divided into low-risk (score < 258), moderate-risk (258 ≤ score < 363) and high-risk (score ≥ 363) (**Figure 5**). Similarly, patients were classified into three subgroups based on total score (< 255, 255 to 364, and ≥ 364) for CSS (**Figure 5**).

Additionally, the Kaplan–Meier survival curves were subsequently delineated and are shown in **Figure 6.** In the training group, the low-risk cohort owned the longest median OS (36-month) and CSS (38-month), followed by the moderate-risk cohort (17-month OS and 18-month CSS) and the high-risk

cohort (5-month for OS and CSS). We obtained consistent results in the validation cohort (low-risk group: 37-month median OS and 40-month median CSS; moderate-risk group: 18-month median OS and CSS; high-risk group: 5-month median OS and CSS).

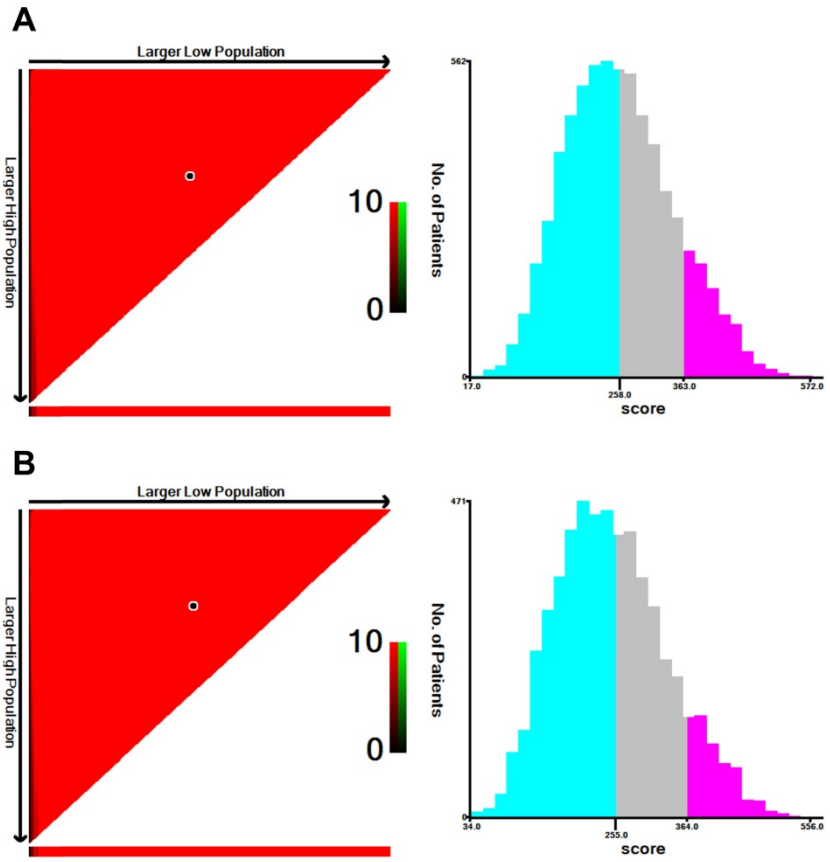

Figure 5. The cut-off values were calculated by using X-tile based on the total scores of patients in the training cohort. **A.** According to the cut-off values of the nomogram for OS, SCLLM were divided into low-risk (score < 258), moderate-risk (258 ≤ score < 363) and high-risk (score ≥ 363). **B.** According to the cut-off values of the nomogram for CSS, SCLLM were divided into low-risk (score < 255), moderate-risk (255 ≤ score < 364) and high-risk (score ≥ 364).

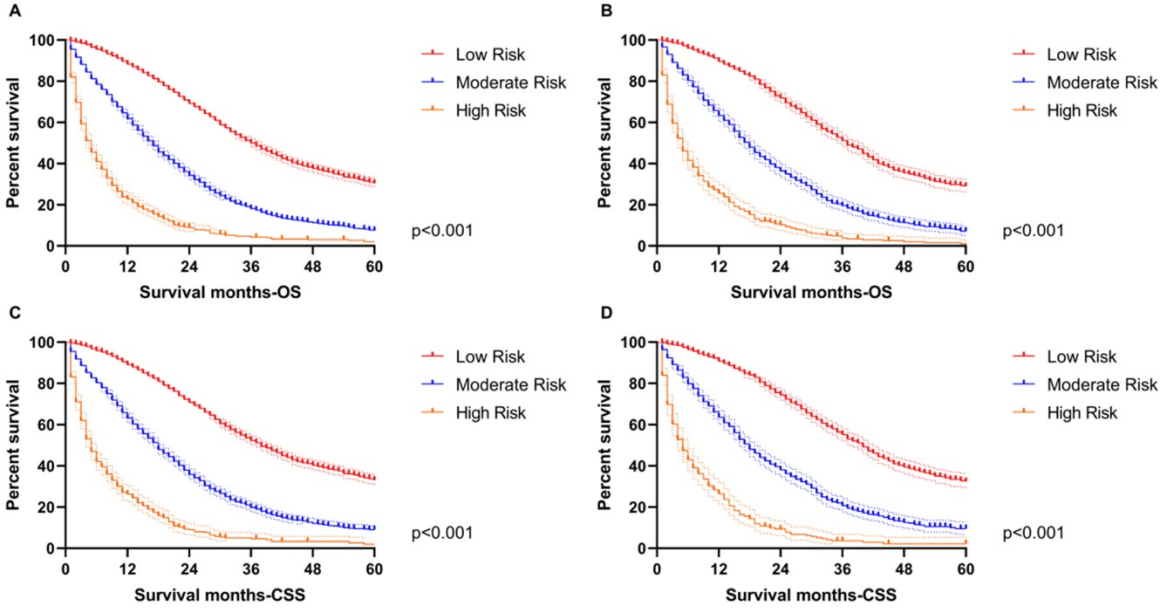

Figure 6. The survival analysis in the subgroup. **A.** The low-risk cohort owned the longest median OS (36-month) followed by the moderate-risk cohort (17-month OS) and high-risk cohort (5-month for OS) in the training group. **B.** The low-risk cohort owned the longest median OS (37-month) followed by the moderate-risk cohort (18-month OS) and high-risk cohort (5-month for OS) in the validation group. **C.** The low-risk cohort owned the longest median CSS (38-month) followed by the moderate-risk cohort (18-month CSS) and high-risk cohort (5-month for CSS) in the training group. **D.** The low-risk cohort owned the longest median CSS (40-month) followed by the moderate-risk cohort (18-month OS) and high-risk cohort (5-month for OS) in the validation group.

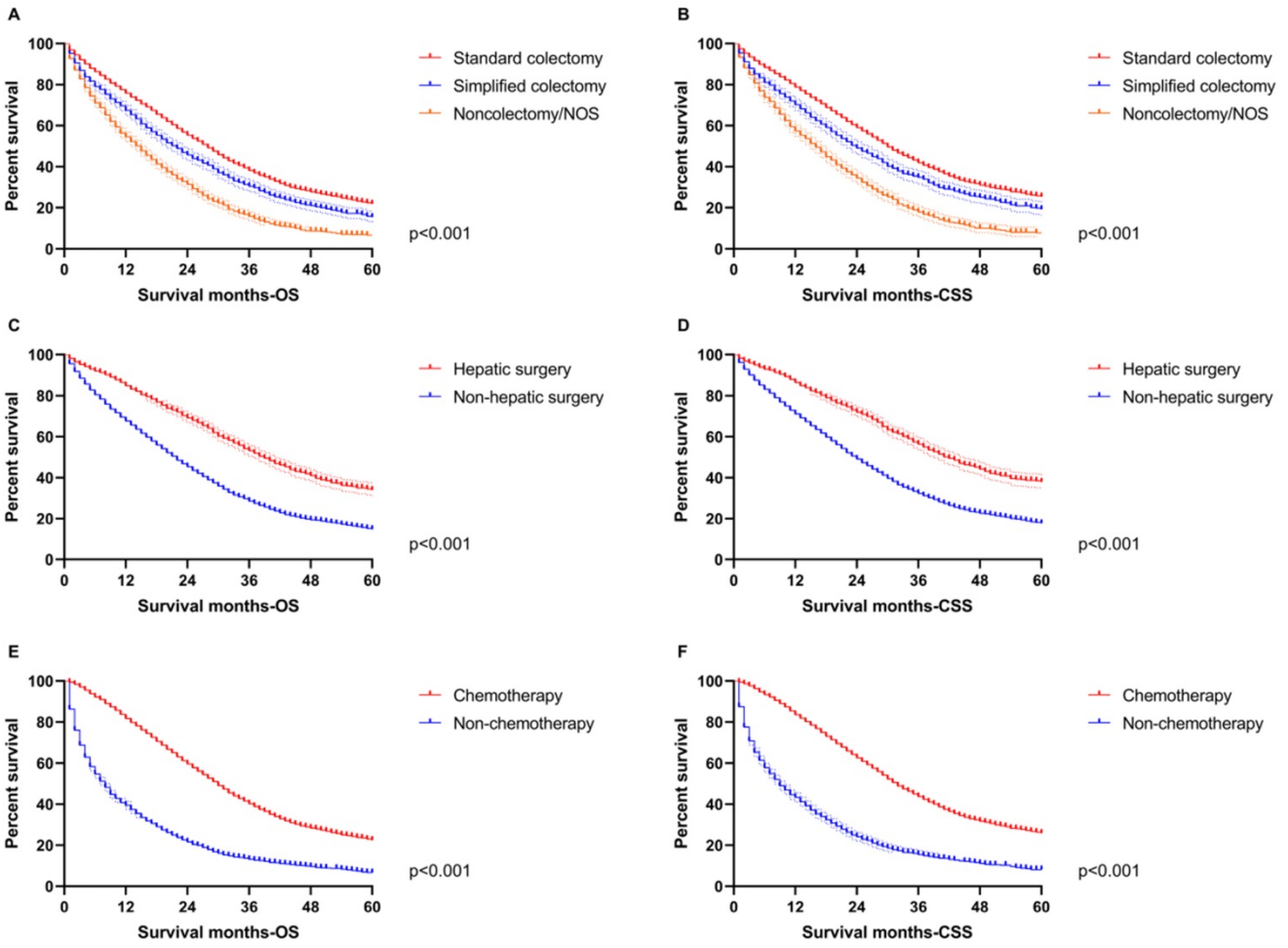

Figure 7. The survival analysis for therapeutic features in the total population. **A.** The difference of OS among standard colectomy (median OS: 28-month), simplified colectomy (median OS: 22-month) and non-colectomy/NOS (median OS: 15-month). **B.** The difference of CSS among standard colectomy (median CSS: 30-month), simplified colectomy (median CSS: 24-month) and non-colectomy/NOS (median CSS: 16-month). **C.** The difference of OS between hepatic surgery (median OS: 39-month) and non-hepatic surgery (median OS: 22-month). **D.** The difference of CSS between hepatic surgery (median CSS: 42-month) and non-hepatic surgery (median CSS: 24-month). **E.** The difference of OS between chemotherapy (median OS: 30-month) and non-chemotherapy (median OS: 8-month). **F.** The difference of CSS between chemotherapy (median CSS: 32-month) and non-chemotherapy (median CSS: 9-month).

In order to highlight the role of therapeutic variables, survival curves were also drawn to indicate the benefit from treatment based on the total population in this study. All primary surgery, hepatic operation and chemotherapy improved OS and CSS distinctly (p<0.001, **Figure 7**), which was consistent with the nomograms.

Discussion

This study provided a significant contribution through the use of a large cohort of patients with SCLLM who were treated in the U.S. from 2010 to 2016 to construct nomograms predicting OS and CSS, which were capable of providing individualized estimates of potential survival benefit and can aid individualized management decisions for SCLLM. Other scoring systems, including various clinicopathological factors, have been developed to evaluate survival for SCLLM [9], however, the limitations of such risk scoring systems included a lack of reproducibility when applied at other institutions [10]. The SEER database, with cancer incidence and survival data from population-based cancer registries covering approximately 34.6% of the population from U.S. [11], provides available, authentic and reliable data, which can make up for limitations regarding perfect reproducibility. Meanwhile, the comprehensive nomograms with an absolute net benefit advantage over any single prognostic factor in DCA curves provided excellent value for clinical practice. Moreover, the superior accuracy, sensitivity and specificity of nomograms predicting OS and CSS were able to ensure effectiveness in clinical practice.

Chemotherapy is recommended for all CRC patients with synchronous metastatic diseases. The nomograms demonstrated the ginormous risk in SCLLM patients without chemotherapy, which was similar in the survival curves. However, an optimal chemotherapy regimen remains controversial, along

with the order of surgery and chemotherapy. Regrettably, this study failed to explore further due to limitations of the SEER database. Moreover, several researches suggested that surgical resection should not be performed unless all known tumors can be completely removed (R0 resection), because incomplete resection or debulking (R1/R2 resection) did not provide survival beneficial for CRC patients with metastatic diseases [12, 13]. Did patients with SCLLM really not get any survival beneficial from the separate primary resection? The multivariable Cox regression analyses believed that surgical resection for the primary tumor could be used as an independent predictor. Moreover, the proportion of primary resections was significantly higher than that of hepatic surgery in our study. We then delineated the survival curves to definitely compare the difference among non-colectomy, standard and simplified colectomy in patients without hepatic surgery (**Figure S1**). All the evidences indicated that SCLLM patients could receive survival benefit from the separate resection for a primary tumor. Results from one study also suggested that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases [14]. Separate analyses of the National Cancer Data Base also identified a survival benefit of primary tumor resection in this setting [15]. More importantly, colectomy with RNE ≥12 provided a longer OS and CSS than one without, reminding surgeons that lymph node dissection cannot be ignored in colorectal cancer with synchronous liver-limited metastasis.

Age was also an important prognostic factor in this study. Increasing age was accompanied by an elevated risk score, especially in patients over 70-year-old. Marital status was also able to affect the OS and CSS of patients with SCLLM. Single persons suffered the greatest risk, but persons with a stable marriage status owned the lowest risk. It may be that the company of a significant other is supportive. In addition, the different survival among ethnic groups should also be given attention.

A growing body of data indicated that primary tumor location can be a prognostic factor in metastasis colorectal cancer [16-18], which was consistent with the nomograms in this study. Increasing research reported multitudinous differences between right and left colon cancer, involving embryonic origin, molecular genetics, pathological type as well as demographic characteristics such as gender and age [19-23]. Moreover, cetuximab and panitumumab, as monoclonal antibodies directed against EGFR, confer little benefit to patients with metastatic colorectal cancer if the primary tumor originated on the right side [16-18]. Therefore, some scholars suggested that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colorectum and, enables a better biologic understanding of the observed difference in response to EGFR inhibitors [6].

The roles of pathological grade, histological type and CEA in the nomograms were in line with our notions. However, T and N stages were not completely consistent with our knowledge. The nomograms reminded that SCLLM patients with early T stage should be given more attention because the risk score of T1 was even more than that of T2-3. Additionally, patients with negative regional lymph nodes, but positive tumor deposits (TD) in specific site were divided into a N1c stage [6], that obtained an equal or even a lower risk score comparing with N1a. Therefore, it is worth considering whether the risk degree of TD needs to be redefined in the TNM stage system for patients with synchronous metastases. Moreover, PNI was included as a high-risk factor for systemic recurrence [6], but did not affect the survival of patients with metastasis.

Currently, there are different definitions of synchronous metastasis for colorectal cancer [24-26]. Although some definitions include metastases detected up to 6 months following diagnosis [25, 26], most include detection at or before diagnosis or surgery of the primary tumor [24]. Moreover, Adam R, et al. also believed that synchronous metastasis for colorectal cancer should be defined as synchronously detected [27]. There are still some shortcomings in this study: (1) further validation is necessary due to the typical limits of a retrospective study; (2) some important information is missing in the SEER database, such as Ras and B-raf; and (3) a lack of detailed data precluded an ability to compare the pros and cons of chemotherapy regimens. However, the excellent clinical value should not be masked by these shortcomings.

Conclusion

Our research investigated a national cohort of almost 10000 patients to create and verify nomograms based on pathological, therapeutic and demographic features to predict OS and CSS for SCLLM. The nomograms may act as an excellent tool to integrate clinical characteristics to guide the therapeutic choice for SCLLM patients.

Supplementary Material

Supplementary figure S1.
http://www.jcancer.org/v11p6213s1.pdf

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Data availability statement

These data were derived from the Surveillance, Epidemiology and End Results (SEER) database (https://seer.cancer.gov/) and identified using the SEER*Stat software (Version 8.3.5) (https://seer.cancer.gov/seerstat/).

Ethics approval

Approval from the ethical board for this study was not required because of the public nature of all the data.

Informed consent

Patients' informed consent was waived because of the retrospective nature of the study design.

Authors' contributions

Yuqiang Li, Fengbo Tan and Haiping Pei conceived and designed the study. Yuqiang Li and Wenxue Liu wrote the article. Lilan Zhao downloaded and screened the data from SEER database. All authors participated in analyzing the data. All authors read and approved the final manuscript.

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Competing Interests

The authors have declared that no competing interest exists.

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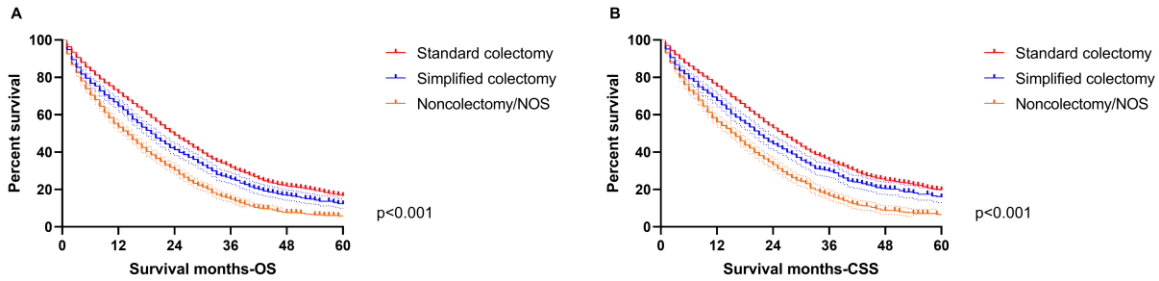

Supplementary Fig.1 the survival curves compared the difference among noncolectomy, standard and simplified colectomy in patients without hepatic surgery definitely. A: The median OS were 24-month, 19-month and 14-month for standard colectomy, simplified colectomy and non-colectomy respectively. B: The median CSS were 26-month, 21-month and 16-month for standard colectomy, simplified colectomy and non-colectomy respectively

1.4 Predicting pathological complete response by comparing MRI‐based radiomics pre‐ and postneoadjuvant radiotherapy for locally advanced rectal cancer

Li Y, Liu W, Pei Q, Zhao L, Güngör C, Zhu H, Song X, Li C, Zhou Z, Xu Y, Wang D, Tan F, Yang P, Pei H.
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ORIGINAL RESEARCH

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Predicting pathological complete response by comparing MRI-based radiomics pre- and postneoadjuvant radiotherapy for locally advanced rectal cancer

Yuqiang Li[1,2] | Wenxue Liu[3,4] | Qian Pei[1] | Lilan Zhao[5] | Cenap Güngör[2] | Hong Zhu[6] | Xiangping Song[1] | Chenglong Li[1] | Zhongyi Zhou[1] | Yang Xu[2] | Dan Wang[1] | Fengbo Tan[1] | Pei Yang[1,7] | Haiping Pei[1]

[1]Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, China

[2]Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[3]Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

[4]Department of Cardiology, Xiangya Hospital, Central South University, Changsha, China

[5]Department of Thoracic surgery, Fujian Provincial Hospital, Fuzhou, China

[6]Department of Oncology, Xiangya Hospital, Central South University, Changsha, China

[7]Department of Oncology, Hunan Cancer Hospital, Changsha, China

Correspondence
Haiping Pei, Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, P.R. China.
Email: peihaiping1966@hotmail.com

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Abstract

Background: Total mesorectal excision following neoadjuvant chemoradiotherapy (nCRT) is recommended in the latest treatment of locally advanced rectal cancer (LARC).

Objective: To predict whether patients with LARC can achieve pathologic complete response (pCR), comparing MRI-based radiomics between before and after neoadjuvant radiotherapy (nRT) was performed.

Methods: One hundred and sixty-five MRI-based radiomics features in axial T2-weighted images were obtained quantitatively from Imaging Biomarker Explorer Software. The specific features of conventional and developing radiomics were selected with the analysis of least absolute shrinkage and selection operator logistic regression, of which the predictive performance was analyzed with receiver operating curve and calibration curve, and applied to an independent cohort.

Results: One hundred and thirty-one target patients were enrolled in the present study. A radiomics signature founded on seven radiomics features was generated in the primary cohort. A remarkable difference about Rad-score between pCR and non-pCR group occurred in both of primary ($P < .001$) or validation cohorts ($P < .001$). The value of area under the curves was 0.92 (95% CI, 0.86-0.99) and 0.87 (95% CI, 0.74-1.00) in the primary and validation cohorts, respectively. The Rad-score (OR = 23.581; $P < .001$) from multivariate logistic regression analysis was significant as an independent factor of pCR.

Conclusion: Our predictive model based on radiomics features was an independent predictor for pCR in LARC and could be a candidate in clinical practice.

KEYWORDS
locally advanced rectal cancer, MRI-based radiomics, neoadjuvant chemoradiotherapy, pathologic complete response, predictive model

Yuqiang Li, Wenxue Liu, Qian Pei and Lilan Zhao contributed equally to this article.

1 | INTRODUCTION

Colorectal cancer (CRC) is considered as the third top malignancy in the world,[1] approximate 30%-50% of which is rectal cancer.[2] Currently, the recommended treatment for locally advanced rectal cancer (LARC, T3-4 or N+) is total mesorectal excision (TME) after neoadjuvant chemoradiotherapy (nCRT).[3] And neoadjuvant radiotherapy (nRT) plays an important role in nCRT. However, different patients bring the wide variabilities out of the response of LARC to nCRT, with a ladder from no tumor regression to pathologic complete response (pCR).[4] Although the necessity of surgery in LARC patients with pCR is a subject of ongoing argument, the majority of patients are still undergoing surgery in practice. Considering surgical complications, especially after nCRT, and outstanding long-term outcomes in pCR patients apart from surgery, Habr-Gama et al proposed the "watch-and-wait" approach first.[5] Thus, the identification of pCR before surgery gains more and more concerns in therapeutic management.

Radiomics, which extracted excavatable high-dimensional data from digital images, revealed nonvisual information associated closely with underlying pathophysiology and even tumor heterogeneity.[6,7] Recently, the development of radiomics has shown great potential for therapy guidance and tumor prognosis across various types of cancer.[8-11]

Despite of diverse outcomes, several researches displayed the potential significance of imaging modalities.[12-16] Among all modalities, magnetic resonance imaging (MRI) was regarded as the most recommended and promising method because it showed high soft tissue resolution without radiation to damage human body, and had a wide routine clinical application for the evaluation of rectal cancer. Several predicting models also based tumor response to nCRT on MRI-related radiomics in LARC. However, all of the studies only focused on the MR images prior to nCRT, which might have inherent limitations to reflect the impact of nCRT on target population.

Therefore, we were planning to investigate whether the difference of quantitative MRI-based radiomics analysis between pre-nRT and post-nRT can be of great help to predict pCR in LARC.

2 | MATERIALS AND METHODS

2.1 | Patients

This study collected the medical information of consecutive patients with LARC, who treated with nCRT followed by radical surgery (total mesorectal excision) between March 2011 and March 2018 in Xiangya hospital. Biopsy-proven rectal adenocarcinoma was performed before receiving radiotherapy and/or chemotherapy for patients. Locally advanced rectal cancer was defined as T3-4 or N+ (c-Stage II-III) without any evidence of distant metastases in clinical stage, and evaluated by pelvic magnetic resonance imaging (MRI), chest X-ray, digital rectal examination, abdomen, pelvis and/or chest contrast-enhanced computed tomography (CT), endorectal ultrasonography (ERUS), and/or bone single-photon emission computed tomography (SPECT). Exclusion criteria contained short-course radiotherapy only, synchronous tumors, lack of pre- or postradiation MR images, interval between the end of nRT and surgery <5 weeks or >12 weeks, and previous pelvic radiotherapy (Figure 1).

2.2 | Protocol of image acquisition and extraction of radiomic features

MR images were acquired with a 1.5-T superconductive unit (MAGNETOM Sonata, Siemens, Erlangen, Germany; Singa HDxt, GE Medical Systems, Umatilla, FL, USA). Coronal, sagittal turbo spin-echo T2-weighted images, and transverse T1/T2-weighted images were included in the sequences. The pre-nRT MRI was obtained within 2 weeks before nRT and post-nRT MRI was gained within 1 week after nRT.

One hundred and sixty-five MRI-based radiomics features (Supplementary material S1), which can quantify tumor's volume, intensity, and texture property, were extracted from manual segmentation, including pre- and post-nRT MR images, by imaging biomarker explorer software (IBEX). The regions of interest (ROI) were outlined along the edge of tumor, and it took approximately 5 min to proceed segmentation manually for each tumor. Segmentations of ROI were operated manually by Y.P—a radiotherapist with 10 years of experience in rectal MR imaging and reaffirmed by H.Z—a radiologist with 20 years of experience. The two radiotherapists were both blinded to the clinical data. Radiomic features for each of included patient were automatically calculated by the software following tumor segmentation.

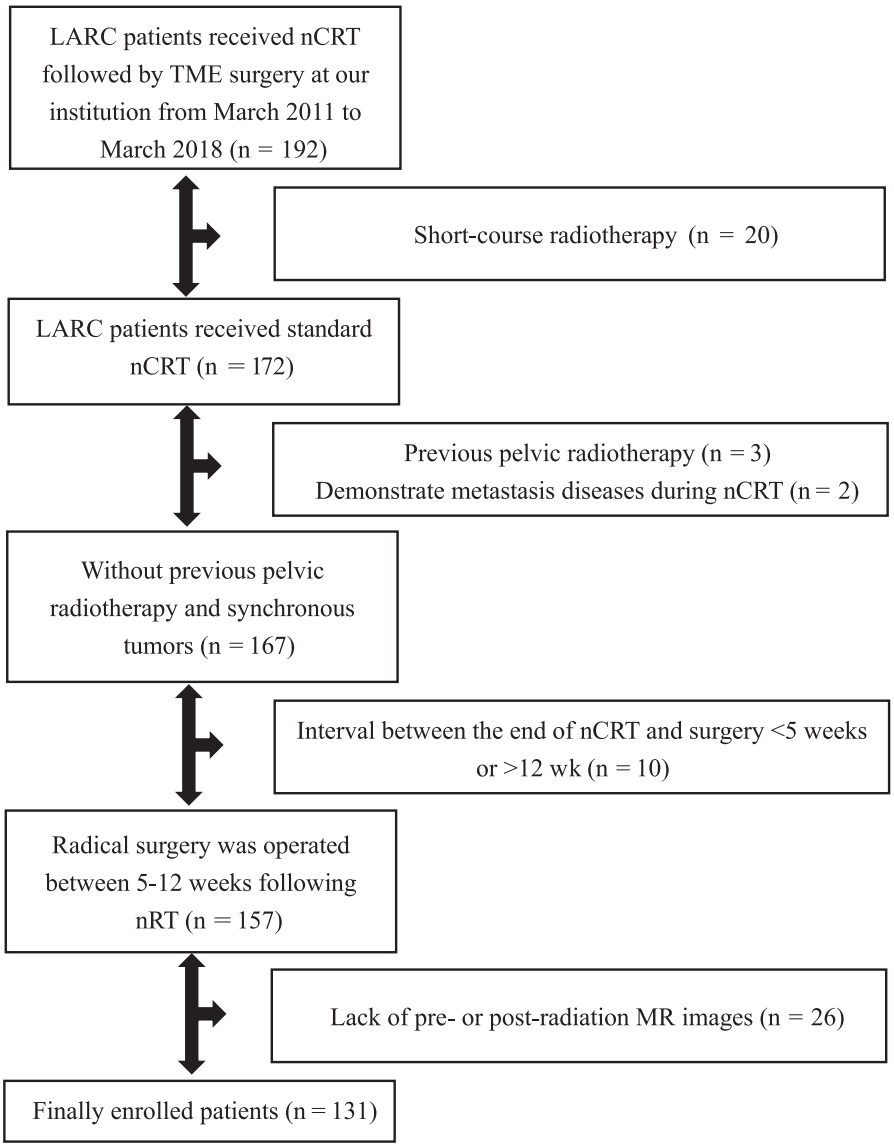
The data we used for statistical analysis were obtained by subtracting quantitative MRI-based radiomic features of post-nRT from that of pre-nRT.

2.3 | Treatment

The 6-week administration of neoadjuvant radiotherapy was at a dose of 46-50 Gy in 23-25 fractions (2 Gy/fraction, 5 d/wk) for the whole pelvis, and 6-8Gy in 3-4 fractions for the primary tumor. Radiotherapy machine included Trilogy, 23EX, D-2100CD (Varian) and TomoTherapy H^{TM} Series 2.1.x Hi Art 5.1x (Accuray Incorporated). All patients had a CT emulation of three-dimensional conformal planning and intensity-modulated radiotherapy (IMRT), concomitant with a three-field treatment plan involving a 6-MV photon posterior-anterior field and 15-MV photon opposed lateral fields.

All patients received the treatments of neoadjuvant concurrent chemotherapy based on 5-fluorouracil (5-FU).

FIGURE 1 Flowchart



Either of the two programs was selected: mono-chemotherapy of 5-FU: bolus injection [400 mg/m^2/d] for continuous 5 days in the first and last weeks of radiotherapy or oral capecitabine [825 mg/m^2] twice per day during weekend breaks of radiotherapy; combined chemotherapy: mFOLFOX6 (bolus infusion of 5-FU [400 mg/m^2] 2 hours on d1, continuous intravenous drip of 5-FU [1200 mg/m^2/d] 46 hours on d1-2, intravenous drip of leucovorin [400mg/m^2] 2 hours on d1, intravenous drip of oxaliplatin [85 mg/m^2] 2 hours on d1, 2 weeks per cycle) or CAPOX (oral capecitabine [1000 mg/m^2] twice daily d1-14, intravenous drip of oxaliplatin [130 mg/m^2] 2 hours on d1, 3 weeks per cycle).

TME surgery was operated between 5 and 12 weeks following nRT, and the surgical strategy, including abdominoperineal resection (APR), trans-anal resection (TAR), low anterior resection (LAR), and LAR plus prophylactic ileostomy, was made by surgeon.

2.4 | Tumor response evaluation

The tumor tissue was sampled prior to paraffin embedding and slicing into 4-mm-thick sections to evaluate the tumor response to nCRT after resection. pCR, no viable tumor cells in the bowel wall (T stage) and regional nodes (N stage)--ypT0N0, was equivalent to the tumor regression grade (TRG) 0,[17] which is fibrotic mass, acellular mucin pools or hyaline degeneration only, without detecting tumor cells (complete regression). The other pathological conditions, including TRG 1-4[17] (no regression, minimal regression, moderate regression, and near-complete regression), were defined as non-pCR.

2.5 | Data collection

The parameters were appraised as latent clinical predictors of tumor response to nCRT as follows: age, gender, Body

Mass Index (BMI), clinical T (cT) stage, clinical lymph node (cN) status, distance from the anal verge, histologic type, pre-nCRT CEA level, concurrent chemotherapy regimen and interval time between nCRT and surgery.

Clinical T classification was judged by pelvic MRI and/or ERUS. Smallest diameter of a regional lymph node ≥5 mm observed on pelvic MRI was defined as positive lymph node involvement.[18] The distance between the tumor and the anal verge was measured by MRI. The clinical TNM staging was originated from the 8th edition of the American Joint Committee on Cancer (AJCC) Staging system. The peripheral blood within 2 weeks prior to nCRT under the condition of abrosia was extracted for the examination of pre-nCRT serum tumor markers levels.

2.6 | Construction of Rad-score with the LASSO regression model

Since the multicollinearity among radiomics features existed, the optimal subset of radiomic features was selected by the LASSO binary logistic regression model in order to establish the radiomic signature score (Rad-score). And a penalty parameter (also called as tuning parameter) was brought into the mechanism of the LASSO regression to penalize the coefficient of variables embodying in the LASSO regression model, averting the issue of overfitting. With the raise of tuning parameter (λ), more coefficients were installed to zero (less variables were chosen), and more shrinkage was applied among the nonzero coefficients. The region under the receiver operating characteristic curve was constructed vs log(λ) to find out the optimal value of log(λ) with the minimum criterion and the one standard error of the minimum criterion. LASSO binary logistic regression analysis was performed in the Bglmnet^ package of R software, and the process of programming is presented in the Supplementary material S1.[19-21]

2.7 | Statistics

Intergroup comparisons were analyzed using Pearson's chi-square test, Mann-Whitney *U* test, Fisher's exact test, or Student's *t* test, according to the nature of the data. The independent prognostic factors were selected by multivariable logistic regression analysis. The performance of the model was evaluated in the primary and validation cohorts. The discrimination of the signature was evaluated through the area under the curve (AUC). The apparent calibration curve was drawn with model-predicted probability vs actual probability of invasive adenocarcinoma, and the bias-corrected curve was generated from 1000 bootstrap resamples. SPSS from Windows, version 20.0 (IBM) was used for statistical analysis. A difference was considered significant at $P < .05$ with two sides.

3 | RESULTS

3.1 | Patients characteristics

One hundred and thirty-one target patients were contained in our study. The parameter of patients in the primary and validation cohorts was listed in Table 1. Patients were randomly distributed into primary cohort and validation cohort in the ratio of 2:1 to build the pCR predictive model. In the primary cohort, 63.22% of target population was male, whose age was 51.18 years in average. In the validation cohort, more than half of patients were male (59.09%) with an average age of 51.64.

The percentages of patients with pCR in the primary cohort and the validation cohort were 20.69% (18/87) and 20.45% (9/44), respectively. Chemotherapy regimen was significantly different between the pCR and non-pCR groups for the primary ($P = .006$) but not validation ($P = .548$) cohorts. Conversely, there was a conspicuous difference of pre-CEA level between the pCR and non-pCR groups in the validation ($P < .001$) but not primary ($P = .608$) cohorts. The difference about clinical T staging, clinical N staging and the interval weeks between CRT and surgery were not observed in both of the primary or validation cohort.

3.2 | Feature selection of the radiomic signature

Aggregate 165 features were obtained from T2-weighted images for individuals (both pre-nRT and post-nRT) by IBEX software. In order to incarnate the variations on 165 MRI-based features in the process of concurrent chemoradiotherapy, the analytical data were obtained by subtracting quantitative features of post-nRT from that of pre-nRT. A set of features with corresponding numbers were selected by LASSO and used to calculate the Rad-scores for the pCR model.

λ was chosen by 10-fold cross-validation in the LASSO model, and log(λ) of −2.85 was the optimal subset for seven radiomics features, at which these potential predictors, including GOH-Skewness, GLRLM-Run Length Non-uniformity, ID-Local Entropy Max, ID- Local Range Min, NIDM-Coarseness, maximum 3D diameter, and Surface Area Density, were extracted from 165 radiomic features with nonzero coefficients of the LASSO logistic regression model for the primary cohort (Figure 2). Both Figure 1A,B showed that the number of variables contained into the model was decreased, and the absolute values of the coefficients for the variables also sank toward zero as log(λ) altered from 6 to 0.

The radiomic signature score (Rad-score) was assessed for each patient founded on the seven radiomic features (Supplementary material S1). Waterfall plots showed the

TABLE 1 Characteristics of patients in the primary and validation cohorts

Characteristic	Primary cohort(n = 87)			Validation cohort(n = 44)		
	non-pCR	pCR	*P*	non-pCR	pCR	*P*
Gender			.837			.614
Male	44 (63.77%)	11 (61.11%)		20 (57.14%)	6 (66.67%)	
Female	25 (36.23%)	7 (38.89%)		15 (42.86%)	3 (33.33%)	
Age (y)	51.35 ± 11.49	50.56 ± 10.31	.791	50.49 ± 11.14	56.11 ± 9.49	.173
BMI (kg/m^2)	22.69 ± 3.18	22.19 ± 2.75	.546	21.90 ± 2.92	23.20 ± 2.68	.234
Distance from the anal verge (mm)	40.97 ± 14.33	35.82 ± 9.99	.155	38.49 ± 14.65	39.88 ± 13.13	.797
Pathology type			.989			.210
Well/moderately differentiated	49 (71.01%)	12 (66.67%)		29 (82.86%)	9 (100%)	
Poor differentiated	13 (18.84%)	5 (27.78%)		2 (5.71%)	0 (0.00%)	
Mucinous carcinomas	7 (10.15%)	1 (5.55%)		4 (11.43%)	0 (0.00%)	
Clinical T staging			.508			.090
cT2	8 (11.59%)	3 (16.67%)		3 (8.57%)	1 (11.11%)	
cT3	46 (66.67%)	12 (66.66%)		20 (57.14%)	7 (77.78%)	
cT4	15 (21.74%)	3 (16.67%)		12 (34.29%)	1 (11.11%)	
Clinical N staging			.740			.732
cN0	18 (26.09%)	4 (22.22%)		6 (17.14%)	2 (22.22%)	
cN1	14 (20.29%)	3 (16.67%)		7 (20.00%)	1 (11.11%)	
cN2	37 (53.62%)	11 (61.11%)		22 (62.86%)	6 (66.67%)	
pre-CEA (ng/mL)	3.49 (1.42-11.85)	4.75 (1.92-6.14)	.608	6.77 (2.71-15.46)	0.98 (0.76-1.89)	.000
Chemotherapy regimen			.006			.548
Mono-chemotherapy	61 (88.41%)	11 (61.11%)		28 (80.00%)	8 (88.89%)	
Combined chemotherapy	8 (11.59%)	7 (38.89%)		7 (20.00%)	1 (11.11%)	
Interval to surgery (wk)	7 (6-9.25)	8 (6-11)	.101	9 (5.5-11.5)	9 (7-10)	.988
Rad-score	−1.74 (−2.16 to −1.40)	−0.57 (−1.01 to 0.10)	<.001	−1.77 (−2.20 to −1.21)	−0.55 (−1.23 to −0.10)	<.001

Rad-score for individuals in primary (Figure 3A) and validation cohort (Figure 3B). There was a marked difference of Rad-score between pCR and non-pCR group regardless of the primary ($P < .001$) or validation cohort ($P < .001$). pCR was associated with higher mean value of Rad-score in both the primary and validation cohort (−0.57 and −0.55, respectively) compared to non-pCR group (–1.74 and –1.77, respectively).

3.3 | Performance of the radiomics signature

Variables with differences ($P < .2$) in univariate analysis were selected into the Logistic regression model of multivariate analysis. Rad-score (OR = 23.581; $P < .001$) was identified as independent factors in multivariate logistic regression analysis (Table 2). The value of AUCs was 0.92 (95% CI, 0.86- 0.99) in the primary cohort and 0.87 (95% CI, 0.74-1.00) (Figure 4) in the validation cohort. The calibration curve of the signature was presented in Figure 5, indicating that the model made accurate predictions.

4 | DISCUSSION

Increasing data supported that pCR following nCRT in LARC was linked to prominent enhanced local control, reduced incidence of distant metastasis, and long-term survival compared with non-pCR.[22] With the excellent advantage, it had been prompting nonoperative managements, including a “watch-and-wait” proposal, in selected LARC patients.[5] However, the pCR rate was unsatisfactorily low, hovering at around 20% (range 15%-27%).[22] Our pCR incidence (20.61%) was also within the range. Hence, identifying the predictive factors of pCR played a key role while attempting to improve the pCR, especially in term

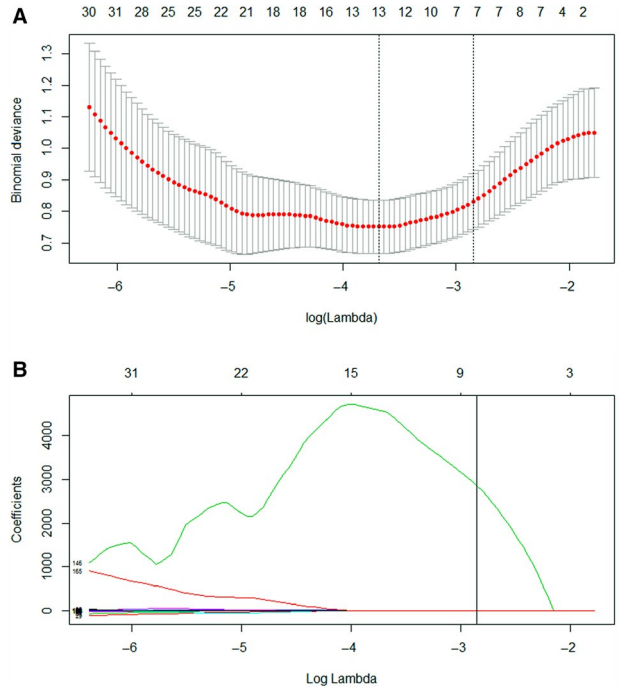


FIGURE 2 Radiomic feature selection using LASSO regression model. A, Optimal feature selection according to AUC value; (B) LASSO coefficient profiles of the 165 radiomic features. Vertical line was drawn at the selected value using 10-fold cross-validation, where optimal λ resulted in 7 nonzero coefficients

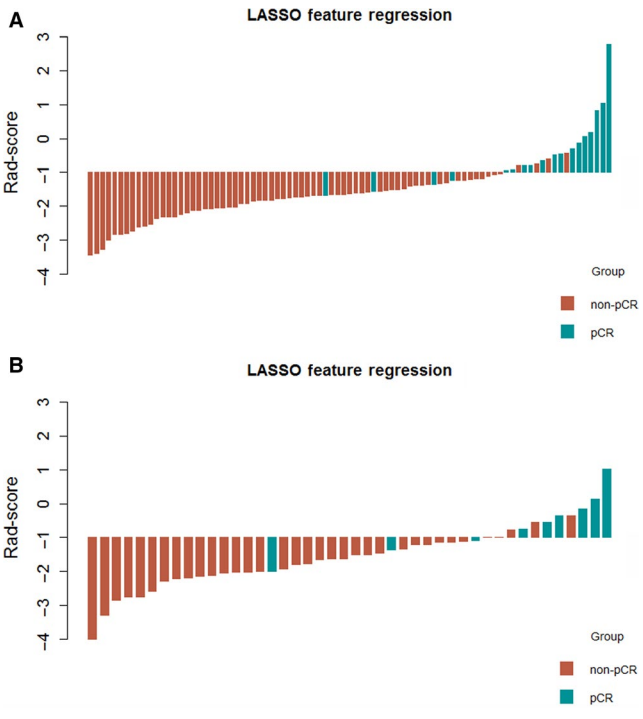


FIGURE 3 Rad-score for patients in (A) the primary cohort and (B) the validation cohort

of averting more invasive treatments. Due to the superiority of effective availability and broad applicability, clinical characteristics were broadly discussed. Although there

TABLE 2 Results of multivariate logistic regression analysis

Characteristic	*β*	Odds ratio (95% CI)	*P*
Intercept	4.861		
Distance from the anal verge (mm)	−0.041	0.959 (0.900-1.023)	.205
Chemotherapy regimen	0.808	2.244 (0.320-15.749)	.416
Interval to surgery (wk)	−0.121	0.886 (0.621-1.624)	.504
Rad-score	3.160	23.581 (4.445-125.090)	<.001

Abbreviations: *β*, regression coefficient; CI, confidence interval.

were few researches showing that clinical characteristics affect pCR after nCRT, some potent clinical predictive factors, especially radiomics, emerges and gain more attentions. Numerous studies indicated that radiomic model can evaluate tumor heterogeneity, and correlate radiological findings with underlying genomic and biological characteristics, including treatment response and prognosis.[6,23] Moreover, the large amount of previous evidences supported the application of advanced MRI-based radiomic features for predict of tumor responses to nCRT in LARC patients.[24,25]

Our study was in general consistent with prior researches. Nie[26] and Cui[27] reported a relatively satisfactory result by using a radiomics method, with AUCs of 0.84 and 0.94 for pCR prediction, respectively. However, there was an obvious predominance in our study compared to their studies. First, we innovatively compared variation on MRI-based features in the process of concurrent chemoradiotherapy, which was a promising guidance in the tumor change and treatment response. All other studies only analyzed preradiotherapy MRI images but ignored postradiotherapy. In fact, the development of functional MRI sequences has enabled us to assess tumor characteristics of post-nCRT MRI.[28] A large prospective trial in the MRI and Rectal Cancer European Equivalence (MERCURY) study revealed that standard morphological MRI (T_2 weighted) had a close association with survival outcomes,[29] indicating the important role of post-nRT MRI assessment of tumor regression grade in prognosis. Second, our radiomic features were acquired from only one sequence, such as the T2-weighted images. The T2-weighted images are commonly used in clinical practice, which is familiar to radiologists. In addition, T2-weighted images are quite stable and can be acquired easily. In contrast, diffusion-weighted images (DWI) are prone to distortion and susceptibility artifacts, causing the inaccuracy of tumor segmentation and data extraction. Similarly, other sequences including T1-weighted dynamic contrast enhanced images depend on the amount and distribution of the injected contrast-enhancing

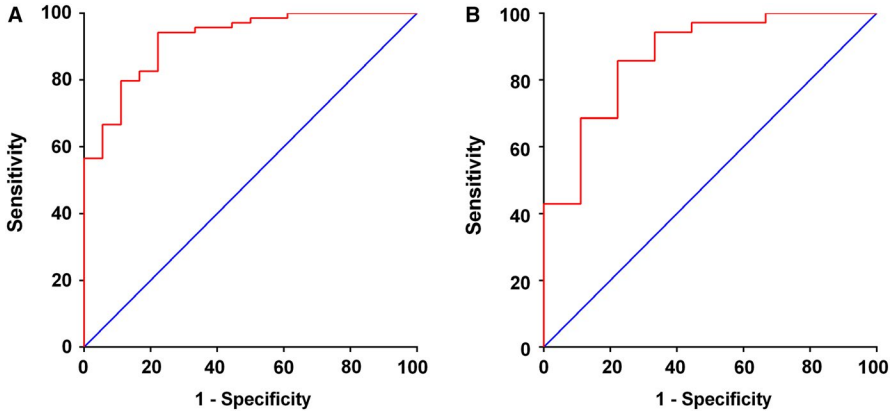


FIGURE 4 Area under the curve (AUC) of MRI-based radiomics model in (A) the primary cohort and (B) the validation cohort

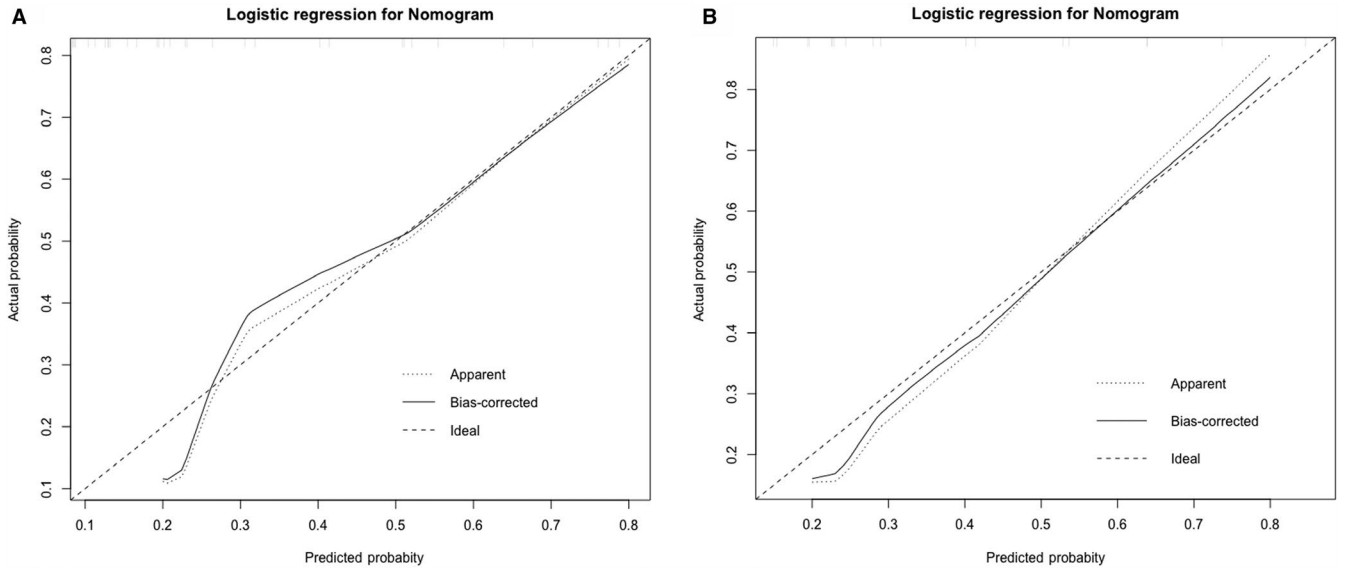


FIGURE 5 Calibration curve showing the predicted vs actual probability for pCR. Calibration curve of radiomics signature in (A) the primary cohort and (B) the validation cohort

agent, which might be influenced by the variable hemodynamic conditions in the patients.

It was already clear that CRC is a heterogeneous disease, and tumor spatial heterogeneity is a critical predictor for prognosis. Image texture analysis is a feasible approach of quantifying heterogeneity.[30] Our study suggested that a creative radiomic signature founded on seven radiomic features was an independent predictor for pCR in LARC after nCRT. Among these seven features, GOH-Skewness, ID-Local Entropy Max, ID- Local Range Min, GLRLM-Run Length Non-uniformity, and NIDM-Coarseness associated with the heterogeneity of tumor.[23,30] GOH-Skewness, ID-Local Entropy Max, and ID-Local Range Min were gained from various histograms of voxel intensities. NIDM-Coarseness is the level of alterations in the intensity of spatial rate. GLRLM-Run Length Non-uniformity assesses the distribution of runs over the run lengths. Radiomics can have objective reflections on both the attenuation and dispersion of gray level intensity through quantitative analysis for MR images, which may be less apparent in direct visual assessment.[31] Although the best way to determine tumor heterogeneity is to detect molecular subtypes using tissue specimens, which taken by colonoscopy are only sufficient for pathological diagnosis. Therefore, MRI-based radiomics analysis helps us to deepen the understanding of CRC disease, improve the diagnosis, and assessment therapy response after nCRT.

As a conventional diagnostic performance, diminutive tumor size was associated with pCR in several studies.[32] Our previous research also reached the same conclusion.[33] However, the value of AUC for tumor size was not ideal[33]—only 0.629 in the previous study. In this study, our radiomics model contained not only an indicator of tumor size—Max 3D Diameter, but also a tumor density indicator—Surface Area Density, whose variation might not be evident on direct visual assessment. Therefore, we believe that our predictive model can improve the accuracy of prediction and ameliorate the applicability in clinic.

Interestingly, our study demonstrated that there was a marked difference about chemotherapy regimen between the pCR and non-pCR groups in the primary ($P = .006$) but not validation ($P = .548$) cohorts. Meanwhile, there was no difference in multivariate logistic regression analysis between combined chemotherapy regimens and mono-chemotherapy in primary cohort ($P = .416$). Therefore, this study believed that the advantage of combined chemotherapy regimen requires further clinical studies to confirm, concerning that only a few studies indicated a higher pCR under the condition of another agent added to 5-FU-based nCRT.[34] Conversely, pCR was associated with pre-CEA level compared with non-pCR groups in the validation ($P < .001$) but not primary ($P = .608$) cohorts. Another study suggested that pre-nCRT CEA levels could be a predictor for prognosis of local tumor control but not for pCR.[35] In fact, both of chemotherapy regimen and pre-nCRT CEA were meaningless in multivariate analysis.

This predictive model in our study can report the sensitivity of neoadjuvant chemoradiation better, which was closely related to survival.[33] Moreover, the predictive model can provide more reliable information on whether patients can achieve pCR, which can be a firm support for patients to perform "watch-and-wait" proposal. Retrospective data with the limited number of patients from single institution may affect the reliability to some extent in our study. Consequently, more prospective randomized trials from various regions are exactly needed to get a better comprehension in promoting the individualized nCRT for LARC.

In conclusion, our study showed a predictive model with radiomic features was promising to predict pCR to neoadjuvant chemoradiation in LARC patients. In addition, our method developing with information from the clinical obtained T2-weighted sequence may be pragmatic as a complement in clinical strategy making.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study was approved by the Medical Ethics Committee of Xiangya Hospital, Central South University with approval no. 2018121147. Patients' informed consent was waived because of the retrospective nature of the study design.

ORCID

Yuqiang Li https://orcid.org/0000-0003-1517-3687
Wenxue Liu https://orcid.org/0000-0003-0569-3064
Chenglong Li https://orcid.org/0000-0002-9054-2836

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supplementary material

I : Definition of radiomics features

We evaluated a total number of 165 MRI radiomics features, all radiomics features were calculated automatically with Imaging Biomarker Explorer Software (IBEX). The 161 features were divided in 7 groups as follows: (1) Shape, (2) Gray Level Cooccurrence Matrix-3D(GLCM-3D), (3) Gray Level Run Length Matrix (GLRLM), (4) Neighborhood Intensity Difference Matrix-3D(NIDM-3D). (5) Intensity Direct (ID), (6) Intensity Histogram (IH), (7) Gradient Orientation Histogram (GOH).

Group 1. Shape[1, 2]

1.Compactness 1 = (Volume)/(sqrt(pi)*(SurfaceArea)^(2/3)

2.Compactness 2 = 36*pi*(Volume^2)/((SurfaceArea)^3)

3.Convex : Measure the proportion of the pixels in the convex hull that are also in the region.

4.Convex Hull Volume: The mean volume of the 2D convex hulls that are the convex envelopes of each slice's binary mask.

5.Convex Hull Volume 3D: 3D volume of the convex hull that is the convex envelope of binary mask.

6.Max 3D Diameter: largest pairwise Euclidean distance between voxels on the surface of the tumor volume.

7.Mean Breadth: Denotes integral of mean curvature

8.Number Of Voxel : The number of voxels treating the edge voxels differently.

9.Orientation: Measures the angle between the x-axis and the major axis of the ellipse in 2D.

10.Roundness: Measures how much the binary mask is close to circle in 2D.

11.Spherical Disproportion $spherical\ disproportion = \frac{A}{4\pi R^2}$

12.Sphericity $sphericity = \frac{\pi^{\frac{1}{3}}(6V)^{\frac{2}{3}}}{A}$

13.Surface Area:The surface area of the binary mask. $A = \sum_{i=1}^{N} \frac{1}{2} | a_i b_i \times a_i c_i |$

14.Surface Area Density = (surface area of the binary mask)/(volume of the binary mask).

15.Volume: The physical volume treating the edge voxels differently.

16. Voxel Size: an important component of image quality. Voxel is the 3-D analog of a pixel. Voxel size is related to both the pixel size and slice thickness.

Group 2.Gray Level Cooccurrence Matrix-3D(GLCM-3D)[1, 3-5]

A GLCM is defined as p (i, j, δ, α), a matrix with size $N_g \times N_g$ describing the second order joint probability function of an image, where the (i, j)th element represents the number of times the combination of intensity levels i and j occur in two pixels in the image, that are separated by a distance of δ pixels in direction α, and N_g is the number of discrete gray level intensities. In our study, distance δ was set to 1 and direction α to each of the 13 directions in three-dimensions.

Each 3D gray level co-occurrence based feature was calculated as the mean of the feature calculations for each of the 13 directions.

Let:

P (i, j) be the co-occurrence matrix for an arbitrary δ and α,

N_g be the number of discrete intensity levels in the image,

μ be the mean of P (i, j),

$p_x(i) = \sum_{j=1}^{N_g} \mathrm{P}\ (i, j)$ be the marginal row probabilities,

$p_y(i) = \sum_{i=1}^{N_g} \mathrm{P}\ (i, j)$ be the marginal column probabilities,

μ_x be the mean of p_x,

μ_y be the mean of p_y,

σ_x be the standard deviation of p_x,

σ_y be the standard deviation of p_y,

$p_{x+y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \mathrm{P}\ (i, j)\ , i + j = k, k = 2,3 \ldots, 2N_g,$

$p_{x-y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \mathrm{P}\ (i, j)\ , |i - j| = k, k = 0,1 \ldots, N_g - 1,$

$\mathrm{HX} = -\sum_{i=1}^{N_g} p_x(i) \log_2[p_x(i)]$ be the entropy of p_x,

$\mathrm{HY} = -\sum_{i=1}^{N_g} p_y(i) \log_2[p_y(i)]$ be the entropy of p_y,

$\mathrm{H} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \mathrm{P}\ (i, j) \log_2[P(i, j)]$ be the entropy of P (i, j),

$\mathrm{HXY1} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \mathrm{P}\ (i, j) \log(p_x(i)\, p_y(j))$

$\mathrm{HXY2} = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p_x(i) p_y(j) \log(p_x(i)\, p_y(j))$

17. Autocorrelation=$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} ijP\ (i, j)$

18. Cluster prominence=$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [i + j - \mu_x(i) - \mu_y(j)]^4\ P\ (i, j)$

19.Cluster shade=$\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [i + j - \mu_x(i) - \mu_y(j)]^3\ P\ (i, j)$

20. Cluster tendency=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}[i+j-\mu_x(i)-\mu_y(j)]^2\,P\,(i,j)$

21. Correlation=$\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_g} ijP\,(i,j)-\mu_i(i)\mu_j(j)}{\sigma_x(i)\sigma_y(j)}$

22. Contrast=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}|i-j|^2P\,(i,j)$

23. Difference entropy=$\sum_{i=0}^{N_g-1}P_{x-y}(i)\log_2[P_{x-Y}(i)]$

24. Dissimilarity=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}|i-j|P\,(i,j)$

25. GLCM Energy=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}[P(i,j)]^2$

26.GLCM Entropy=$-\sum_{i,j}^{Formula} g(i,j)\log_2(i,j)$

27. Homogeneity1=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{P(i,j)}{1+|i-j|}$

28. Homogeneity2=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{P(i,j)}{1+|i-j|^2}$

29. Informational measure of correlation 1(IMC1)=$\frac{HXY-HXY1}{\max\{HX,HY\}}$

30. Informational measure of correlation 2(IMC2)=$\sqrt{1-e^{-2(HXY2-HXY)}}$

31. Inverse difference moment normalized(IDMN)= $\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{P(i,j)}{1+\frac{|i-j|^2}{N^2}}$

32. Inverse difference normalized(IDN)= $\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{P(i,j)}{1+\frac{|i-j|}{N}}$

33. Inverse variance=$\sum_{i=1}^{N_g}\sum_{j=1}^{N_g}\frac{P(i,j)}{|i-j|^2}, i\neq j,$

34. Maximum probability=max{ P (i,j)}

35. Sum average=$\sum_{i=2}^{2N_g}[iP_{x+y}(i)]$

36. Sum entropy=$-\sum_{i=2}^{2N_g}P_{x+y}(i)\log_2[P_{x+y}(i)]$

37. Sum variance=$\sum_{i=2}^{2N_g}(i-SE)^2P_{x+y}(i)$

38.Variance $\sum_i\sum_j(i-\mu)^2p(i,j).$

Group 3. Gray Level Run Length Matrix[6]

Run-Length metrics quantify gray level runs in an image. A gray level run is defined as the length in numbers of pixels, of consecutive that have the same gray level value. In a gray level run-length matrix p (i,j,θ), the (i,j)th element describes the number of times j a gray level i appears consecutively in the direction specified by θ, and N_g is the number of discrete gray level intensities.

Let:

p (i,j,θ) be the (i,j)th entry in the given run-length matrix p for a direction θ,

N_g the number of discrete intensity values in the image,

N_r the number of different run lengths,

N_p the number of voxels in the mage,

39. Short run emphasis(SRE)=$\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\frac{\mathrm{p}\,(i,j,\theta)}{j^2}]}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\mathrm{p}\,(i,j,\theta)]}$

40. Long run emphasis(LRE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} j^2\,\mathrm{p}\,(i,j,\theta)}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)}$

41. Gray level non-uniformity(GLN)= $\frac{\sum_{i=1}^{N_g}[\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)]^2}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)}$

42: Run length non-uniformity(RLN)= $\frac{\sum_{j=1}^{N_r}[\sum_{i=1}^{N_g}\mathrm{p}\,(i,j,\theta)]^2}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)}$

43. Run percentage(RP)= $\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\frac{\mathrm{p}\,(i,j,\theta)}{N_p}$

44. Low gray level run emphasis(LGLRE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\frac{\mathrm{p}\,(i,j,\theta)}{i^2}]}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\mathrm{p}\,(i,j,\theta)]}$

45. High gray level run emphasis(HGLRE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} i^2\,\mathrm{p}\,(i,j,\theta)}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)}$

46. Short run low gray level emphasis(SRLGLE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\frac{\mathrm{p}\,(i,j,\theta)}{i^2 j^2}]}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\mathrm{p}\,(i,j,\theta)]}$

47. Short run high gray level emphasis(SRHGLE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\frac{\mathrm{p}\,(i,j,\theta)i^2}{j^2}]}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\mathrm{p}\,(i,j,\theta)]}$

48. Long run low gray level emphasis(LRLGLE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\frac{\mathrm{p}\,(i,j,\theta)j^2}{i^2}]}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}[\mathrm{p}\,(i,j,\theta)]}$

49. Long run high gray level emphasis(LRHGLE)= $\frac{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r} i^2 j^2\,\mathrm{p}\,(i,j,\theta)}{\sum_{i=1}^{N_g}\sum_{j=1}^{N_r}\mathrm{p}\,(i,j,\theta)}$

Group 4.Neighborhood Intensity Difference Matrix-3D(NIDM-3D)[7]

50.Coarseness

$$f_{\cos}=\left[\epsilon+\sum_{i=0}^{G_h}p_i s(i)\right]^{-1}$$

51.Contrast

$$f_{\mathrm{con}}=\left[\frac{1}{N_g(N_g-1)}\sum_{i=0}^{G_h}\sum_{j=0}^{G_h}p_i p_j(i-j)^2\right]\left[\frac{1}{n^2}\sum_{i=0}^{G_h}s(i)\right]$$

52.Busyness

$$f_{bus} = \left[\sum_{i=0}^{G_h} p_i s(i) \right] \Big/ \left[\sum_{i=0}^{G_h} \sum_{j=0}^{G_h} ip_i - jp_j \right]$$

53.Complexity

$$f_{com} = \sum_{i=0}^{G_h} \sum_{j=0}^{G_h} \left\{ (|i-j|) \Big/ \left(n^2 (p_i + p_j) \right) \right\} \{ p_i s(i) + p_j s(j) \}$$

54.Texture Strength

$$f_{str} = \left[\sum_{i=0}^{G_h} \sum_{j=0}^{G_h} (p_i + p_j)(i-j)^2 \right] \Big/ \left[\epsilon + \sum_{i=0}^{G_h} s(i) \right]$$

Group 5.Intensity Direct(ID)[1]

55.Energy=$\sum_i^N X(i)^2$

56.Energy Norm

57.Global Entropy: The intensity entropy among all the voxels.

58.Global Max:The intensity maximum among all the voxels.

59.Global Mean:The intensity mean among all the voxels.

60.Global Median:The intensity median among all the voxels.

61.Global Min:The intensity minimum among all the voxels.

62.Global Std:The intensity standard deviation among all the voxels.

63.Global Uniformity:The intensity uniformity among all the voxels.

64.Inter-Quartile Range:The interquartile range of the intensity values among all the voxels.

65.Kurtosis:Measure the peakedness of all the voxels' intensity.

66.Local Entropy Max:First, at each voxel, compute entropy in its neighborhood region. Then, compute the maximum among all the voxel's entropy calculated from step 1.

67.Local Entropy Mean:First, at each voxel, compute entropy in its neighborhood region. Then, compute the mean among all the voxel's entropy calculated from step 1.

68.Local Entropy Median:First, at each voxel, compute entropy in its neighborhood region. Then, compute the median among all the voxel's entropy calculated from step 1.

69.Local Entropy Min:First, at each voxel, compute entropy in its neighborhood region. Then, compute the minimum among all the voxel's entropy calculated from step 1.

70.Local Entropy Std:First, at each voxel, compute entropy in its neighborhood region. Then, compute the standard deviation among all the voxel's entropy calculated from step 1.

71.Local Range Max:First, at each voxel, compute range value (Max Value-Min Value) in its neighborhood region. Then, compute the median among all the voxel's range value calculated from step 1.

72.Local Range Mean:First, at each voxel, compute range value (Max Value-Min Value) in its neighborhood region. Then, compute the mean among all the voxel's range value calculated from step 1.
73.Local Range Median:First, at each voxel, compute range value (Max Value-Min Value) in its neighborhood region. Then, compute the median among all the voxel's range value calculated from step 1.
74.Local Range Min:First, at each voxel, compute range value (Max Value-Min Value) in its neighborhood region. Then, compute the minimum among all the voxel's range value calculated from step 1.
75.Local Range Std:First, at each voxel, compute range value (Max Value-Min Value) in its neighborhood region. Then, compute the standard deviation among all the voxel's range value calculated from step 1.
76.Local Std Max:First, at each voxel, compute standard deviation in its neighborhood region. Then, compute the maximum among all the voxel's standard deviation value calculated from step 1.
77.Local Std Mean:First, at each voxel, compute standard deviation in its neighborhood region. Then, compute the mean among all the voxel's standard deviation value calculated from step 1.
78.Local Std Median:First, at each voxel, compute standard deviation in its neighborhood region. Then, compute the median among all the voxel's standard deviation value calculated from step 1.
79.Local Std Min:First, at each voxel, compute standard deviation in its neighborhood region. Then, compute the minimum among all the voxel's standard deviation value calculated from step 1.
80.Local Std Std:First, at each voxel, compute standard deviation in its neighborhood region. Then, compute the standard deviation all the voxel's standard deviation value calculated from step 1.
81.Mean Absolute Deviation:The mean absolute deviation of the intensity values among all the voxels.
82.Median Absolute Deviation:The median absolute deviation of the intensity values among all the voxels.
83-101.Percentile:Percentiles of the intensity values among all the voxels. There were 19 percentiles from Percentile5 to Percentile95 with the interval of 5.

102-106.Quantile:Quantiles of the intensity values among all the voxels. Here, we have 5 quantiles, including Quantile0.025, Quantile0.25, Quantile0.5, Quantile0.75, Quantile0.975.

107.Range:The intensity range (Max Value-Min Value) among all the voxels.

108.Root mean square=$\sqrt{\frac{\sum_i^N X(i)^2}{N}}$

109.Skewness: Measure the asymmetry of all the voxels' intensity.

110. Variance=$\frac{1}{N-1}\sum_{i=1}^{N}(X(i)-\bar{X})^2$

Group 6. Intensity Histogram[1]

111.Inter-Quartile Range:The interquartile range of the occurrence probability values in the histogram.

112.Kurtosis:Measure the peakedness of the occurrence probability values in the histogram.

113.Mean Absolute Deviation:The mean absolute deviation of the occurrence probability values in the histogram.

114.Median Absolute Deviation:The median absolute deviation of the occurrence probability values in the histogram.

115-133.Percentile :Percentiles of the occurrence probability values in the histogram. There were 19 percentiles from Percentile5 to Percentile95 with the interval of 5.

134-152.Percentile Area:Percentiles of values in the accumulative histogram. There were 19 percentile Areas from PercentileArea5 to PercentileArea95 with the interval of 5.

153-157.Quantile:Quantiles of the occurrence probability values in the histogram. Here, we have 5 quantiles, including Quantile0.025, Quantile0.25, Quantile0.5, Quantile0.75, Quantile0.975.

158.Range:Measures the range (Max Value-Min Value) of the occurrence probability values in the histogram.

159.Skewness:Measure the asymmetry of the occurrence probability values in the histogram.

Group 7.Gradient Orientation Histogram(GOH)[8]

160.Inter-Quartile Range:The interquartile range of the occurrence probability values in the histogram.

161.Kurtosis:Measure the peakedness of the occurrence probability values in the histogram.

162.Mean Absolute Deviation:The mean absolute deviation of the occurrence probability values in the histogram.

163.Median Absolute Deviation:The median absolute deviation of the occurrence probability values in the histogram.

164.Range:Measures the range (Max Value-Min Value) of the occurrence probability values in the histogram.

165.Skewness:Measure the asymmetry of the occurrence probability values in the histogram.

Rad-score = – 1.707223965

+ (3.025922752 * GOH-Skewness)

+ (2.555072335 * GLRLM-Run Length Non-uniformity)

+ (0.082640557 * ID-Local Entropy Max)

+ (0.033768506 * ID- Local Range Min)

+ (2850.029899 * NIDM-Coarseness)

–(0.326002518* Max 3D diameter)
+(0.098407946* Surface Area Density)

Probability of pCR = e^x / (1 + e^x), where e is the base of natural logarithms.

I. Programing of Lasso logistic analysis in R

```
library("glmnet")
df <- dataset #this is the required dataset and the first column should be the dependent variable.
x <- as.matrix(df [,-1])
y <- as.factor(df [,1])
cvfit <- cv.glmnet(x,y,family= "binomial")
plot(cvfit)
coef_n <- coef(cvfit, s = "lambda.1se")
coef_n
glmmod <- glmnet(x,y, alpha = 1,family = "binomial")
plot (glmmod, xvar = "lambda")
abline (v = log(cvfit$lambda.1se), lty = 2, lwd = 1)
```

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1.5 Accurate Nomograms with an Excellent Clinical Value for Locally Advanced Rectal Cancer

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Original Article

Accurate nomograms with excellent clinical value for locally advanced rectal cancer

Yuqiang Li[1,2], Da Liu[3], Lilan Zhao[4], Cenap Güngör[2], Xiangping Song[1], Dan Wang[1,2], Wenxue Liu[5,6], Fengbo Tan[1]

[1]Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, Changsha, China; [2]Department of General Visceral and Thoracic Surgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]Shanxi Medical University, Taiyuan, China; [4]Department of Thoracic surgery, Fujian Provincial Hospital, Fuzhou, China; [5]Department of Cardiology, Xiangya Hospital, Central South University, Changsha, China; [6]Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

Contributions: (I) Conception and design: Y Li, W Liu, F Tan; (II) Administrative support: W Liu, F Tan; (III) Provision of study materials or patients: L Zhao; (IV) Collection and assembly of data: Y Li, W Liu, L Zhao; (V) Data analysis and interpretation: Y Li, W Liu, D Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Fengbo Tan, PhD. Department of Gastrointestinal Surgery, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, China. Email: fengbotan@hotmail.com; Wenxue Liu, MD. Department of Cardiology, Xiangya Hospital, Central South University, Changsha, China; Department of Rheumatology, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China. Email: liuwenxue25@yeah.net.

Background: Rectal cancer accounts for approximately 30–50% of colorectal cancer. Despite its widespread use and convenience, the American Joint Committee on Cancer (AJCC) staging system for predicting survival is prone to inaccuracy, even including a survival paradox for locally advanced rectal cancer (LARC). An accurate risk stratification of LARC is essential for proper treatment selection and prognostic evaluation. Therefore, we aimed to create prognostic nomograms for LARC capable of assessing overall survival (OS) and cancer-specific survival (CSS) precisely and intuitively.

Methods: The Surveillance, Epidemiology, and End Results (SEER) database was accessed. All of the significant variables in the multivariate analysis were integrated to build the nomograms.

Results: Data for a total of 23,055 patients with LARC were collected from the SEER database in this study. Based on the multivariate Cox regression analysis, both OS and CSS were significantly associated with 13 variables: age, marital status, race, pathological grade, histological type, T stage, N stage, surgery, radiotherapy, chemotherapy, regional nodes examined (RNE), tumor size, and carcinoembryonic antigen (CEA). These were included in the construction of nomograms for OS and CSS. Time-dependent receiver operating characteristic (ROC) curves, decision curve analysis (DCA), concordance index, and calibration curves demonstrated the discriminative superiority of the nomograms.

Conclusions: The nomograms, which effectively solve the issue of the survival paradox in the AJCC staging system regarding LARC, may act as excellent tools for integrating clinical characteristics and to guiding therapeutic choices for LARC patients.

Keywords: Locally advanced rectal cancer (LARC); overall survival (OS); cancer-specific survival (CSS); nomogram

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Introduction

Rectal cancer accounts for approximately 30–50% of all colorectal cancer cases (1), placing it third as the most common malignancy worldwide (2). With the advances in treatment technology, the survival rates of patients with locally advanced rectal cancer (LARC) have improved significantly over the past few decades (3).

The combination of surgical resection, chemotherapy, and/or radiation therapy is the conventional treatment for LARC (3). Updated surgical equipment and concepts constitute the major advancements in surgical resection technology. Total mesorectal resection (TME) has become the standard surgical procedure for radical resection of rectal cancer (4,5). In addition, the refinement of colorectal cancer surgery is attributed to the application of laparoscopy and robot-assisted laparoscopy (6,7). Chemotherapy for patients with rectal cancer has evolved substantially over the past decades, together with the concept of neoadjuvant therapy, as well as the increased marketing of irinotecan, oxaliplatin, bevacizumab, and cetuximab. The adoption of TME combined with adjuvant oncological treatment for LARC has reduced local recurrence rates and improved long-term survival (8). In particular, advancements in chemotherapy regimens have been the main contributor to the upswing of colorectal cancer survival in the past decades (3).

Patients who have colon and rectal cancers are generally analyzed in the context of statistical homogeneity, despite having different etiologies, anatomy, and treatments (9). Thus, it is necessary to conduct a specific analysis for LARC that is different from colon cancer owing to the apparent distinctions in treatment, the universal involvement of neoadjuvant chemoradiotherapy (nCRT), and the performance of TME in the surgical technique (10,11).

Despite its widespread use and convenience, the American Joint Committee on Cancer (AJCC) staging system for the prediction of survival with this malignancy has proven inaccurate. The AJCC staging has even produced a survival paradox for LARC, in that those patients with T3-4N– were found to develop worse survival outcomes than those with T1-2N+ (12-14). A precise risk stratification of LARC is imperative for proper treatment selection and prognostic evaluation. As a visible representation of a mathematical model, a nomogram can not only integrate certain features together to estimate specific endpoints, but also provide pragmatic and comprehensive prediction for clinical practice. Meanwhile, national databases, such as the Surveillance, Epidemiology, and End Results (SEER) database, can provide the available clinical factors and ample patient data to build a reliable statistical model for the prediction of survival.

Therefore, we aimed to create SEER-based prognostic nomograms for patients with LARC based that could accurately and conveniently assess overall survival (OS) and cancer-specific survival (CSS). We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-4144).

Methods

Data collection

Data in this retrospective analysis were extracted from the SEER Linked database. The SEER Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States that is updated annually. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval from the ethical board for this study was not required because of the public nature of all the data. Patients' informed consent was waived because of the retrospective nature of the study design.

Patient screening

The target population was limited to patients with stage II and III (T34 and/or N+) rectal adenocarcinoma [International Classification of Diseases for Oncology 3rd edition (ICD-O-3): 8,140, 8,144, 8,210, 8,211, 8,213, 8,245, 8,255, 8,260, 8,261, 8,262, 8,263, 8,310, 8,323, 8,480, 8,481, 8,490], resulting in a total of 23,444 patients. The exclusion criteria were as follows: diagnosed at autopsy or death certificate (n=11); survival months 0 (n=209); lack of positive histology (n=34); and T0 and Tx according to the 6th edition AJCC staging (n=135). The final study sample contained 23,055 patients (*Figure 1*).

Patients were chosen from the period between 2004 and 2011, since the follow-up time of who after 2011 was less than 5 years. The cutoff for follow-up was December 31, 2016. The endpoints of this study were OS and CSS. The median follow-up was estimated as the median observed survival time. OS was computed from the time of diagnosis to the time of death due to any cause or the time of last follow-up for patients still alive. CSS was computed as the time of diagnosis to the time of death attributed to rectal cancer or survival at last follow-up. The OS and CSS curves

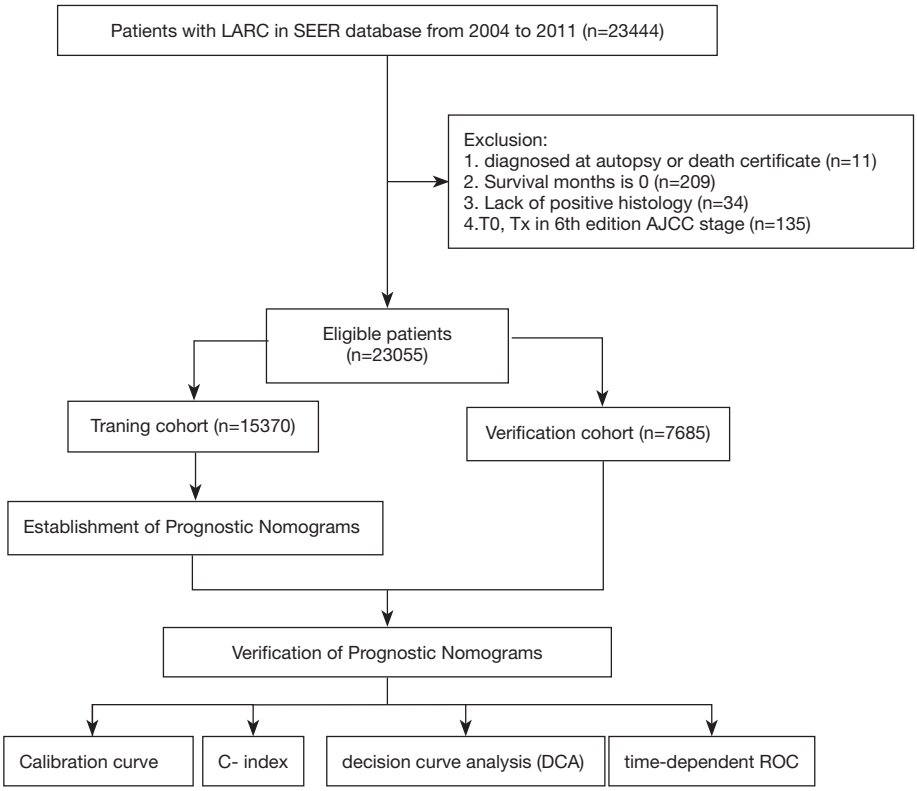

Figure 1 The workflow of the establishment of nomograms to predict OS and CSS of patients with LARC. OS, overall survival; CSS, cancer-specific survival; LARC, locally advanced rectal cancer.

were evaluated by the Kaplan–Meier method and compared by the log-rank test. For each patient, the following data were acquired: age at diagnosis, marital status, gender, race, tumor size, grade, histological type, T stage, N stage, regional nodes examined (RNE), carcinoembryonic antigen (CEA), surgery, radiotherapy, and chemotherapy. All patients were randomly separated into 2 groups (training group, n=15,370 and validation group, n=7,685).

Construction and validation of the nomogram

Univariate and multivariate Cox regression analyses were applied to calculate the weight of variables in OS and CSS, as presented with odds ratio (OR), and were used to identify independent risk factors. The variables with significant differences in the univariate analysis were included in the Cox regression model for multivariate analysis. All of the significant variables in the multivariate analysis were integrated to build the nomograms for OS and CSS. The probabilities could be estimated for 2-, 3-, and 5-year OS and CSS after summing the scores related to each variable and casting total scores to the bottom scale. The total points in each case of the 2 survival groups were calculated using the established nomograms to verify the effect. The calibration curves were used to demonstrate the reliability of the nomograms. The distinguishing ability of the nomogram was evaluated by concordance index (C-index) and receiver operating characteristic (ROC) curve analysis. Decision curve analysis (DCA) was carried out to compare the latent profit of the prognostic nomograms.

Statistical analysis

The OR and a 95% confidence interval (CI) were evaluated by univariate and multivariate Cox regression analysis. Variables with significant differences in the univariate analysis were included in the Cox regression model for multivariate analysis. Missing data were marked as NOS (not otherwise specified) for analysis. R software (version 3.6.1, http://www.r-project.org) was used to build the nomograms, plot the calibration curves, Sankey diagrams, ROC curves, and DCA curves, and to calculate the C-index.

The survival curves were drawn by GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA). The univariate and multivariate Cox regression models were performed with IBM SPSS statistics trial ver. 22.0 (IBM, Armonk, NY, USA). All reported P values <0.05 were considered significant.

Results

Patient characteristics

A total of 389 patients with rectal cancer were not included in the final study [diagnosed at autopsy or death certificate (n=11); survival months 0 (n=209); lack of positive histology (n=34); T0 and Tx according to the 6th edition AJCC staging (n=135)] (*Figure 1*). Eventually, data for 23,055 eligible patients with LARC were collected from the SEER database in this study. The characteristics of the patients are summarized in *Table 1*. More than half of the patients were male (59.97%), of whom 68.80% had moderately differentiated adenocarcinoma. The patients with mucinous cell carcinoma (MCC) or signet ring cell carcinoma (SRCC) accounted for 8.55% of the total population. The majority of LARCs were smaller than 5 cm in size (57.41%), and the proportion of patients with increased levels of CEA reached 26.54% in this study. The median OS and CSS were 69 and 72 months, respectively.

In addition, 10.25% of patients with LARC did not undergo surgical resection, 25.65% did not undergo radiotherapy, and 22.95% did not undergo chemotherapy. As an important indicator of surgical quality in the SEER database (3), RNE >12 was only present in 50.50% of patients in this study.

Establishment of prognostic nomograms

Univariate and multivariate Cox regression analyses were applied to calculate the weight of variables in OS and CSS (presented as OR) and were used to identify independent risk factors.

The variables with significant differences in the univariate analysis were included in the Cox regression model for multivariate analysis, where both OS and CSS were significantly associated with 13 variables, namely, age, marital status, race, pathological grade, histological type, T stage, N stage, surgery, radiotherapy, chemotherapy, RNE, tumor size, and CEA (*Tables 2,3*).

All of the significant variables were integrated to build the nomograms for OS and CSS. The prognostic nomogram for 2-, 3-, and 5-year OS is shown in *Figure 2*, and the nomogram for 2-, 3-, and 5-year CSS is shown in *Figure 3*. The probabilities could be estimated for 2-, 3-, and 5-year OS and CSS after summing the scores related to each variable and casting total scores to the bottom scale.

Validation of prognostic nomograms

Various methods have been used to demonstrate the superiority of nomograms, including C-index, time-dependent ROC curves, DCA, and calibration curves. C-indices were used to comprehensively assess the discriminatory power of the predictive models in this study. The nomograms obtained a superior C-index compared with the AJCC staging system [OS: 0.718 (95% CI, 0.712–0.723) *vs.* 0.597 (95% CI, 0.588–0.605) in the training cohort; 0.712 (95% CI, 0.704–0.720) *vs.* 0.579 (95% CI, 0.567–0.591) in the validation cohort; CSS: 0.718 (95% CI, 0.710–0.725) *vs.* 0.646 (95% CI, 0.635–0.656) in the training cohort; 0.711 (95% CI, 0.700–0.722) *vs.* 0.625 (95% CI, 0.610–0.640) in the validation cohort] (*Table 4*).

The sensitivity and specificity of predicting the prognosis of LARC were identified by time-dependent ROC curves. *Figure 2B,C* illustrates the 2-, 3-, and 5-year values of the area under the curve (AUC) regarding the nomogram for OS (training group: 2-year OS 79.51%; 3-year OS 78.33%; 5-year OS 76.20%; validation group: 2-year OS 78.73%; 3-year OS 77.35%; 5-year OS 75.43%). The AUC values of the nomogram predicting CSS are displayed in *Figure 3B,C* (training group: 2-year CSS 80.26%; 3-year CSS 78.66%; 5-year CSS 75.82%; validation group: 2-year CSS 79.97%; 3-year CSS 77.98%; 5-year CSS 74.72%).

In addition, the calibration curves demonstrated a high degree of reliability of the nomograms in this study owing to the minor deviations from the reference line (*Figure 2D,E* for OS; *Figure 3D,E* for CSS). DCA is able to identify predictive models that help clinicians make better decisions (15). The DCA curves for the novel nomograms and each predictor are presented in *Figure 2F,G* for OS and *Figure 3F,G* for CSS. The superior net benefits revealed that the nomograms in this study showed more pinpoint values than individual predictors in clinical application.

Risk stratification

X-tile software (version 3.6.1; Yale University, New Haven, CT, USA) was used to calculate the cutoff values

Table 1 Characteristics of patients with LARC in the training and validation group

Characteristics	Total (n=23,055)		Training group (n=15,370)		Validation group (n=7,685)	
	N	%	N	%	N	%
Gender						
Female	9,229	40.03	6,138	39.93	3,091	40.22
Male	13,826	59.97	9,232	60.07	4,594	59.78
Age (years)						
≤60	9,650	41.86	6,403	41.66	3,247	42.25
61–70	5,710	24.77	3,839	24.98	1,871	24.35
>70	7,695	33.38	5,128	33.36	2,567	33.40
Marital status						
Married	13,269	57.55	8,845	57.55	4,424	57.57
Unmarried/NOS	9,786	42.45	6,525	42.45	3,261	42.43
Race						
White	18,811	81.59	12,534	81.55	6,277	81.68
Black	1,961	8.51	1,325	8.62	636	8.28
Other/NOS	2,283	9.90	1,511	9.83	772	10.05
Pathological grade						
I	1,398	6.06	947	6.16	451	5.87
II	15,861	68.80	10,570	68.77	5,291	68.85
III	3,452	14.97	2,303	14.98	1,149	14.95
IV	281	1.22	179	1.16	102	1.33
Unknown	2,063	8.95	1,371	8.92	692	9.00
Histologic type						
Adenocarcinomas	21,083	91.45	14,073	91.56	7,010	91.22
MCC/SRCC	1,972	8.55	1,297	8.44	675	8.78
T stage						
T1	772	3.35	504	3.28	268	3.49
T2	1,768	7.67	1,161	7.55	607	7.90
T3	18,184	78.87	12,114	78.82	6,070	78.99
T4	2,331	10.11	1,591	10.35	740	9.63
N stage						
N0	10,506	45.57	6,965	45.32	3,541	46.08
N1	8,903	38.62	5,941	38.65	2,962	38.54
N2	3,646	15.81	2,464	16.03	1,182	15.38
Surgery						
Yes	20,693	89.75	13,788	89.71	6,905	89.85

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=23,055)		Training group (n=15,370)		Validation group (n=7,685)	
	N	%	N	%	N	%
No	2,362	10.25	1,582	10.29	780	10.15
Radiotherapy						
Neoradiotherapy	11,002	47.72	7,338	47.74	3,664	47.68
Radiotherapy*	6,139	26.63	4,102	26.69	2,037	26.51
No/unknown	5,914	25.65	3,930	25.57	1,984	25.82
Chemotherapy						
Yes	17,763	77.05	11,866	77.20	5,897	76.73
No/Unknown	5,292	22.95	3,504	22.80	1,788	23.27
RNE						
<3	4,290	18.61	2,848	18.53	1,442	18.76
3–5	1,697	7.36	1,116	7.26	581	7.56
6–8	2,375	10.30	1,579	10.27	796	10.36
9–11	2,799	12.14	1,831	11.91	968	12.60
≥12	11,642	50.50	7,832	50.96	3,810	49.58
NOS	252	1.09	164	1.07	88	1.15
Tumor size (cm)						
≤5	13,237	57.41	8,752	56.94	4,485	58.36
5–10	5,176	22.45	3,498	22.76	1,678	21.83
>10	338	1.47	243	1.58	95	1.24
NOS	4,304	18.67	2,877	18.72	1,427	18.57
CEA						
Negative	7,813	33.89	5,191	33.77	2,622	34.12
Positive	6,119	26.54	4,149	26.99	1,970	25.63
NOS	9,123	39.57	6,030	39.23	3,093	40.25
OS (months)	69 (33 to 101)		69 (33 to 100)		69 (33 to 102)	
CSS (months)	72 (37 to 104)		72 (37 to 103)		72 (37 to 105)	

*, not neoadjuvant. MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, regional nodes examined; NOS, not otherwise specified.

concerning the total scores of LARC patients by summing the ones related to each variable. The cutoff values were 181 and 307 for OS, and 172 and 263 for CSS (*Figure 4*). Therefore, LARC patients were classified as high risk (score >307), moderate risk (181< score ≤ 307), and low risk (score ≤181) for OS. In addition, patients with LARC were classified as high risk (score >263), moderate risk (172 < score ≤263), and low risk (score ≤172) for CSS. Although it is widely used to evaluate the prognosis of various tumors, the AJCC staging system produces a survival paradox for LARC, in that rectal cancer patients with T3–4N0 (stage II) showed worse survival compared to patients with T1–2N+ (stage III) (*Figure 5; Figure 5A* for OS and *Figure 5E* for CSS). *Figure 5B,F* show the correspondence between

Table 2 Univariable and multivariable Cox regression model analyses of OS for nomogram

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Gender			0.373			
Female		Reference	1		NA	
Male	1.021	0.976–1.068	0.373			
Age (years)			<0.001			<0.001
≤60		Reference	1		Reference	1
61–70	1.410	1.327–1.499	<0.001	1.366	1.284–1.452	<0.001
>70	3.011	2.859–3.171	<0.001	2.565	2.427–2.710	<0.001
Marital status			<0.001			<0.001
Married		Reference	1		Reference	1
Unmarried/NOS	1.478	1.414–1.544	<0.001	1.203	1.150–1.258	<0.001
Race			<0.001			<0.001
White		Reference	1		Reference	1
Black	1.264	1.174–1.361	<0.001	1.256	1.165–1.354	<0.001
Other/NOS	0.869	0.804–0.940	<0.001	0.904	0.836–0.977	0.011
Pathological grade			<0.001			<0.001
I		Reference	1		Reference	1
II	0.998	0.909–1.096	0.970	1.024	0.932–1.125	0.622
III	1.412	1.273–1.567	<0.001	1.338	1.204–1.486	<0.001
IV	1.709	1.398–2.087	<0.001	1.471	1.203–1.799	<0.001
Unknown	1.149	1.023–1.291	0.019	1.007	0.896–1.132	0.907
Histological type			<0.001			<0.001
Adenocarcinomas		Reference	1		Reference	1
MCC/SRCC	1.344	1.249–1.445	<0.001	1.262	1.171–1.359	<0.001
T stage			<0.001			<0.001
T1		Reference	1		Reference	1
T2	1.024	0.866–1.211	0.781	1.015	0.857–1.201	0.864
T3	1.481	1.284–1.709	<0.001	1.482	1.280–1.717	<0.001
T4	2.786	2.391–3.246	<0.001	2.469	2.109–2.890	<0.001
N stage			<0.001			<0.001
N0		Reference	1		Reference	1
N1	0.924	0.880–0.971	0.002	1.262	1.197–1.330	<0.001
N2	1.430	1.348–1.518	<0.001	2.035	1.908–2.172	<0.001
Surgery			<0.001			<0.001
Yes		Reference	1		Reference	1

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
No	2.938	2.764–3.122	<0.001	2.024	1.839–2.227	<0.001
Radiotherapy			<0.001			<0.001
Neoradiotherapy		Reference	1		Reference	1
Radiotherapy*	1.577	1.495–1.664	<0.001	1.043	0.979–1.111	0.194
No/Unknown	2.046	1.942–2.157	<0.001	1.220	1.132–1.315	<0.001
Chemotherapy			<0.001			<0.001
Yes		Reference	1		Reference	1
No/Unknown	2.030	1.936–2.129	<0.001	1.448	1.351–1.551	<0.001
RNE			<0.001			<0.001
<3		Reference	1		Reference	1
3–5	0.556	0.508–0.610	<0.001	0.856	0.771–0.951	0.004
6–8	0.541	0.498–0.586	<0.001	0.794	0.721–0.875	<0.001
9–11	0.503	0.465–0.544	<0.001	0.730	0.663–0.803	<0.001
≥12	0.473	0.448–0.500	<0.001	0.651	0.601–0.705	<0.001
NOS	0.738	0.604–0.903	0.003	0.965	0.786–1.183	0.730
Tumor size (cm)			<0.001			<0.001
≤5		Reference	1		Reference	1
5–10	1.281	1.214–1.351	<0.001	1.113	1.053–1.175	<0.001
>10	1.561	1.323–1.840	<0.001	1.360	1.152–1.606	<0.001
NOS	1.158	1.092–1.227	<0.001	1.051	0.988–1.117	0.117
CEA			<0.001			<0.001
Negative		Reference	1		Reference	1
Positive	1.543	1.457–1.633	<0.001	1.354	1.278–1.435	<0.001
NOS	1.341	1.271–1.414	<0.001	1.215	1.151–1.282	<0.001

*, not neoadjuvant. MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, regional nodes examined; NOS, not otherwise specified, NA, Unavailable.

AJCC stage and the risk stratification in this study. The risk stratification effectively avoided the survival paradox in this study. The low-risk group had the highest 5-year CSS rate of 84.71% and a 5-year OS rate of 79.71%, followed by the moderate-risk group (61.06% for CSS and 50.78% for OS), and the high-risk group (30.05% for CSS and 17.86% for OS) in the training cohort (*Figure 5C,G*). The validation group confirmed the results of the low-risk group having the highest 5-year OS (78.17%) and CSS (83.48%) rate, followed by the moderate-risk group (51.09% for OS and 62.25% for CSS), and the high-risk group (17.58% for OS and 28.26% for CSS) (*Figure 5D,H*).

Discussion

Numerous studies have reported that the AJCC staging system's ability to predict survival is insufficiently inaccurate for the medical demands of rectal cancer (16-18), especially for LARC. In order to develop a precise scoring system with clinical value, nomograms that could evaluate OS and

Table 3 Univariable and multivariable Cox regression model analyses of CSS for nomogram

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
Gender			0.486			
Female		Reference	1		NA	
Male	0.979	0.921–1.040	0.486			
Age (years)			<0.001			<0.001
≤60		Reference	1		Reference	1
61–70	1.115	1.032–1.204	0.006	1.119	1.035–1.209	0.005
>70	2.008	1.876–2.150	<0.001	1.840	1.712–1.979	<0.001
Marital status			<0.001			<0.001
Married		Reference	1		Reference	1
Unmarried/NOS	1.498	1.412–1.590	<0.001	1.247	1.173–1.326	<0.001
Race			<0.001			<0.001
White		Reference	1		Reference	1
Black	1.421	1.291–1.564	<0.001	1.322	1.199–1.457	<0.001
Other/NOS	0.926	0.836–1.025	0.137	0.925	0.835–1.024	0.134
Pathological grade			<0.001			<0.001
I		Reference	1		Reference	1
II	1.075	0.941–1.227	0.285	1.078	0.944–1.231	0.269
III	1.696	1.468–1.960	<0.001	1.519	1.313–1.758	<0.001
IV	1.997	1.520–2.624	<0.001	1.594	1.211–2.098	0.001
Unknown	1.352	1.153–1.586	<0.001	1.042	0.887–1.225	0.615
Histological type			<0.001			<0.001
Adenocarcinomas		Reference	1		Reference	1
MCC/SRCC	1.535	1.396–1.689	<0.001	1.410	1.279–1.555	<0.001
T stage			<0.001			<0.001
T1		Reference	1		Reference	1
T2	0.936	0.741–1.181	0.576	0.925	0.732–1.169	0.514
T3	1.472	1.210–1.791	<0.001	1.561	1.277–1.907	<0.001
T4	3.344	2.720–4.110	<0.001	2.898	2.343–3.586	<0.001
N stage			<0.001			<0.001
N0		Reference	1		Reference	1
N1	1.147	1.072–1.228	<0.001	1.505	1.401–1.616	<0.001
N2	2.001	1.851–2.164	<0.001	2.717	2.496–2.957	<0.001
Surgery			<0.001			<0.001
Yes		Reference	1		Reference	1

Table 3 (*continued*)

Table 3 (*continued*)

Characteristics	Univariable analysis			Multivariable analysis		
	OR	95% CI	P	OR	95% CI	P
No	3.295	3.044–3.567	<0.001	2.221	1.947–2.533	<0.001
Radiotherapy			<0.001			0.003
Neoradiotherapy		Reference	1		Reference	1
Radiotherapy*	1.534	1.431–1.644	<0.001	0.994	0.914–1.081	0.891
No/Unknown	1.638	1.519–1.765	<0.001	1.178	1.062–1.306	0.002
Chemotherapy			<0.001			<0.001
Yes		Reference	1		Reference	1
No/Unknown	1.553	1.447–1.667	<0.001	1.293	1.172–1.427	<0.001
RNE			<0.001			<0.001
<3		Reference	1		Reference	1
3–5	0.504	0.444–0.572	<0.001	0.800	0.690–0.928	0.003
6–8	0.485	0.434–0.542	<0.001	0.728	0.635–0.833	<0.001
9–11	0.463	0.416–0.515	<0.001	0.662	0.579–0.756	<0.001
≥12	0.441	0.410–0.475	<0.001	0.589	0.527–0.657	<0.001
NOS	0.710	0.546–0.925	0.011	0.864	0.660–1.131	0.288
Tumor size (cm)			<0.001			.001
≤5		Reference	1		Reference	1
5–10	1.341	1.248–1.441	<0.001	1.114	1.035–1.200	0.004
>10	1.925	1.569–2.361	<0.001	1.407	1.144–1.730	0.001
NOS	1.282	1.187–1.385	<0.001	1.088	1.002–1.180	0.043
CEA			<0.001			<0.001
Negative		Reference	1		Reference	1
Positive	1.702	1.577–1.836	<0.001	1.450	1.342–1.566	<0.001
NOS	1.336	1.242–1.438	<0.001	1.251	1.162–1.346	<0.001

*, not neoadjuvant. MCC, mucinous cell carcinoma; SRCC, signet ring cell carcinoma; RNE, Regional nodes examined; NOS, Not otherwise specified, NA, Unavailable.

CSS in patients with LARC were constructed and examined based on a large population from the SEER database. The nomograms not only incorporated pathological variables but also therapeutic and demographic ones, and can therefore provide comprehensive guidance for clinical practice.

The positive status of regional lymph nodes, without the intervention of T stage, is classified as stage III in the AJCC staging system. However, those patients with T34N– developed worse survival outcomes than T1–2N+ (12-14), which was consistent with our study. Increasing research has focused on the survival paradox in the AJCC staging system, suggesting that the T stage has more influence than the N stage on survival in rectal cancer (19), which was further demonstrated by the nomograms of OS and CSS in our study. The poor predictive performance of the AJCC staging system for LARC has spurred clinicians to seek a new method of risk stratification that would effectively avoid the survival paradox.

Currently, (nCRT) is recommended for patients with LARC (20). Consequently, numerous studies have actively

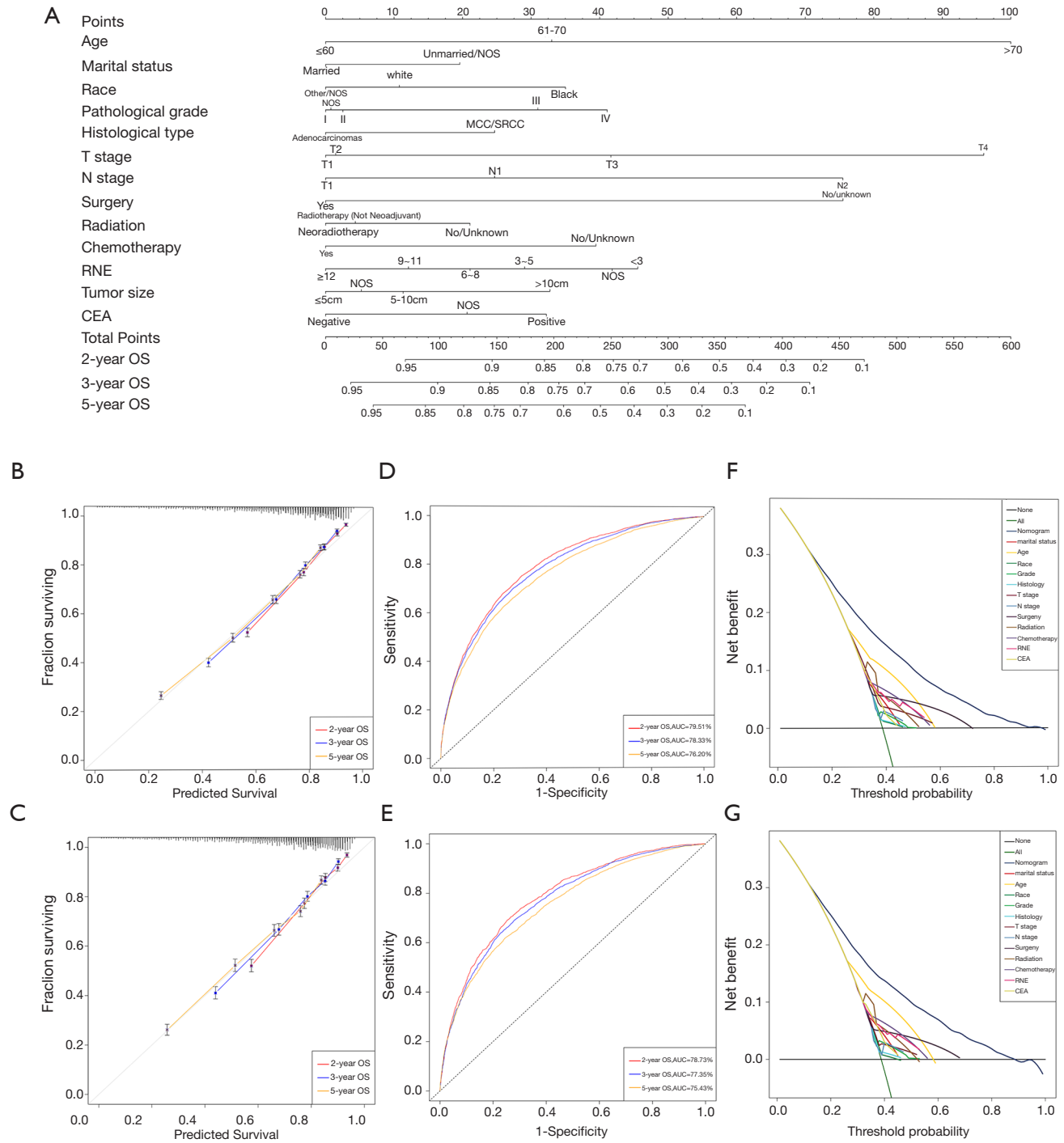

Figure 2 Development and validation of the nomogram predicting OS. (A) The nomogram predicting OS for patients with locally advanced rectal cancer (LARC). (B) The calibration curves predicting OS in the training group. (C) The calibration curves predicting OS in the validation group. (D) The time-dependent ROC curves of the nomogram predicting OS in the training group. (E) The time-dependent ROC curves of the nomogram predicting OS in the validation group. (F) The decision curve analysis of the nomogram and all prognostic factors for OS in the training cohort. (G) The decision curve analysis of the nomogram and all prognostic factors for OS in the validation group. ROC, receiver operating characteristic; OS, overall survival; LARC, locally advanced rectal cancer.

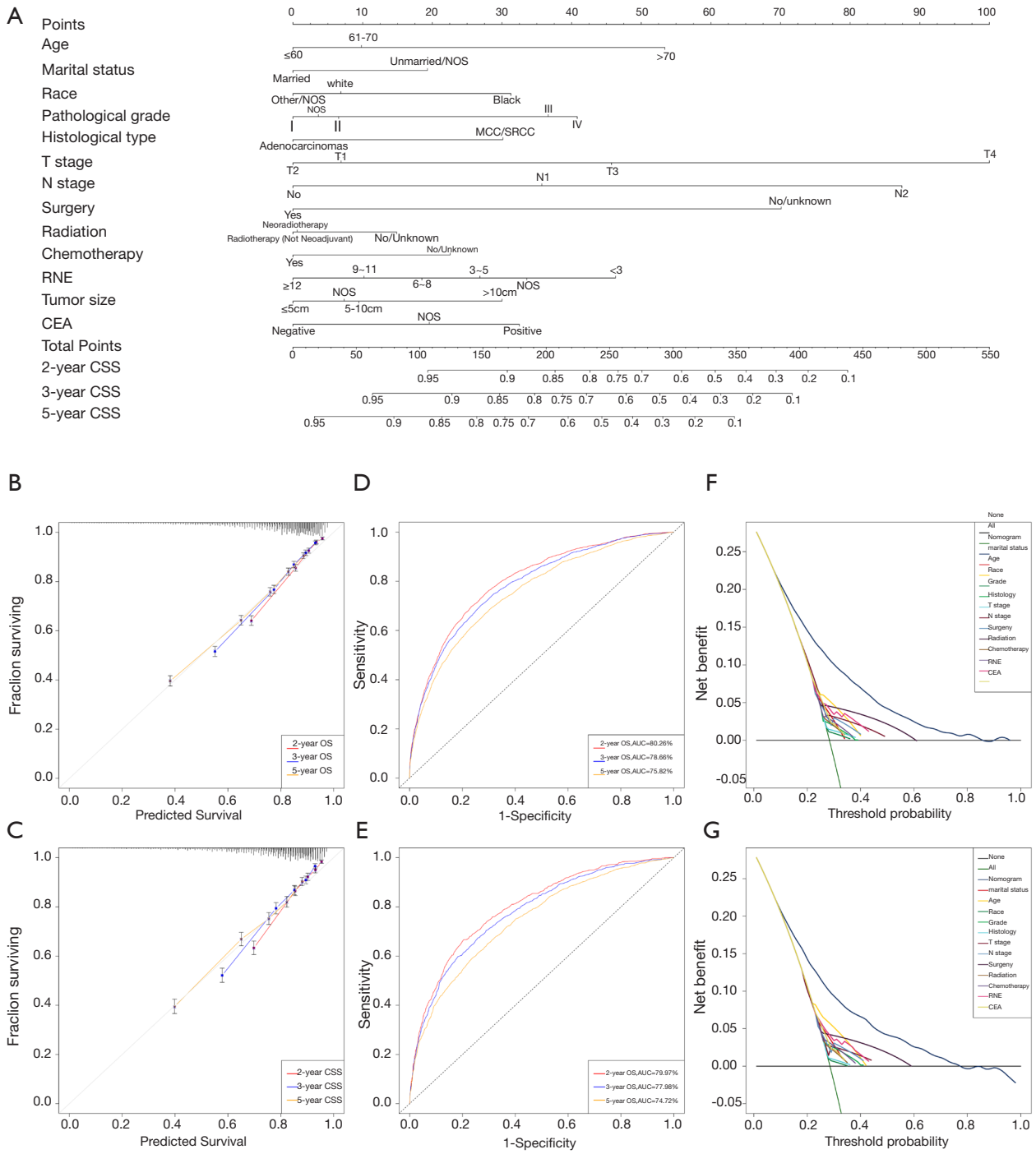

Figure 3 Development and validation of the nomogram predicting CSS. (A) The nomogram predicting CSS for patients with LARC. (B) The calibration curves predicting CSS in the training group. (C) The calibration curves predicting CSS in the validation group. (D) The time-dependent receiver operating characteristic (ROC) curves of the nomogram predicting CSS in the training group. (E) The time-dependent ROC curves of the nomogram predicting CSS in the validation group. (F) The decision curve analysis of the nomogram and all prognostic factors for CSS in the training cohort. (G) The decision curve analysis of the nomogram and all prognostic factors for CSS in the validation group. CSS, cancer-specific survival; LARC, locally advanced rectal cancer.

Table 4 The C-indices for predictions of OS and CSS

	OS		CSS	
	C-index	95% CI	C-index	95% CI
Training group-Nomogram	0.718	0.712–0.723	0.718	0.710–0.725
Training group-AJCC stage	0.597	0.588–0.605	0.646	0.635–0.656
Validation group-Nomogram	0.712	0.704–0.720	0.711	0.700–0.722
Validation group-AJCC stage	0.579	0.567–0.591	0.625	0.610–0.640

OS, overall survival; CSS, cancer-specific survival; C-index, index of concordance; CI, confidence interval.

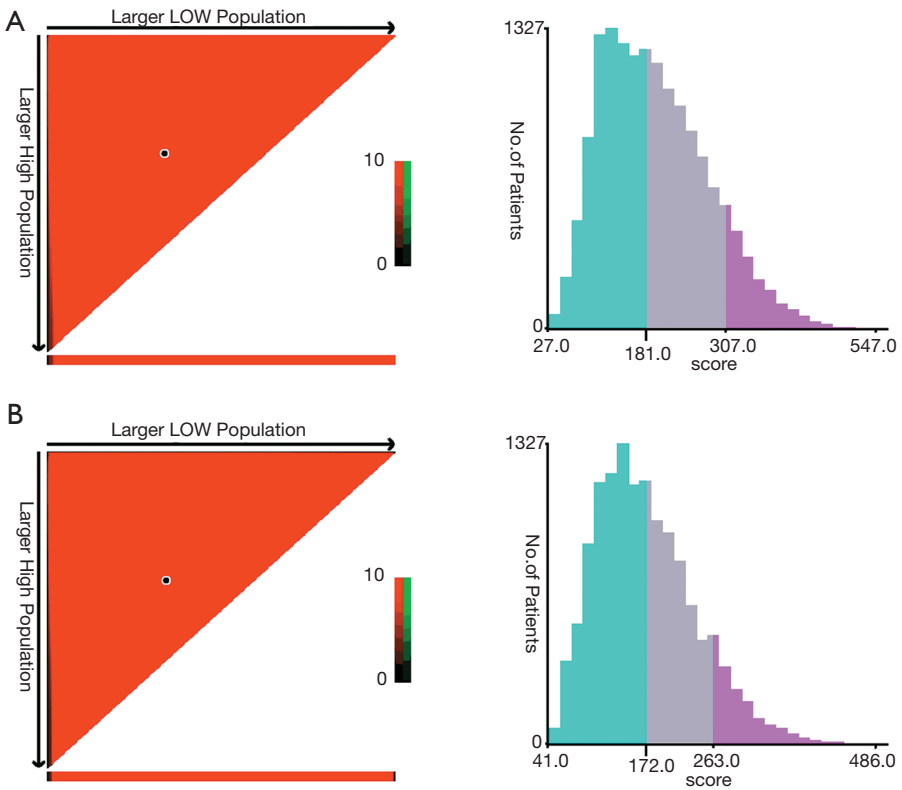

Figure 4 The cutoff values were calculated by using X-tile based on the total scores of patients summing the ones related to each variable. (A) The cutoff values were 181 and 307 for OS. (B) The cutoff values were 172 and 263 for CSS. OS, overall survival; CSS, cancer-specific survival.

explored the positive response of LARC to nCRT (21-23). However, our study did not find that neoadjuvant radiotherapy (nRT) conferred significantly superior survival to other radiotherapy regimens (OS: P=0.194; CSS: P=0.891). It is well-established that nRT can be conducive to sphincter preservation for low rectal cancer. Nevertheless, nRT may be abandoned in patients with mid-high rectal cancer without the issue of sphincter preservation, due to increased surgical complications after nRT. In addition, the intuitive nomograms, which showed noteworthy survival benefits from surgery, chemotherapy, and radiotherapy, support the active treatment of LARC. Furthermore, RNE has been utilized to measure the quality of surgery in other research (3) and is a major factor in the nomograms, which can remind surgeons of the importance of regional lymph node dissection.

The effect of tumor size on survival has long been

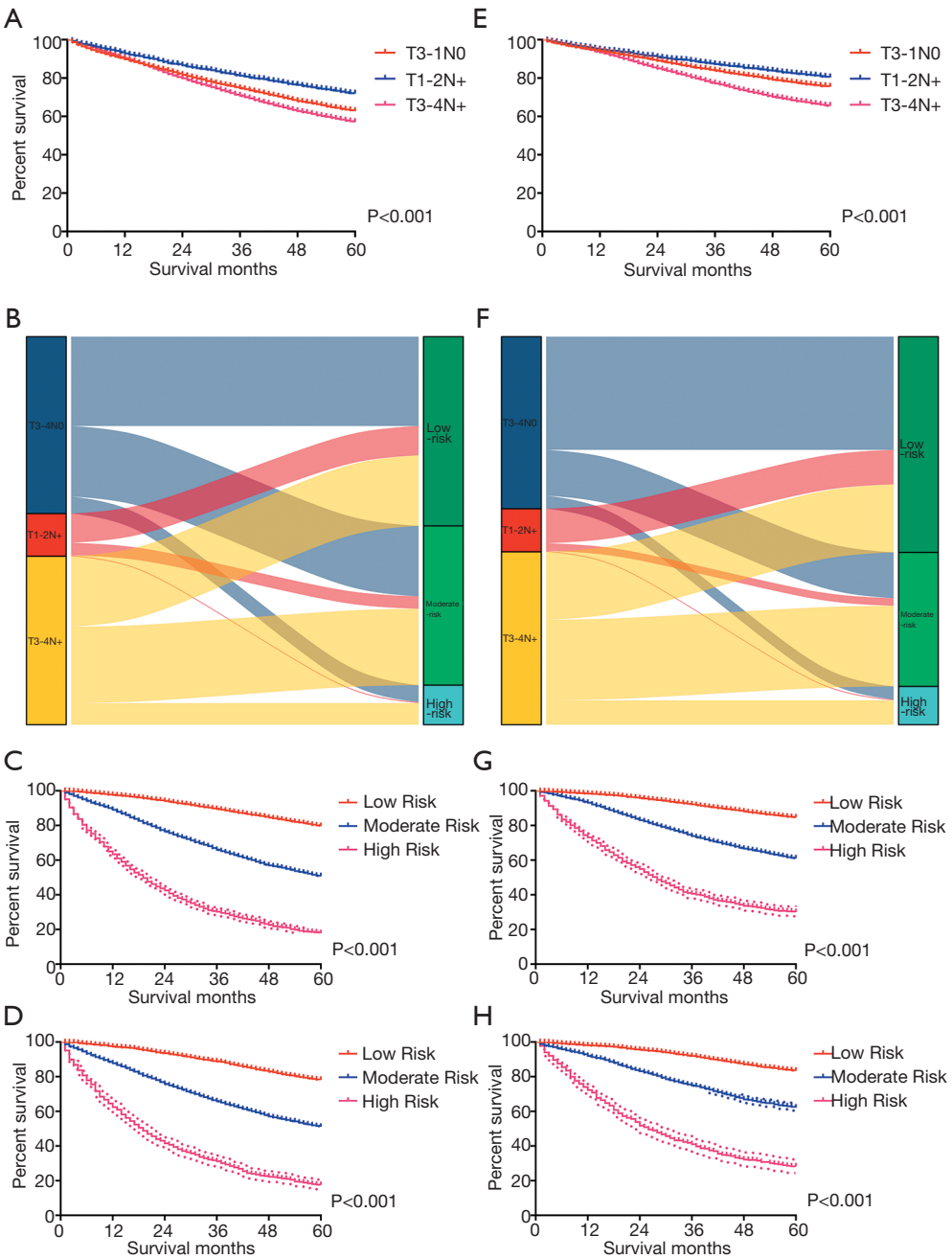

Figure 5 Performance of the nomograms in stratifying on the basis of risk points. (A) The difference in OS among T3–4N0, T1–2N+, and T3–4N+ patients. (B) The correspondence between the AJCC stage and the risk stratification based on the nomogram predicting OS. (C) OS in the subgroups according to the risk stratification in the training cohort. (D) OS in the subgroups according to the risk stratification in the validation cohort. (E) The difference in CSS among T3–4N0, T1–2N+, and T3–4N+ patients. (F) The correspondence between AJCC stage and the risk stratification based on the nomogram predicting CSS. (G) CSS in the subgroups according to the risk stratification in the training cohort. (H) CSS in the subgroups according to the risk stratification in the validation cohort. OS, overall survival; CSS, cancer-specific survival; AJCC, American Joint Committee on Cancer.

ignored in cavity organs. However, many studies have suggested that tumor size is related to the response of LARC to chemoradiotherapy (21,22), which may also affect the prognosis of LARC. CEA has been revealed to have a close association with chemosensitivity and survival of rectal cancer patients in various studies (24,25). Similarly, an elevated CEA was confirmed to be an indicator of poor prognosis in this study. Other essential prognostic factors were also incorporated into the study, including age, marital status, pathological grade, and histological type. Cancers can increase the risk of death from geriatric diseases, which is why age contributed a higher weight in the nomogram of OS compared to CSS. Furthermore, it is worth noting that patients with MCC/SRCC had a worse survival. The prognosis of LARC that was well/moderately differentiated was significantly better than that of poorly differentiated/undifferentiated LARC, which was in agreement with previous studies. Interestingly, marital status has been found to correlate with the prognosis of various tumors (26-28), which was also applicable to rectal cancer in our study.

One-third of the patients were randomly selected as the validation group to confirm the superiority of the nomograms in this study. The excellent results, including C-index, time-dependent ROC curves, DCA, and calibration curves, in the validation group ensure the generalizability of the novel nomograms. However, some limitations were nonetheless present in our study. Firstly, as a retrospective study, the nomograms still need to be validated in the future by prospective studies. Secondly, we adopted the sixth edition of AJCC staging, rather than the latest editions, since the cases studied were taken from 2004 to 2011, which reduced, to some extent, the accuracy of the AJCC stage in that it lacked the T4 and N+ subgroups. Moreover, we still need more real-world data to verify the efficacy of the nomograms. These limitations notwithstanding, the study results attest to the excellent sensitivity, specificity, and outstanding clinical value of the nomograms.

Conclusions

Our nomograms, which effectively solved the issue of the survival paradox of the AJCC staging system regarding LARC, may serve as excellent tools for integrating clinical characteristics and guiding therapeutic choices for LARC patients.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-4144). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Approval from the ethical board for this study was not required because of the public nature of all the data. Patients' informed consent was waived because of the retrospective nature of the study design.

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2. Overview (Presentation of the publications)

Many kinds of cancers have been transformed from the death penalty to preventable and curable diseases by identifying and controlling cancer risk factors, improving early detection and developing effective therapies in the past decades. However, cancer with rapidly growing incidence and mortality have became the biggest public health problem in the world. The reasons are complex but reflect both aging and growth of the population, as well as changes in the prevalence and distribution of the main risk factors for cancer, several of which are associated with socioeconomic development (Bray et al., 2018). GLOBOCAN estimated that 18.1 million people were diagnosed with cancer, and 9.6 million people died from cancer worldwide in 2018 (Bray et al., 2018). Both incidence and mortality of digestive system tumors, including colorectal cancer, pancreatic cancer, stomach cancer, liver cancer etc., rank as the first among various systems.

Colorectal cancer (CRC) is the most common adult digestive cancer in the world with an estimated 1.8 million cases and 881,000 deaths annually (Bray et al., 2018). Pancreatic cancer is one of the leading causes of cancer mortality in developed countries and one of the most lethal malignant neoplasms worldwide (Ferlay et al., 2015). The main histological type of pancreatic tumor is pancreatic ductal adenocarcinoma (PDAC), which accounts for about 85% of cases (Hidalgo et al., 2015; Vincent et al., 2011). Early locoregional metastasis, an unusual aggressiveness, and distant spread of pancreatic cancer cells are the basis of the urgent need for new therapeutic options for patients with PDAC, as its incidence is still nearly equal to its mortality in western countries (Güngör et al., 2014).

My research projects can be subdivided into 2 parts: 1) clinical projects: exploring the most important contributor to the improved survival and establishing predictive models to improve clinical decision making for colorectal and pancreatic cancer; 2) experimental studies: a series of experiments, including transfection, western blot, MTT assay, immunochemistry, shRNA etc., to explore the regulatory effects and molecular mechanism of RFTN2 on proliferation and migration in PDAC cells.

2.1 The main contributor to the upswing of survival in locally advanced colorectal cancer: an analysis of the SEER database

Treatment for locally advanced colorectal cancer includes surgical resection (Kim et al., 2016), chemotherapy (Manjelievskaia et al., 2017), and/or radiation therapy (Ren et al., 2012). Advances in surgical resection techniques are attributed to updated surgical equipment and

concept. Total mesorectal excision (TME) and complete mesocolic excision (CME) have become the consensus of all colorectal surgeons (Bertelsen et al., 2015; Miskovic et al., 2015). Additionally, application of laparoscopy and robot-assisted laparoscopy contributes to the refinement of colorectal cancer surgery (Mushtaq et al., 2019; van der Pas et al., 2013). Adjuvant chemotherapy for locally advanced colorectal cancer (LACRC) patients with high-risk stage II and III has substantially evolved over the past decades, concomitant with progress of marketing of oxaliplatin, irinotecan, cetuximab and bevacizumab as well as the concept of neoadjuvant therapy. The uptake of TME or CME combined with adjuvant oncological treatment for locally advanced colorectal cancer has reduced local recurrence rates and improved long-term survival (Brown and Solomon, 2018). However, the most important contributor to the upswing of colorectal cancer survival is still unclear.

Data in this retrospective analysis were extracted from the Surveillance, Epidemiology, and End Results (SEER) linked database. We selected the period 1989-1990 as a baseline for comparison because the management of LACRC started to evolve rapidly from the 1990s (Brown and Solomon, 2018) and chose patients from the period 2009-2010. The main chemotherapy regimen for colorectal cancer was 5-FU/leucovorin in the 1990s (1992). FOLFOX (Oxaliplatin/5-FU/leucovorin) have become the first-line treatment for colorectal cancer since the beginning of the 21st century (2004). Total mesorectal excision was proposed by Heald et al. in 1982 (Heald et al., 1982) and has become the standard for surgery of rectal cancer after more than 20 years of practice (Watanabe et al., 2015). Owing to the successful experience of TME, CME was quickly recognized by colorectal surgeons which was initially introduced in 2009 (Hohenberger et al., 2009; West et al., 2010). Therefore, both colon and rectal cancer can benefit from advances in surgical equipment, but the revolutionary concept was only proposed in the treatment of colon cancer during from 1989-1990 to 2009-2010.

The interesting findings of this study include: (1) although advancements of surgical treatment had not significantly prolonged the survival of colorectal cancer, surgeons should explore a more appropriate area of surgical resection and improve short-term outcomes without affecting the long-term survival of LACRC; (2) an effective drug is the key to cancer treatment since chemotherapy is the main contributor to the progress of treating colorectal cancer; (3) oncologists should tailor whether the administration of radiotherapy can be abandoned for patients with mid-low rectal cancer if radiotherapy does not affect sphincter preservation. In conclusion, advancements of chemotherapy regimen were the main contributor to the upswing of colorectal cancer survival. The improvement of surgery had a limited effect on better

colorectal cancer survival. The short-term survival of LACRC patients in 2009-2010 was even lower than that in 1989-1990.

As mentioned in this article, radiotherapy can be abandoned for those mid-low rectal cancer patients without influencing the sphincter preservation. Therefore, we conducted a study to investigate the therapeutic response or benefit of locally advanced rectal cancer following neoadjuvant radiotherapy (introduced in section 2.4). The treatment of locoregional colorectal cancer has made great progress in recent years. Nevertheless, hepatic metastasis is still the leading cause of death in CRC patients (Foster, 1984). Patients with colorectal liver-limited metastasis account for one-third of deaths from colorectal cancer (Kemeny, 2006). This difficult situation prompted me to study colorectal liver-limited metastasis in another study, which was as follows: "*Nomograms Predicting Overall Survival and Cancer-specific Survival for Synchronous Colorectal Liver-limited Metastasis*" (introduced in section 2.3).

2.2 The Main Bottleneck for Non-Metastatic Pancreatic Adenocarcinoma in Past Decades: A Population-Based Analysis

Treatment for PDAC involves surgical resection, chemotherapy, and/or radiotherapy. The development of surgical resection has involved perfection of surgical concepts and equipment. Several techniques, including total mesopancreatic excision (TMpE) and accurate assessment of the resection margins, which have been learned from the experience in treating colorectal cancer, are used by pancreatic surgeons (Adham and Singhirunnusorn, 2012; Konstantinidis et al., 2013). Additionally, application of robot-assisted laparoscopy contributes to the refinement of surgery (Liao et al., 2016). Adjuvant chemotherapy for patients with PDAC was converted from 5-FU-based regimens in the early 1990s to gemcitabine-based regimens in the 2000s (H A Burris 3rd et al., 1997; Kurosaki et al., 2004) and FOLFIRINOX in the 2010s. Intensity-modulated radiation therapy (IMRT), which can not only adjust the dose of radiotherapy and increase the radiation dose of tumor but also reduce the radiation damage of normal tissues, emerged due to the development of CT technology and three-dimensional conformal radiotherapy (3D-CRT) (Ben-Josef et al., 2004; Milano et al., 2004). Despite recent advances in surgical techniques, chemotherapy, and radiation therapy, the 5-year survival rate of patients with PDAC remains a dismal 8.2% (Biron-Shental et al., 2008). The present study explored whether improved surgical resection, chemotherapy, and radiotherapy regimens have helped patients with PDAC obtain a longer survival, as well as to identify the main barriers to improved survival in non-metastatic PDAC, in recent decades. Thus, the purpose of the present study was

to determine the impact of therapeutic advancements by comparing the overall survival (OS) of patients with PDAC between the periods 1988-1996 and 2010-2014.

Patient data were extracted from the Surveillance, Epidemiology, and End Results (SEER) linked database in this retrospective analysis. We chose the period 1988-1996 as a baseline because partial data, which included tumor size, regional nodes examined, and lymph nodes, were available since 1988 and gemcitabine was recommended as first-line chemotherapy for pancreatic cancer in 1997. We chose patients from the period 2010-2014, which was the latest for the 2-year follow-up, since the FOLFIRINOX regimen emerged as a new treatment option for metastatic pancreatic cancer in 2010 (Conroy et al., 2013; Faris et al., 2013). Unlike as the results of colorectal cancer, development of chemotherapy and radiotherapy has been slow, especially for unresectable pancreatic cancer. Although advances in surgery were major contributors to the improvement of survival in resectable patients, lack of early diagnostic tools, which resulted in low resection rates, was still an obstacle for all PDAC patients. Moreover, do advanced surgical concepts allow more resectable PDAC patients to avoid multi-drug chemotherapy or even chemotherapy? In a following study, we looked into a scoring system based on survival nomograms to screen out low-risk resectable PDAC patients, who cannot obtain survival benefit from chemotherapy. This scoring system also successfully confirmed that chemotherapy for all PDAC patients is unreasonable (not yet published). Overall, PDAC is still a deadly disease and it urgently needs to seek new treatment targets for pancreatic cancer.

My experimental research project therefore dealed with the identification and characterization of potentially new therapy targets in pancreatic cancer. Applying total RNA-seq experiments in chemosensitive and chemoresistant pancreatic cancer cell clones, we could identify Raftlin family member 2 (RFTN2) as abundantly expressed in chemoresitant PDAC cells.

RFTN2 is located on chromosome 2q33.1, and the homologue of Raftlin, which also known as lipid raft linker 1 (RFTN1) (Saeki et al., 2009). Raftlin was originally identified as a major raft protein in B cells that co-localized with B cell receptor in the lipid raft before and after B cell receptor stimulation (Saeki et al., 2003). The expression of Raftlin is related to various diseases, including Alzheimer's disease (Wollmer et al., 2007), lymphoma (Boyd et al., 2009), glaucoma (Chen et al., 2012), acute appendicitis (Ozer et al., 2018) as well as sepsis (Lee et al., 2014). Moreover, a recent research reported that Raftlin is able to inhibit migration and control proangiogenic signaling in endothelial cell (Bayliss et al., 2020). However, the research on RFTN2 is still in a blank stage, especially in cancer cells. The only two research available, showed that RFTN2 is related to DNA damage response (Wei et al., 2018a) and

embryonic development in zebrafish (Hong et al., 2010). Therefore, it is also necessary to explore the regulating mechanism of RFTN2 in pancreatic cancer cells due to its unclear role. RFTN2 protein expression levels were investigated in PDAC cell lines as well as in normal pancreatic cells (HPDE) and Panc1, L3.6pl^{res} (gemcitabine resistant), L3.6pl^{wt} (gemcitabine sensitive) and Paca-5061 (primary cancer cell line) exhibited higher-expression levels of RFTN2, whereas HPDE, Bxpc3 and Paca-5072 (primary cancer cell line) cells showed low-expression of RFTN2. Stable RFTN2-knockdown (L3.6pl^{res} and Panc1) and RFTN2-overexpression (Bxpc3 and Paca-5072) cell lines were then established to examine the molecular function of RFTN2. I performed MTT assays and confirmed that elevated RFTN2 expression was able to strengthen the proliferative capacity of PDAC cells *in vitro*. Moreover, the Transwell assays demonstrated that enhenced RFTN2 expression can increase the migrative capacity of PDAC cells *in vitro.*

Initially, we found a significant correlation between RFTN2 and HIF-1α expression in PDAC using the GEPIA database (http://gepia.cancer-pku.cn/). Hypoxic conditions in the tumor microenvironment often contribute to HIF-1α overexpression (Semenza, 2003), which then promotes tumor growth and metastasis through its role in initiating angiogenesis and regulating cellular metabolism to overcome hypoxic stress (Bos et al., 2003). Pancreatic cancer is rich in interstitial components, which greatly reduces the effective transmission of oxygen in blood vessels to tumor cells, forming a hypoxic microenvironment for pancreatic cancer cells to survive. Hypoxic microenvironment may be one of the main reasons for chemotherapy resistance in pancreatic cancer. Hence, I tried to study the regulatory mechanism of pancreatic cancer cell function under hypoxia in my experimental studies. Meanwhile, we hypothesized that hypoxia is able to induce RFTN2 gene expression in PDAC cells. Interestingly, western blot assay results were consistent with my hypothesis that the expression of RFTN2 is enhanced under hypoxic conditions (150μM $CoCl_2$) in PDAC cancer cells, compared to normoxy. MTT assays showed also that PDAC cells having high RFTN2 expression (ectopic overexpression) proliferated substantially faster under hypoxic conditions compared to control cells.

Several previous studies reported that hypoxia can regulate the expression of β-catenin in cancer cells (Liu et al., 2018; Saieva et al., 2020; Zheng et al., 2020). Moreover, the GEPIA database (http://gepia.cancer-pku.cn/) confirmed that the β-catenin expression was positively associated with RFTN2. Therefore, we hypothesized that RFTN2 can regulate the Wnt/β-catenin pathway to affect cell function in pancreatic cancer cells. The nuclear translocation of β-catenin is a hallmark of activated Wnt signaling and cytoplasmic β-catenin protein levels are tightly controlled by a “destruction complex” and the 26S proteasome. Wnt/β-catenin signaling

is already recognized for its ability to orchestrate various biological processes such as differentiation, organogenesis, cell proliferation and tissue regeneration. In cancer cells, Wnt is frequently found abnormally activated, and accumulating evidences shows that the hyperactivation of Wnt plays an important oncogenic role and therefore representing an attractive therapeutic target for cancer treatment (Novellasdemunt et al., 2015). Clinical trials with various Wnt-inhibitors have already been started in solid tumors (www.clinicaltrials.gov). Moreover, active β-catenin signaling depends on its nuclear translocation and is strongly linked with EMT processes and aerobic glycolysis in different cancers (Cai et al., 2018; Fang et al., 2019; Zuo et al., 2020). Dysregulated β-catenin signaling participates in the regulation of tumor invasion, metastasis formation and aerobic metabolism, and various mutations in crucial regulatory factors of the Wnt/β-catenin pathway have already been widely noted (Jiao et al., 2020; Wang et al., 2020; Xue et al., 2020; Zhang et al., 2020). Therefore, I initially analyzed β-catenin expression levels in PDAC cell lines and found, surprisingly, increased β-catenin protein levels in RFTN2 overexpressed cells, compared to control cells. Moreover, overexpressed RFTN2 substantially increased nuclear translocation of β-catenin, suggesting that the β-catenin signaling pathway was activated. In conclusion, I found RFTN2 expression is higher in chemoresistant and more aggressive PDAC cells, and is able to activate the β-catenin pathway to promote the proliferation and migration of PDAC cells.

Collectively, I analyzed the clinical data and concluded that PDAC needs to find an effective therapeutic target. Then I proved that RFTN2 can activate the β-catenin pathway to promote the proliferation and migration of PDAC cells by a series of experimental studies. The molecular impact of RFTN2 will also be investigated in a mice model of PDAC. Therefore, drugs inhibiting the expression of RFTN2 may become a new therapeutic approach and may therefore improve the prognosis of patients suffering from PDAC.

A new manuscript presenting my new research data about the molecular function of RFTN2 in PDAC is currently under preparation.

2.3 Nomograms Predicting Overall Survival and Cancer-specific Survival for Synchronous Colorectal Liver-limited Metastasis

The liver is the most common metastatic site of CRC with 20%-34% of patients suffering synchronous liver metastasis (Hayashi et al., 2010; Muratore et al., 2007). Hepatic metastasis is still the leading cause of death in CRC patients (Foster, 1984). Patients with colorectal liver-limited metastasis account for one-third of deaths from colorectal cancer (Kemeny, 2006). Moreover, some evidence indicated that CRC patients with synchronous liver disease

encountered a worse prognosis and more disseminated disease state comparing with metastatic liver disease that develops metachronously. Accordingly, this study focused on synchronous colorectal liver-limited metastasis (SCLLM). Notwithstanding that technologies and therapeutic strategies have progressed over the last several decades, the survival of CRC patients with synchronous liver-limited metastasis still remains unsatisfactory. It is of high relevance to identify prognostic factors for patients with SCLLM. A nomogram, a simple graphical representation combining and quantifying all independent prognostic factors (Li et al., 2018), plays an increasingly important role in medical research and clinical practice. Large public databases, like the Surveillance, Epidemiology, and End Results (SEER) database provide available, authentic and reliable data to explore different clinical issues.

This research investigated a national cohort of almost 10.000 patients to create and verify nomograms based on pathological, therapeutic and demographic features to predict OS and Cancer-specific Survival (CSS) for SCLLM. The nomograms may act as an excellent tool to integrate clinical characteristics to guide the therapeutic choice for SCLLM patients. Additionally, patients with negative regional lymph nodes, but positive tumor deposits (TD) in specific site were divided into a N1c stage, that obtained an equal or even a lower risk score comparing with N1a in this study. Therefore, it is worth considering whether the risk degree of TD needs to be redefined in the TNM stage system for patients with colorectal cancer. I used propensity score matching to compare the survival differences between N1c and N1b, as well as N1c and N1a in a follow-up study. The preliminary results showed a better prognosis of CRC patients with N1a compared to those with N1c, but a similar survival rate between the prognosis of N1b and N1c. However, these explorations are still not enough. The impact of the number of TD on survival should also be explored in future research settings.

2.4 Predicting pathological complete response by comparing MRI-based radiomics pre- and post-neoadjuvant radiotherapy for locally advanced rectal cancer

Currently, the recommended treatment for locally advanced rectal cancer (LARC, T3-4 or N+) is total mesorectal excision (TME) after neoadjuvant chemoradiotherapy (nCRT) (Watanabe et al., 2015). The neoadjuvant radiotherapy (nRT) plays an important role in nCRT. However, different patients bring the wide variabilities out of the response of LARC to nCRT, with a ladder from no tumor regression to pathologic complete response (pCR) (Yeo et al., 2010). Radiomics, which extracted excavatable high-dimensional data from digital images, revealed non-visual information associated closely with underlying pathophysiology and even

tumor heterogeneity (Gillies et al., 2016; Kiessling, 2018). Recently, the development of radiomics has shown great potential for therapy guidance and tumor prognosis across various types of cancer (Huang et al., 2016; Kickingereder et al., 2016; Kim et al., 2017; Zhang et al., 2017). Despite of diverse outcomes, several researches displayed the potential significance of imaging modalities (Gollub et al., 2017; Nougaret et al., 2016; Sun et al., 2010; van Stiphout et al., 2014; Yu et al., 2017). Among all modalities, magnetic resonance imaging (MRI) was regarded as the most recommended and promising method because it showed high soft tissue resolution without radiation to damage human body, and had a wide routine clinical application for evaluation of rectal cancer. Several models also predicted tumor response to nCRT on MRI-related radiomics in LARC. However, all of the studies only focused on the MR images prior to nCRT, which might have inherent limitations to reflect the impact of nCRT on target population. Therefore, we investigated whether the difference of quantitative MRI-based radiomics analysis between pre-nRT and post-nRT can be of great help to predict pCR in LARC.

In fact, this project is based on my previous research, which aimed to identify predictive factors of tumor response and to evaluate the significance of primary gross tumor volume (pGTV) in predicting tumor response for more effective cancer treatment (Liu et al., 2019). Tumor response is closely related to tumor prognosis. The success rate of a tumor response to nCRT remains disappointing, merely ranging from 40-60% (Giannini et al., 2019; Nahas et al., 2019; Petrillo et al., 2018; Wei et al., 2018b). Therefore, it is crucial to identify which of the patients would benefit from nCRT. Several studies have reported that tumor size might be one of the potential clinical predictive factors (De Felice et al., 2016; Garland et al., 2014), but the methods used for measurement of tumor size vary and are not sufficiently accurate. Furthermore, it is unclear whether tumor diameter, a one-dimensional measurement, can reflect the three-dimensional tumor volume, which represents the actual tumor size. Several studies have already demonstrated that primary gross tumor volume (pGTV), measured during radiotherapy planning, serves as a more reliable surrogate for actual tumor volume than tumor diameter (Sorensen et al., 2001; Studer et al., 2007). However, the value of the area under the receiver operating characteristic curve (AUC) for pGTV was not ideal - only 0.629 (Liu et al., 2019), which urges us to seek more accurate methods to predict tumor response to nCRT.

This study investigated a predictive model with radiomic features to predict pCR to neoadjuvant chemoradiation in LARC patients. In addition, this new model that have been developed with information from the clinically obtained T2-weighted sequence, is may be pragmatic as a complement in clinical strategy making. However, we still need to further improve our research and adopt a multi-omics approach to better predict the effect of

radiotherapy in rectal cancer. At present, we plan to collect pathological tissue from preoperative colonoscopy before nCRT, and will use deep learning to analyze these pathological pictures and predict tumor response to nCRT in future.

Regrettably, this article only studied the short-term endpoint (pCR), and did not use long-term survival as the research endpoint. It remains controversial whether radiotherapy can prolong the survival of LARC patients. In addition, we also need to explore which of the clinicopathological factors can be used as prognostic factors for LARC patients, and the impact of these prognostic factors on survival. Therefore, nomograms predicting OS and CSS for LARC were built in the next study (introduced in section 2.5).

2.5 Accurate Nomograms with an Excellent Clinical Value for Locally Advanced Rectal Cancer

Rectal cancer accounts for approximately 30-50% of colorectal cancer (Bailey et al., 2015). The patients who have colon and rectal cancers generally are analyzed in the context of statistical homogeneity, despite having different embryologic origins, anatomy and treatments (Doumouras et al., 2016). Thus, it is necessary to conduct a specific analysis for locally advanced rectal cancer that is different from colon cancer owing to the apparent distinctions of treatment, the universal involvement of neoadjuvant chemoradiotherapy (nCRT) and the performance of a total mesorectal excision (TME) in surgical technique (Kapiteijn et al., 2001; Tamas et al., 2015). Despite widespread use and convenience, the American Joint Committee on Cancer (AJCC) staging system for prediction of survival has been inaccurate, even including a survival paradox for LARC, that those patients with T3-4N- developed worse survival outcomes than those with T1-2N+ (Gunderson et al., 2010a; Gunderson et al., 2010b; Kim et al., 2015). A precise risk stratification of LARC is imperative for the proper treatment selection and prognostic evaluation. As a visible representation of a mathematical model, a nomogram can not only integrate some certain features together to estimate specific endpoints, but also provide a pragmatic and comprehensive prediction in clinical practice. Moreover, national databases, such as the Surveillance, Epidemiology, and End Results (SEER) database, can provide available clinical factors and ample patients to build a reliable statistical model for the prediction of survival. Therefore, we planned to create prognostic nomograms for patients with LARC based on the SEER database, which can accurately and conveniently assess overall survival (OS) and cancer-specific survival (CSS).

Positive status of regional lymph nodes, without the intervention of T stage, was classified as stage III in the AJCC staging system. However, those patients with T3-4N- developed worse survival outcomes than T1-2N+ (Gunderson et al., 2010a; Gunderson et al., 2010b; Kim et al., 2015), which was consistent with our study. Increasing research has focused on the survival paradox in the AJCC staging system, suggesting that the T stage had more influence than the N stage on survival in rectal cancer (Li et al., 2014). And the T stage, having more weight than the N stage, was further demonstrated by the nomograms of OS and CSS in our study. The poor predictive efficiency of the AJCC stage on locally advanced rectal cancer spurred clinicians to seek a new risk stratification that would effectively avoid the survival paradox. The nomograms, which effectively solved the issue of the survival paradox of the AJCC stage regarding LARC, may act as an excellent tool to integrate the clinical characteristics to guide the therapeutic choice for LARC patients.

3. Summary/Zusammenfassung

A detailed analysis of the impact of advances in surgery, chemotherapy, and radiotherapy on the survival of colorectal cancer and pancreatic cancer：

i advancements of chemotherapy regimen were the main contributor to the upswing of colorectal cancer survival. The improvement of surgery had a limited effect on colorectal cancer survival.

ii the development of chemotherapy and radiotherapy has been slow, especially for unresectable PDAC. Although advances in surgery contributed significantly to improved survival for resectable PDAC, lack of early diagnostic tools, which lead to low resection rates, remain a barrier for all PDAC patients.

Constructing nomograms predicting OS and CSS for patients with SCLLM:

iii the nomograms are capable of providing individualized estimates of potential survival benefit and can aid individualized management decisions for SCLLM.

Building a predictive model based on radiomics features:

iv the predictive model with radiomic features was promising to predict pCR to neoadjuvant chemoradiation in LARC patients. In addition, our method developing with information from the clinical obtained T2-weighted sequence may be pragmatic as a complement in clinical strategy making.

Constructing nomograms predicting OS and CSS for patients with LARC:

v the nomograms, which effectively solved the issue of the survival paradox of the AJCC stage regarding LARC, may act as an excellent tool to integrate the clinical characteristics to guide the therapeutic choice for LARC patients.

3. Zusammenfassung

Eine detaillierte Analyse der Auswirkungen von Fortschritten in der Chirurgie, Chemotherapie und Strahlentherapie auf das Überleben von Darmkrebs und Bauchspeicheldrüsenkrebs:
i Die Weiterentwicklung des Chemotherapie-Regimes trug maßgeblich zum Aufschwung des Überlebens von Darmkrebs bei. Die Verbesserung der Operation hatte einen begrenzten Einfluss auf das Überleben von Darmkrebs.

ii Die Entwicklung von Chemotherapie und Strahlentherapie war langsam, insbesondere bei nicht resezierbarem PDAC. Obwohl Fortschritte in der Chirurgie erheblich zur Verbesserung des Überlebens bei resektablem PDAC beitrugen, bleibt das Fehlen früher diagnostischer Instrumente, die zu niedrigen Resektionsraten führen, ein Hindernis für alle PDAC-Patienten.

Erstellung von Nomogrammen zur Vorhersage von OS und CSS für Patienten mit SCLLM:
iii Die Nomogramme können individuelle Schätzungen des potenziellen Überlebensvorteils liefern und individuelle Managemententscheidungen für SCLLM unterstützen.

Erstellen eines Vorhersagemodells basierend auf Radiomics-Funktionen:
iv Das Vorhersagemodell mit radiomischen Merkmalen versprach, pCR für eine neoadjuvante Radiochemotherapie bei LARC-Patienten vorherzusagen. Darüber hinaus kann unsere Methode, die sich mit Informationen aus der klinisch erhaltenen T2-gewichteten Sequenz entwickelt, als Ergänzung zur klinischen Strategieentwicklung pragmatisch sein.

Erstellung von Nomogrammen zur Vorhersage von OS und CSS für Patienten mit LARC:
v Die Nomogramme, mit denen das Problem des Überlebensparadoxons des AJCC-Stadiums in Bezug auf LARC wirksam gelöst wurde, können als hervorragendes Instrument zur Integration der klinischen Merkmale dienen, um die therapeutische Wahl für LARC-Patienten zu steuern.

4. List of abbreviations

CRC: colorectal cancer

PDAC: pancreatic ductal adenocarcinoma

TME: total mesorectal excision

CME: complete mesocolic excision

LACRC: locally advanced colorectal cancer

SEER: Surveillance, Epidemiology, and End Results

TMpE: total mesopancreatic excision

IMRT: Intensity-modulated radiation therapy

3D-CRT: three-dimensional conformal radiotherapy

OS: overall survival

SCLLM: synchronous colorectal liver-limited metastasis

TD: tumor deposits

LARC: locally advanced rectal cancer

nCRT: neoadjuvant chemoradiotherapy

nRT: neoadjuvant radiotherapy

pCR: pathologic complete response

MRI: Magnetic Resonance Imaging

pGTV: primary gross tumor volume

AUC: the area under the receiver operating characteristic curve

RNE: regional nodes examined

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6. Declaration of the contribution to the publications

Publication: Li Y, Zhao L, Güngör C, Tan F, Zhou Z, Li C, Song X, Wang D, Pei Q, Liu W. The main contributor to the upswing of survival in locally advanced colorectal cancer: an analysis of the SEER database. Therap Adv Gastroenterol. 2019 Jul 18;12:1756284819862154. doi: 10.1177/1756284819862154. PMID: 31360223; PMCID: PMC6640067.
Contribution of Yuqiang Li: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.
Contribution of co-authors: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search; Funds Collection.
The first author, Yuqiang Li, contributed mainly to this article.

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Contribution of Yuqiang Li: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.
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Contribution of Yuqiang Li: Study Design; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.
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Yuqiang Li contributed mainly to this article as first author.

Publication: Li Y, Liu W, Pei Q, Zhao L, Güngör C, Zhu H, Song X, Li C, Zhou Z, Xu Y, Wang D, Tan F, Yang P, Pei H. Predicting pathological complete response by comparing MRI-based radiomics pre- and postneoadjuvant radiotherapy for locally advanced rectal cancer. Cancer

Med. 2019 Dec;8(17):7244-7252. doi: 10.1002/cam4.2636. Epub 2019 Oct 22. PMID: 31642204; PMCID: PMC6885895.

Contribution of Yuqiang Li: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.

Contribution of co-authors: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search Funds Collection.

Yuqiang Li, Wenxue Liu, Qian Pei and Lilan Zhao contributed equally to this article.

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Contribution of Yuqiang Li: Study Design; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.

Contribution of co-authors: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search; Funds Collection.

Yuqiang Li contributed mainly to this article as first author.

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Contribution of Yuqiang Li: Study Design; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search.

Contribution of co-authors: Study Design; Data Collection; Statistical Analysis; Data Interpretation; Manuscript Preparation; Literature Search; Funds Collection.

Yuqiang Li, Guangfeng Zhang, and Xiangping Song contributed equally to this article as co-first authors.

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8. Curriculum Vitae

Personal Information

Name: Yuqiang Li

Date of Birth: 18/03/1990

Gender: Male

Nationality: Chinese

Language: Chinese, English

E-mail: yuli@uke.de

Phone: 0176 3421 7211

Educational Background

2018- Present	Doktor der Medizin (Dr. Med.)
	Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany
2014 – 2018	Master of Clinical Medicine
	Xiangya Hospital, Central South University, Changsha, China;
2009 – 2014	Bachelor of Clinical Medicine
	Dalian Medical University, Liaoning, China

Awards and Honors

2014-2017	Academic Scholarship of Central South University
09/2018	The first prize of Medical Science and Technology Award in Hunan, China

9. Eidesstattliche Versicherung *[als letztes Blatt in die Dissertation einzubinden]*

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
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Unterschrift: Yuqiang Li