

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

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## 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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## 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.<sup>1</sup> 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,<sup>2</sup> chemotherapy<sup>3</sup> and/

or radiation therapy.<sup>4</sup> 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.<sup>5,6</sup> In addition, application of laparoscopy and robot-assisted laparoscopy contribute to the refinement of CRC surgery.<sup>7,8</sup> 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

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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.<sup>9</sup> 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.<sup>10</sup> 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;<sup>9</sup> 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% ( $p < 0.001$ ,

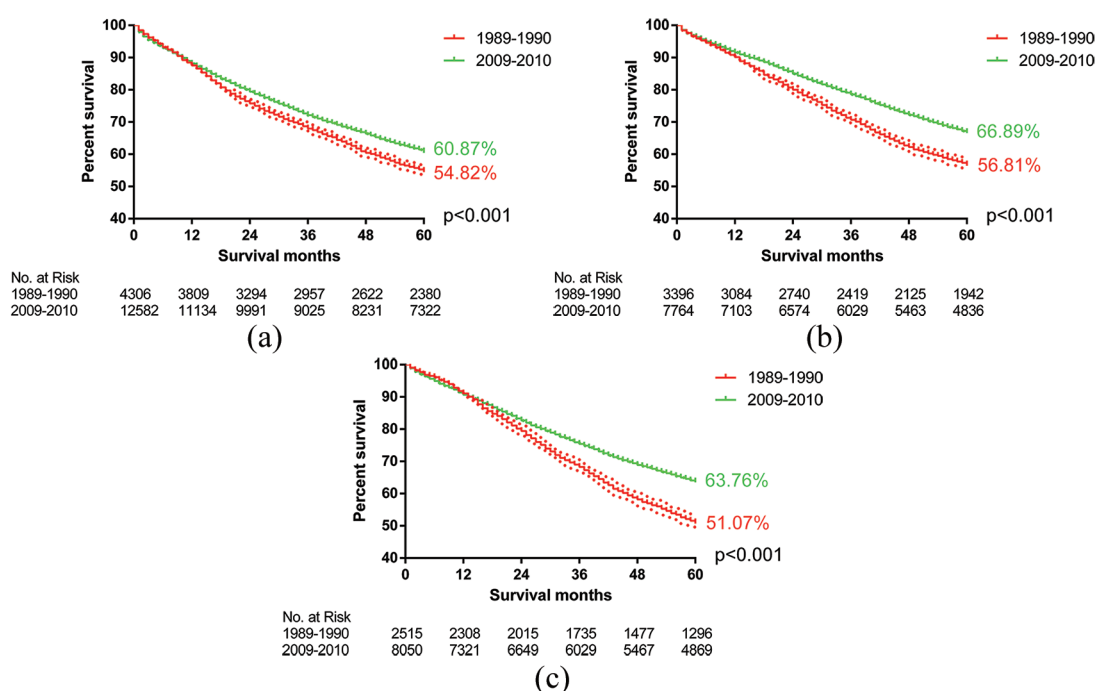
**Table 1.** Characteristics of local advanced colorectal cancer.

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*

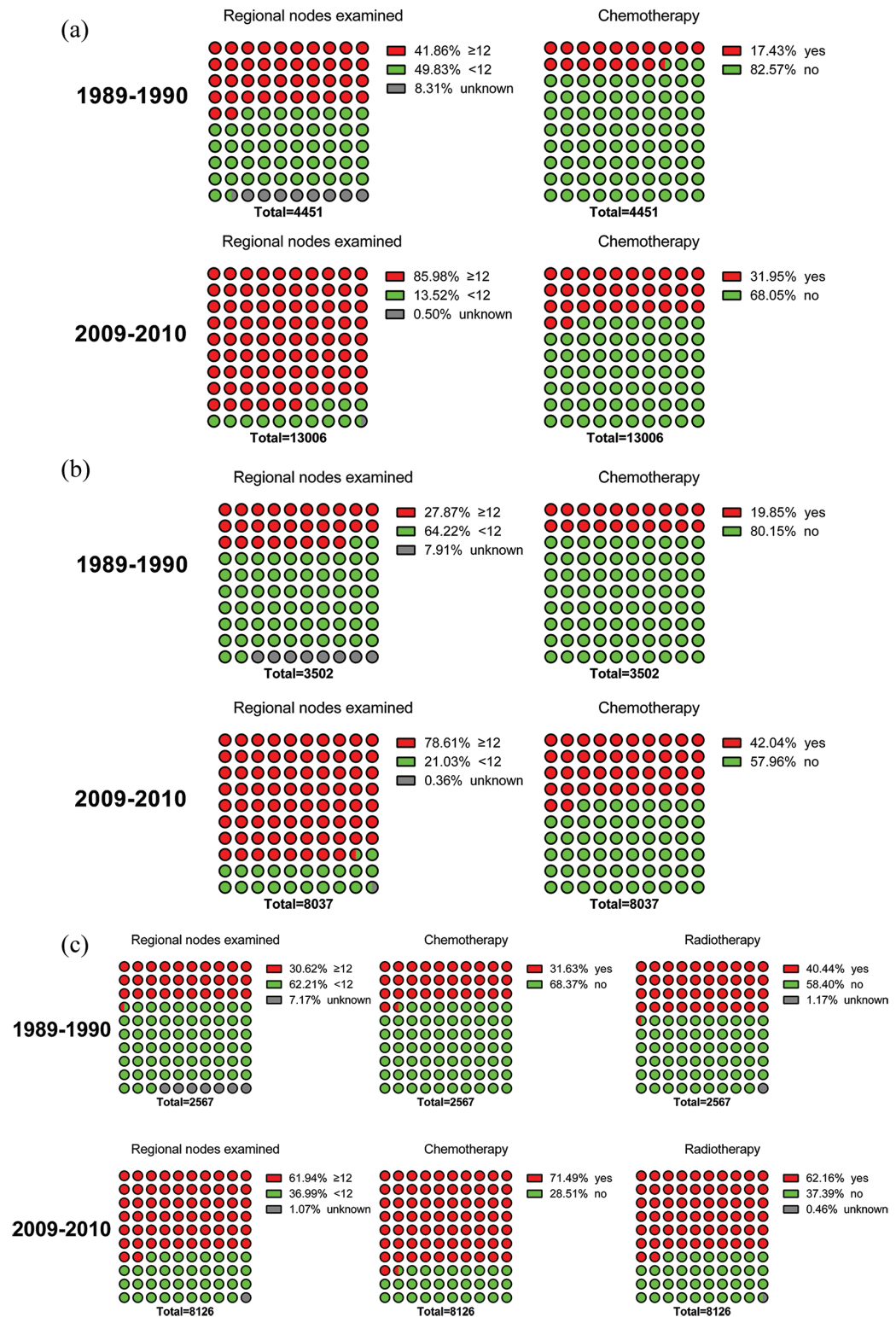
Patients treated with both surgery and chemotherapy were selected for PSM. The variables for PSM consisted of age, gender, race, differentiation, T stage, N stage, radiotherapy and the number of RNE (Supplementary Tables 4–6). A higher likelihood of improved OS occurred in all colorectal cancers after 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).

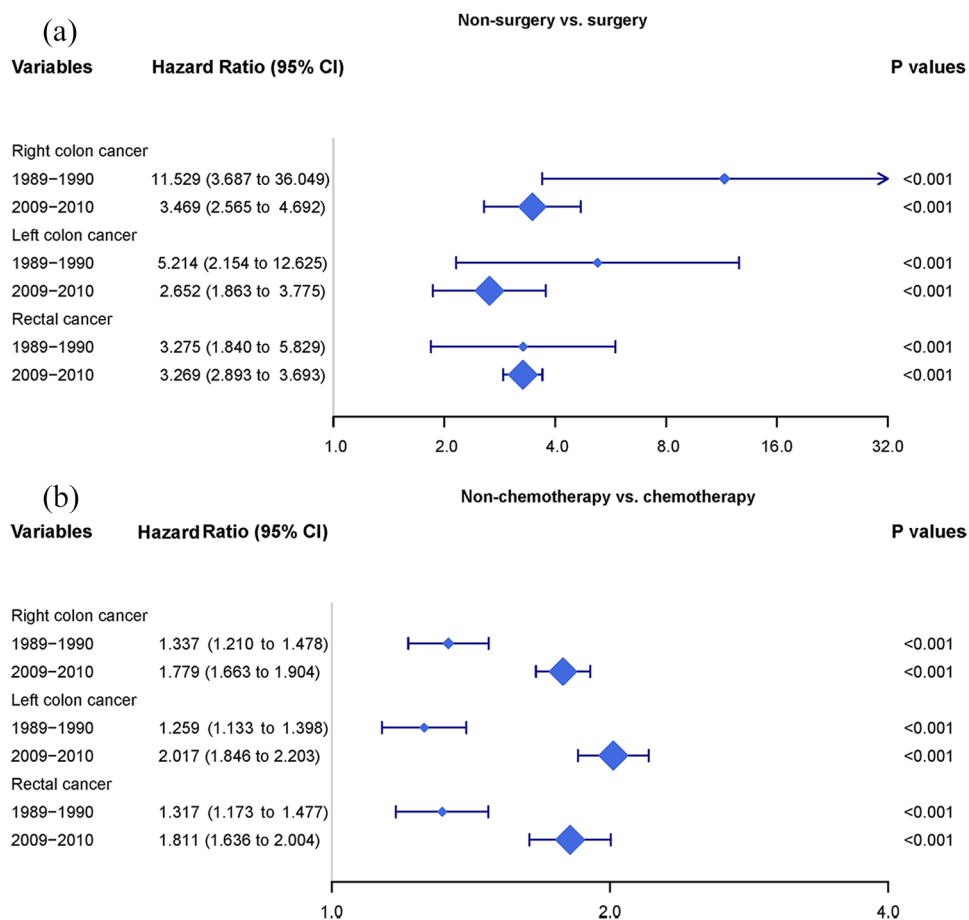
## **Discussion**

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  $\geq 12$ , 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 1.259 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,<sup>11–14</sup> 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<sup>15</sup> and has become the standard for surgery of RC after more than 20 years of practice.<sup>16</sup> Owing to the successful experience of TME, CME was quickly recognized by colorectal surgeons, and was initially introduced in 2009.<sup>17,18</sup> 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)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (years)		<0.001		<0.001
51–70 <i>versus</i> ≤50	1.762 (1.456–2.134)	<0.001	1.296 (1.126–1.492)	<0.001
>70 <i>versus</i> ≤50	4.180 (3.445–5.073)	<0.001	2.903 (2.529–3.333)	<0.001
51–70 <i>versus</i> >70	0.404 (0.373–0.438)	<0.001	0.446 (0.412–0.484)	<0.001
Gender				
Male <i>versus</i> female	NA	NA	1.182 (1.100–1.271)	<0.001
Race		0.204		
Black <i>versus</i> white	1.040 (0.895–1.209)	0.609	NA	NA
Other <i>versus</i> white	0.875 (0.748–1.024)	0.096	NA	NA
Black <i>versus</i> other	1.188 (0.964–1.465)	0.106	NA	NA
Histologic grade				
Poor/undifferentiated <i>versus</i> well/moderately differentiated	1.170 (1.039–1.316)	0.009	1.270 (1.157–1.393)	<0.001
T staging				
T4 <i>versus</i> 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 <i>versus</i> N0	1.271 (1.163–1.389)	<0.001	1.406 (1.289–1.533)	<0.001
N2 <i>versus</i> N0	1.731 (1.513–1.981)	<0.001	2.495 (2.254–2.762)	<0.001
N1 <i>versus</i> N2	0.734 (0.639–0.843)	<0.001	0.563 (0.510–0.623)	<0.001
Surgery				
No <i>versus</i> Yes	5.214 (2.154–12.625)	<0.001	2.652 (1.863–3.775)	<0.001
Chemotherapy				
No <i>versus</i> Yes	1.259 (1.133–1.398)	<0.001	2.017 (1.846–2.203)	<0.001
Regional nodes examined				
<12 <i>versus</i> ≥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.<sup>19</sup>

FOLFOX (oxaliplatin/5-FU/leucovorin) has become the first-line treatment for CRC in the 21st century.<sup>20</sup> We found that there was no intersection about the 95% CIs of chemotherapy between the two groups. Meanwhile, OS of LACRC patients

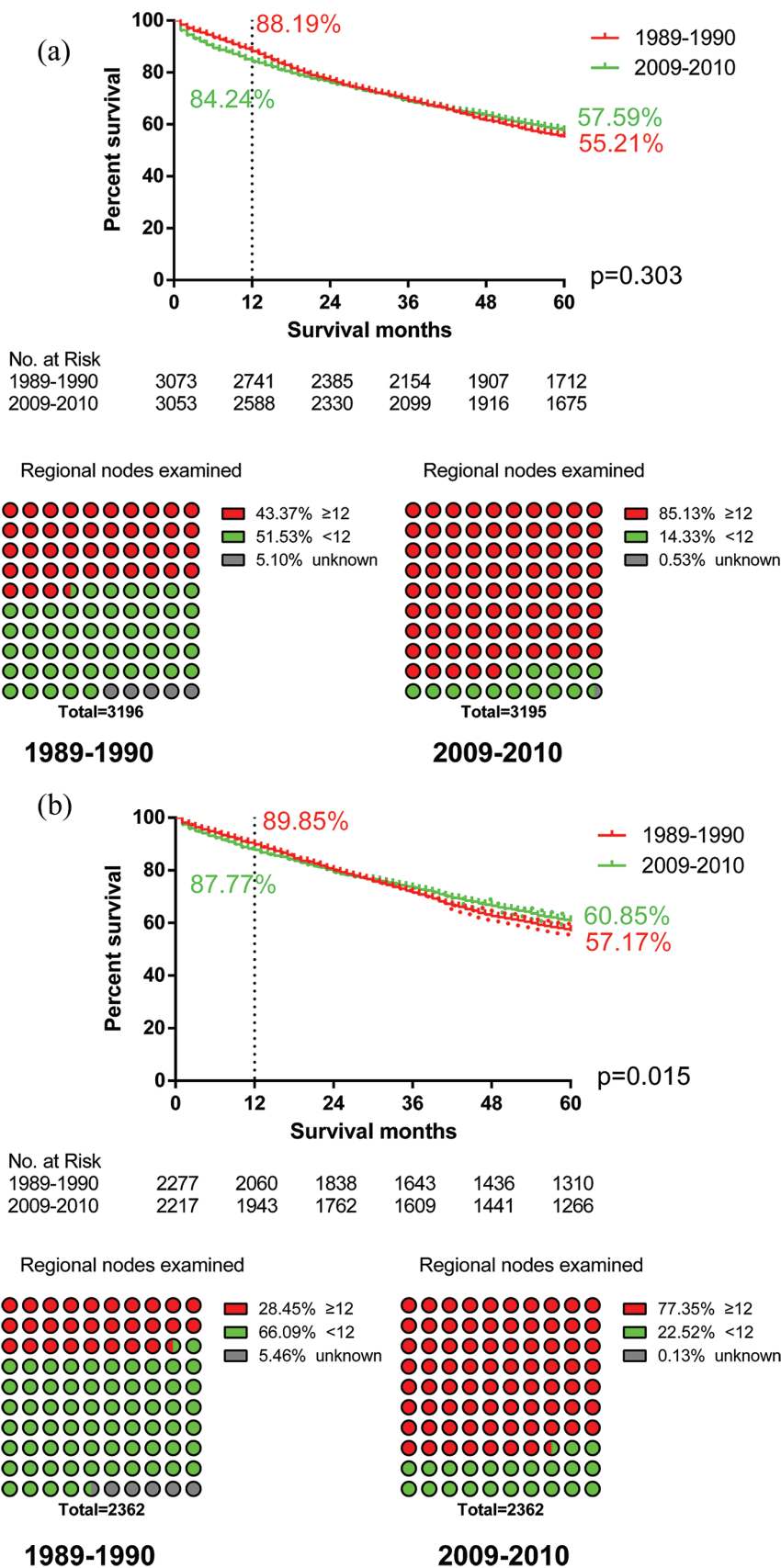
**Table 4.** Multivariate analysis of survival months in rectal cancer patients.

Variables	1989–1990		2009–2010	
	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> 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.				

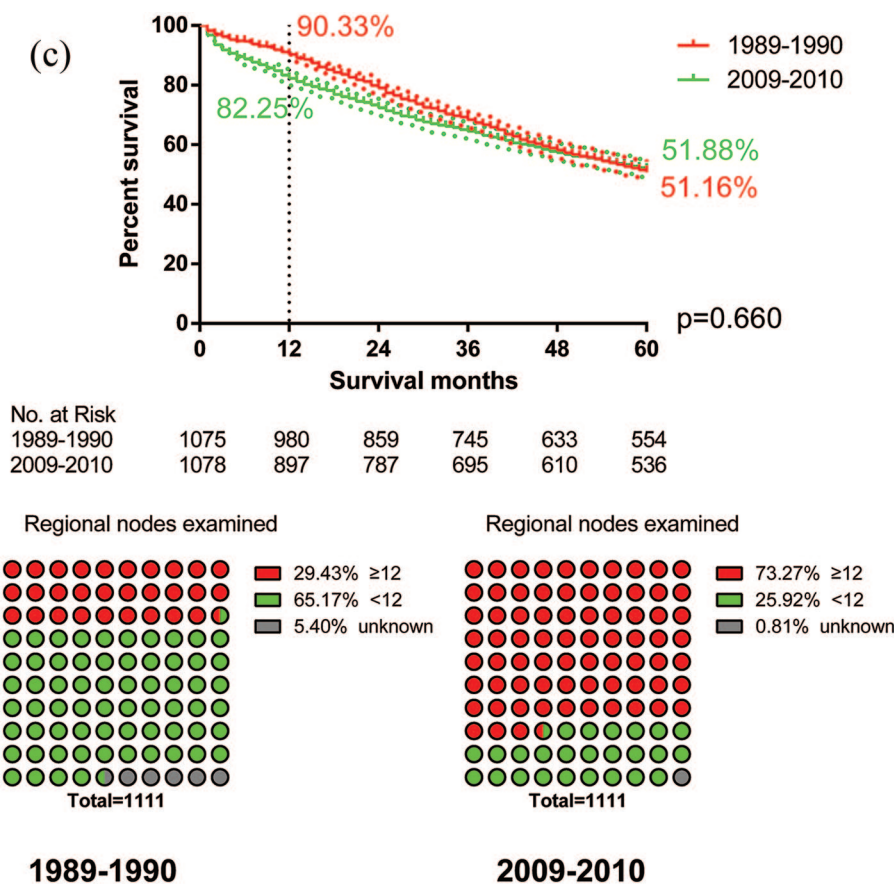
who underwent surgery with chemotherapy improved significantly ( $p=0.017$  in RCC;  $p=0.006$  in LCC;  $p=0.001$  in RC) after PSM, suggesting that the advancements in chemotherapy regimen are the root cause of the improvement in CRC survival.

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



(Figure 4. Continued)



**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

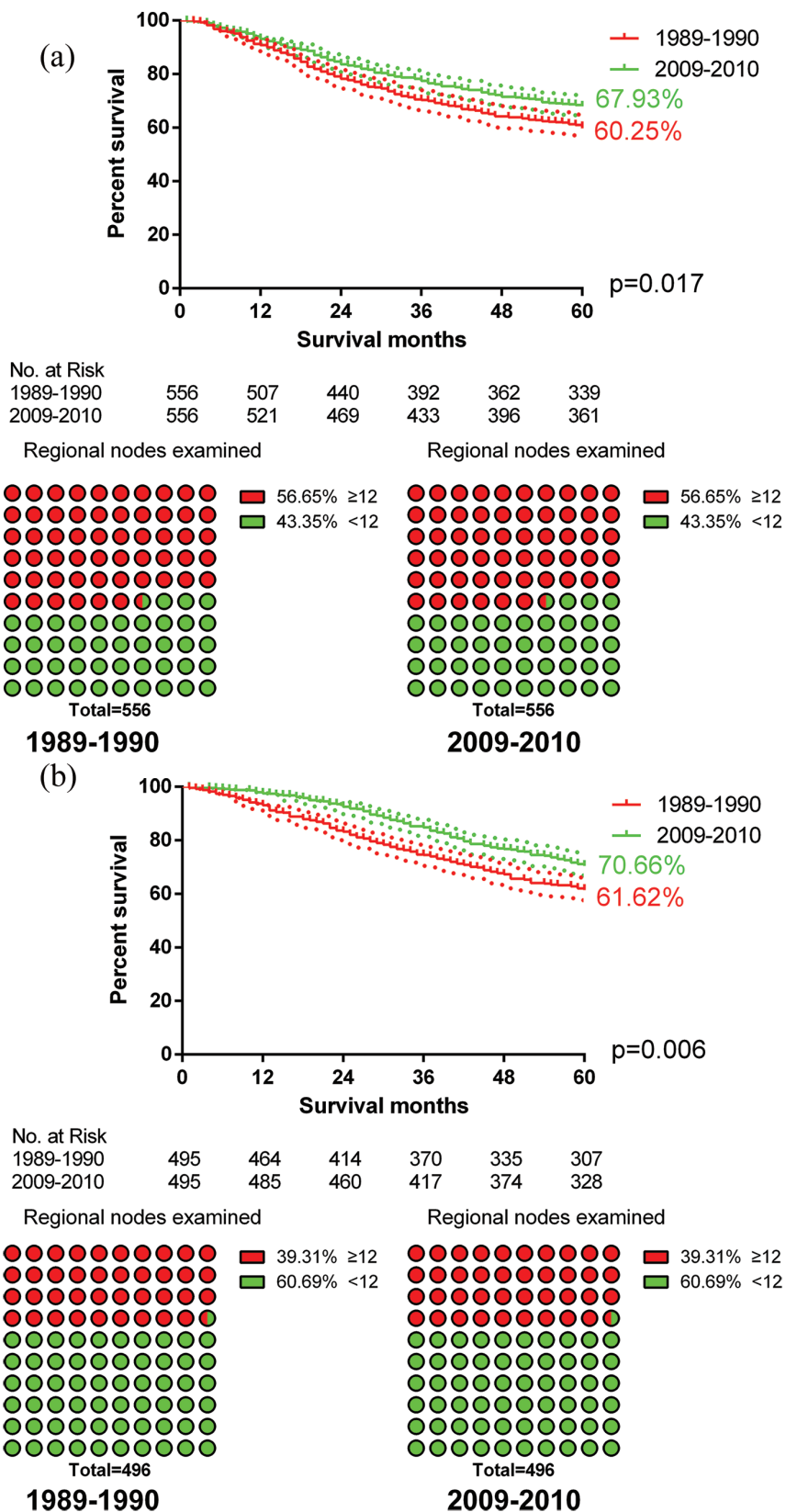
does not affect sphincter preservation. Access to only retrospective data was the main limitation of this study.

### Conclusion

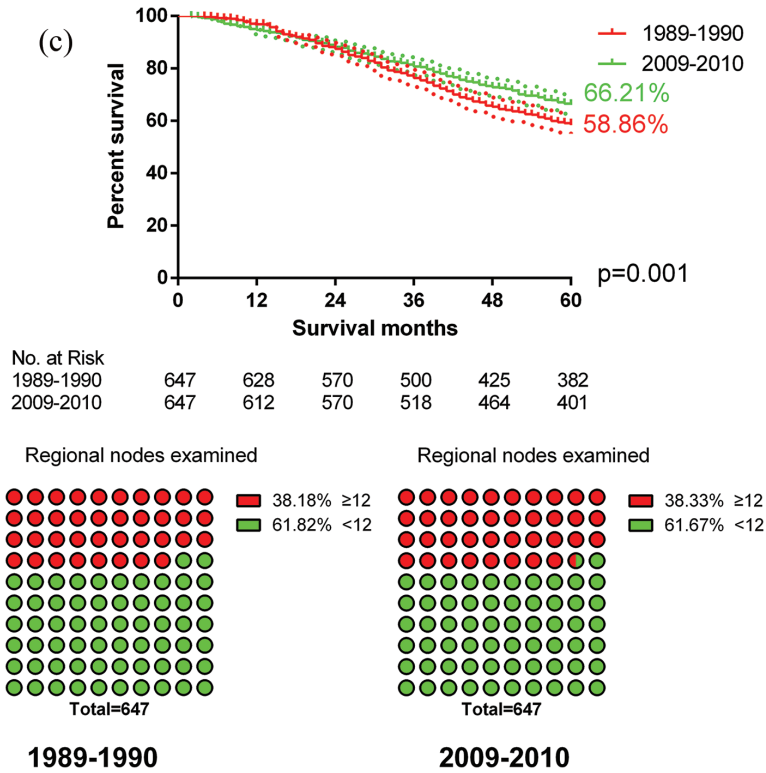
Advancements of chemotherapy regimen were the main contributor to the upswing in CRC survival. The improvements in surgery had a limited effect on improvements in CRC survival. The short-term survival of LACRC patients in 2009–2010 was even lower than that in 1989–1990.

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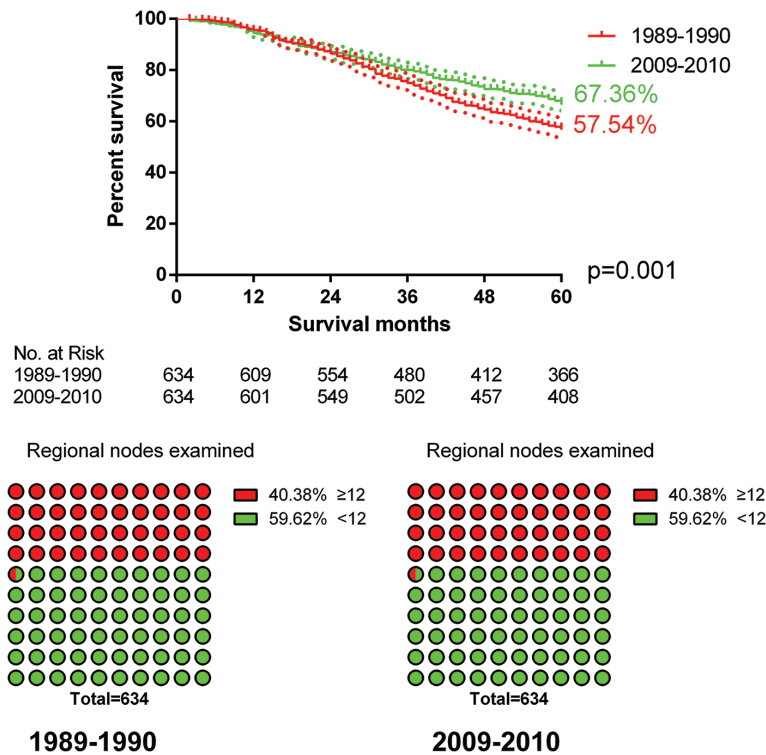
The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results



(Figure 5. Continued)



**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.

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### Supplemental material

Supplemental material for this article is available online.

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