Original Article

Trends in the Outcomes of Colorectal Cancer after Curative Surgery in Taiwan: A Single-Center Analysis of 10-year Experience

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Key Words
Colorectal cancer;
Oncological outcome;
Long-term follow-up

Purpose. Colorectal cancer is one of the leading causes of cancer-related mortality worldwide. Advancements in surgical techniques, chemotherapy, and early screening methods over the last decade have improved cancer prognosis. In this study, we analyzed the trends in colorectal cancer outcomes in Taiwan, particularly focusing on changes in surgical techniques, chemotherapy advancement, and early screening results.

Methods. We retrospectively reviewed the data of patients with colorectal adenocarcinoma who were treated at Wan Fang Hospital, Taipei, Taiwan, between January 2004 and December 2015. The inclusion criteria were having TNM stage I-IV cancer and undergoing curative surgery. The exclusion criteria were having incomplete data; undergoing palliative surgery, emergent surgery, or local excision; and having synchronous cancer. The primary outcomes were 5-year overall survival and disease-free survival.

Results. This study included 528 patients. The patients were stratified into two groups by treatment period: group 1 (2004-2008; n = 252) and group 2 (2011-2015; n = 276). At diagnosis, group 2 was younger than group 1. The proportions of harvested lymph nodes and patients receiving adjuvant chemotherapy were higher in group 2 than in group 1. Although the rate of 5-year overall survival was significantly higher in group 2 than in group 1, no significant between-group difference was noted in the rate of 5-year disease-free survival.

Conclusion. The observed improvement in overall survival in patients with colorectal cancer highlights the dynamic nature of cancer therapy and the importance of continual optimization of medical approaches. The advancements in surgical techniques, chemotherapy, and early screening methods might be relevant factors.

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Although considerable advancements have been made in diagnostic and therapeutic strategies over the last decade, colorectal cancer (CRC) remains one of the leading cause of cancer-related mortality worldwide.[1] Advances in medical technologies, surgical techniques, chemotherapy regimens, and early screening methods have improved CRC prognosis.[2]

Surgical techniques have gradually evolved, shifting from conventional open procedures to minimally invasive approaches, such as laparoscopic and robotic-

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assisted procedures.[3] Minimally invasive approaches reduce the risk of postoperative complications and increase the rate of recovery, thereby improving patients' overall quality of life.[4]

A paradigm shift has occurred in CRC management, with a trend toward tailored and targeted chemotherapy regimens being observed.[5] Chemotherapeutic agents such as oxaliplatin and irinotecan in combination with fluoropyrimidines have become staples in neoadjuvant and adjuvant therapies, yielding favorable survival outcomes.[6] Moreover, the advent of biologic agents, such as bevacizumab and cetuximab, has further revolutionized chemotherapy, opening new avenues for personalized therapy.[7]

Early screening is crucial for the prevention and treatment of CRC.[8] The implementation of comprehensive and accessible screening programs, such as those involving colonoscopy and fecal immunochemical tests, has led to a change in the average cancer stage at diagnosis; an increasing number of patients are receiving an early diagnosis, which improves the likelihood of treatment success.[9]

This study was conducted to analyze the trends in CRC outcomes in Taiwan over the years. Specifically, we assessed changes in surgical techniques, chemotherapy regimens and early screening results to measure the progress in CRC treatment and its implications for future patient care.

Patients and Methods

Patients

We retrospectively reviewed the prospectively collected data of patients with histologically confirmed colorectal adenocarcinoma who received treatment at the Division of Colorectal Surgery, Department of Surgery, Wan Fang Hospital, Taipei, Taiwan, between January 2004 and December 2015. Patients with TNM stage I-IV cancer who underwent curative surgery were included in this study. By contrast, patients with incomplete data; those who underwent noncurative surgery, emergent surgery, or local excision (local transanal wide excision for rectal cancer, endoscopic mucosal resection, or endoscopic submucosal dissection); and those with synchronous cancer were excluded from this study.

Adjuvant therapy protocol

Patients with stage III colon cancer or stage II or III rectal cancer, excluding those who were older than 75 years and had an Eastern Cooperative Oncology Group performance status of 0-2, received a 5-fluorouracil (5-FU)-based adjuvant regimen with or without oxaliplatin. Patients with stage II or III rectal cancer also received adjuvant radiotherapy. If intravenous chemotherapy was not possible, oral chemotherapy was prescribed as an alternative. Notably, adjuvant chemotherapy can be prescribed for some high-risk patients with stage II colon cancer at the discretion of the multidisciplinary team involved in patient care. Patients with stage IV colon cancer received the 5-FU-based regimen with or without oxaliplatin or irinotecan.

Data collection

The primary outcomes were 5-year overall survival (OS) and disease-free survival (DFS). Mortality data (date of death) were collected from the patients' medical records and our hospital's cancer registry and follow-up system. During the primary admission for surgery, data were collected on the patients' demographics, surgical parameters, surgical specimen quality, tumor-related variables, and short-term outcomes. In addition, data on adjuvant therapy were collected. However, because of administrative and system-related problems, the records of patients who received treatment between January 2009 and December 2010 were missing.

Statistical analysis

Categorical data were compared using the Fisher exact test or Pearson chi-square test and are presented in terms of number (percentage) values. Continuous variables were compared using the Mann-Whitney U test or Student *t* test and are presented in terms of

mean ± standard deviation or median [interquartile range] values. Kaplan-Meier curves were generated to evaluate the rates of OS and DFS. In addition, subgroup analyses by TNM stage were performed to evaluate DFS and OS rates. A p value of < 0.05 indicated statistical significance. Statistical analyses were performed using SPSS (version 24; IBM Corporation, Armonk, NY, USA).

Results

A total of 785 patients met the inclusion criteria. Of them, 81 patients who were treated between January 2009 to December 2010 were excluded because of the aforementioned data loss. In addition, we excluded 67, 23, and 75 patients who underwent noncurative surgery, emergent surgery, and local excision, respectively, and 11 patients who had synchronous cancer. Finally, 528 patients were included and stratified into the following two groups by treatment period: group 1 (January 2004 to December 2008; n = 252) and group 2 (January 2011 to December 2015; n = 276). Fig. 1 presents a flowchart depicting the patient inclusion process.

Table 1 presents the baseline characteristics of the patients. At diagnosis, group 2 was significantly younger than group 1 (median age: 64.5 [57-76] vs. 71 [59-79] years; $p = 0.043$). The proportion of harvested lymph nodes was significantly higher in group 2 than in group 1 (21 [15, 29] and 15 [10, 21]; $p < 0.001$). Furthermore, the proportion of patients receiving adjuvant chemotherapy was significantly higher in group 2 than in group 1 (46.0% vs. 5.6%; $p < 0.001$). More patients in group 2 than in group 1 received intravenous chemotherapy (28.6% vs. 1.6%; $p < 0.001$) or oral chemotherapy (17.4% vs. 4.0%; $p < 0.015$). Furthermore, the rate of OS was higher in group 2 than in group 1 (74.3% vs. 50.8%; $p < 0.001$). However, no significant between-group difference was noted in the rate of 5-year DFS (group 2 vs. group 1: 81.2% vs. 77.0%; $p = 0.238$).

Table 2 presents the results of the subgroup analyses by TNM stage. No significant between-group dif-

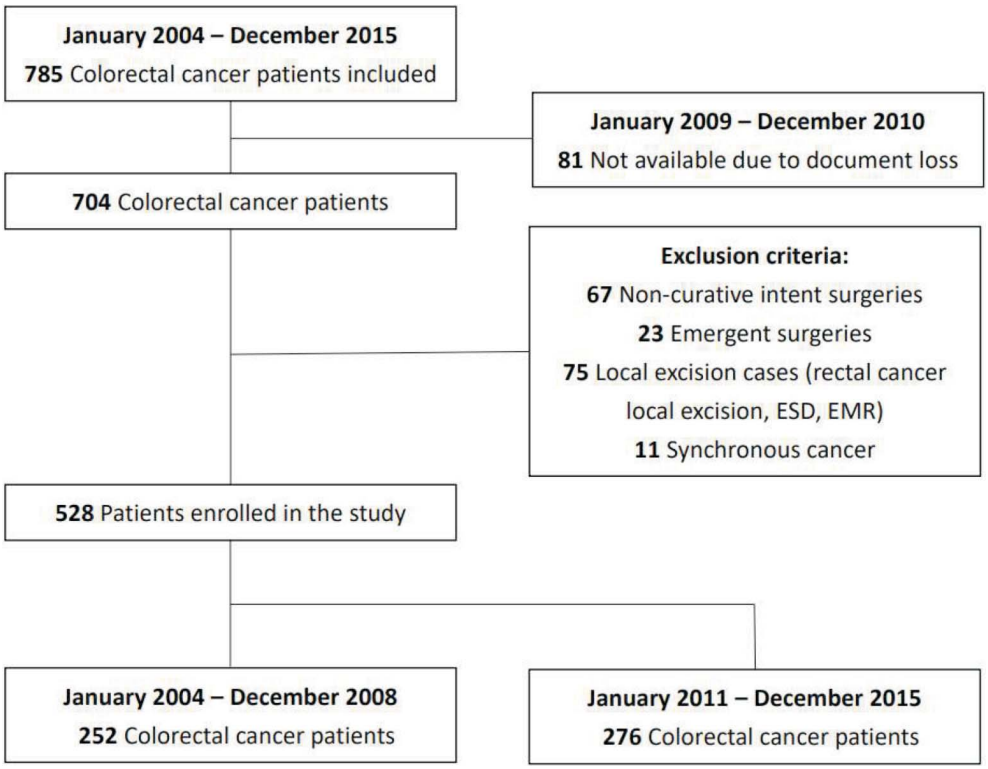

Fig. 1. Study exclusion flowchart. EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

ference was noted in the rate of DFS across cancer stages; the rates in groups 1 and 2, respectively, were as follows: stage I, 95.3% vs. 94.7% ($p = 0.889$); stage II, 86.7% vs. 86.6% ($p = 0.976$); stage III, 70.0% vs. 77.3% ($p = 0.268$); and stage IV, 25.0% vs. 44.4% ($p = 0.236$). However, significant between-group differences were noted in the rate of OS across cancer stages; the rates in groups 1 and 2, respectively, were as follows: stage I, 67.4% vs. 87.7% ($p = 0.014$); stage II, 51.8% vs. 75.6% ($p = 0.001$); stage III, 47.3% vs. 68.9% ($p < 0.001$); and stage IV, 25.0% vs. 61.1% ($p = 0.034$).

Table 3 presents the results of a univariate logistic analysis performed to identify factors influencing DFS in patients with CRC. No significant between-group difference in age, sex, lymph node count, or chemotherapy regimen was noted.

Table 4 presents the results of a univariate logistic analysis performed to identify factors influencing OS in patients with CRC. In group 1, age at diagnosis (95% confidence interval [CI]: 0.0294-0.0713; $p < 0.001$) and male sex (odds ratio: 0.554; 95% CI: 0.044-1.0711; $p = 0.034$) significantly influenced OS. In group 2, age at diagnosis (95% CI: 0.0432-0.0919; $p < 0.001$) and receiving chemotherapy (odds ratio: 0.506; 95% CI: -1.2566 to -0.1272; $p = 0.018$) were significant factors influencing OS.

The Kaplan-Meier curves indicated that the rates of 5-year DFS were 77.0% (194/252) in group 1 and 81.2% (224/276) in group 2 ($p = 0.238$) (Fig. 2). The rates of 5-year OS were 50.8% (128/252) in group 1 and 74.3% (205/276) in group 2 ($p < 0.001$) (Fig. 3). The subgroup analyses in Fig. 4 revealed no between-

Table 1. Background clinical characteristics

	Group 1 (2004-2008) n = 252	Group 2 (2011-2015) n = 276	*p* value
Sex (male/female)	154/98	157/119	0.324
Age in years, median (IQR)	71 (59-79)	64.5 (57-76)	0.043*
Pathological staging			0.717
Stage I	43	57	
Stage II	83	82	
Stage III	110	119	
Stage IV	16	18	
Lymph node, median (IQR)	15 (10, 21)	21 (15, 29)	< 0.001*
Adjuvant chemotherapy (+/-)	14/238 (5.6%)	127/149 (46.0%)	< 0.001*
IV form	4 (1.6%)	79 (28.6%)	< 0.001*
Oral form	10 (4.0%)	48 (17.4%)	0.015*
5-year disease-free (+/-)	194/58 (77.0%)	224/52 (81.2%)	0.238
Disease-free follow-up duration (months, IQR)	123 (25, 172.5)	73 (53.75, 92)	
5-year overall survival (+/-)	128/124 (50.8%)	205/71 (74.3%)	< 0.001*
Overall survival follow-up duration (months, IQR)	127.5 (33.5, 174)	76 (60, 93)	

* $p < 0.05$.

Table 2. Pathological staging subgroup analysis for DFS and OS

	DFS			OS		
	Group 1 (2004-2008)	Group 2 (2011-2015)	*p* value	Group 1 (2004-2008)	Group 2 (2011-2015)	*p* value
Stage I	41/2 (95.3%)	54/3 (94.7%)	0.889	29/14 (67.4%)	50/7 (87.7%)	0.014*
Stage II	72/11 (86.7%)	71/11 (86.6%)	0.976	43/40 (51.8%)	62/20 (75.6%)	0.001*
Stage III	77/33 (70.0%)	91/28 (77.3%)	0.268	52/58 (47.3%)	82/37 (68.9%)	< 0.001*
Stage IV	4/12 (25.0%)	8/10 (44.4%)	0.236	4/12 (25.0%)	11/7 (61.1%)	0.034*

DFS, disease-free survival; OS, overall survival.
* $p < 0.05$.

Table 3. Univariant logistic regression analysis for DFS

	Group 1 (2004-2008)				Group 2 (2011-2015)			
	OR	95% CI		*p* value	OR	95% CI		*p* value
Age		-0.0416	0.0013	0.065		-0.0047	0.0415	0.124
Gender	1.054	-0.5453	0.6667	0.865	1.041	-0.5662	0.6598	0.896
Lymph node		-0.0462	0.0212	0.508		-0.0128	0.041	0.283
Chemotherapy	1.363	-1.0147	1.448	0.613	1.007	-0.6038	06117	0.982

CI, confidence interval; DFS, disease-free survival; OR, odds ratio.
* $p < 0.05$.

Table 4. Univariant logistic regression analysis for OS

	Group 1 (2004-2008)				Group 2 (2011-2015)			
	OR	95% CI		*p* value	OR	95% CI		*p* value
Age		0.0294	0.0713	< 0.001*		0.0432	0.0919	< 0.001*
Gender	0.554	0.044	1.0711	0.034*	1.226	-0.3422	0.7609	0.468
Lymph node		-0.0185	0.0366	0.526		-0.0134	0.0355	0.361
Chemotherapy	0.556	-1.7926	0.5052	0.305	0.506	-1.2566	-0.1272	0.018*

CI, confidence interval; OS, overall survival; OR, odds ratio.
* $p < 0.05$.

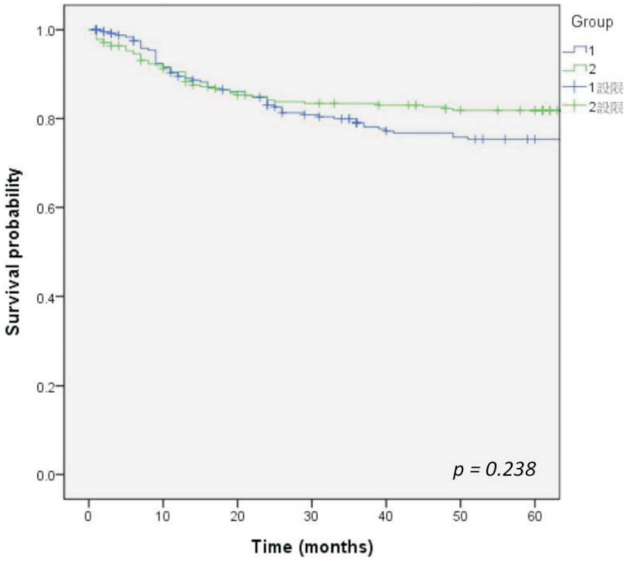

Fig. 2. Five-year disease-free survival rate.

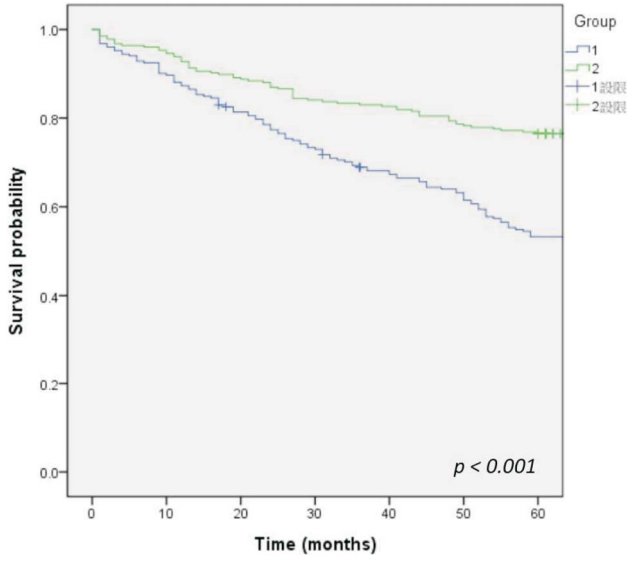

Fig. 3. Five-year overall survival rate.

group difference in the rate of 5-year DFS. However, as shown in Fig. 5, significant between-group difference was noted in the rate of OS in patients with stage I ($p = 0.014$), stage II ($p = 0.001$), stage III ($p < 0.001$), and stage IV ($p = 0.034$) CRC.

Discussion

This article presents trends in survival for patients diagnosed with CRC underwent curative resection in a single teaching medical center in Taiwan. The 5-year OS has improved from 50.8% in 2004-2008 to 74.3% in 2011-2015, and the 5-year DFS has improved from 77.0% in 2004-2008 to 81.2% in 2011-2015. The trend of CRC related survival has also been reported in several national based studies in these decades. In the United States, the 5-year relative survival rate for CRC has increased from 50% in the mid-1970s to 64% during 2009-2015.[10] In Europe, the 5-

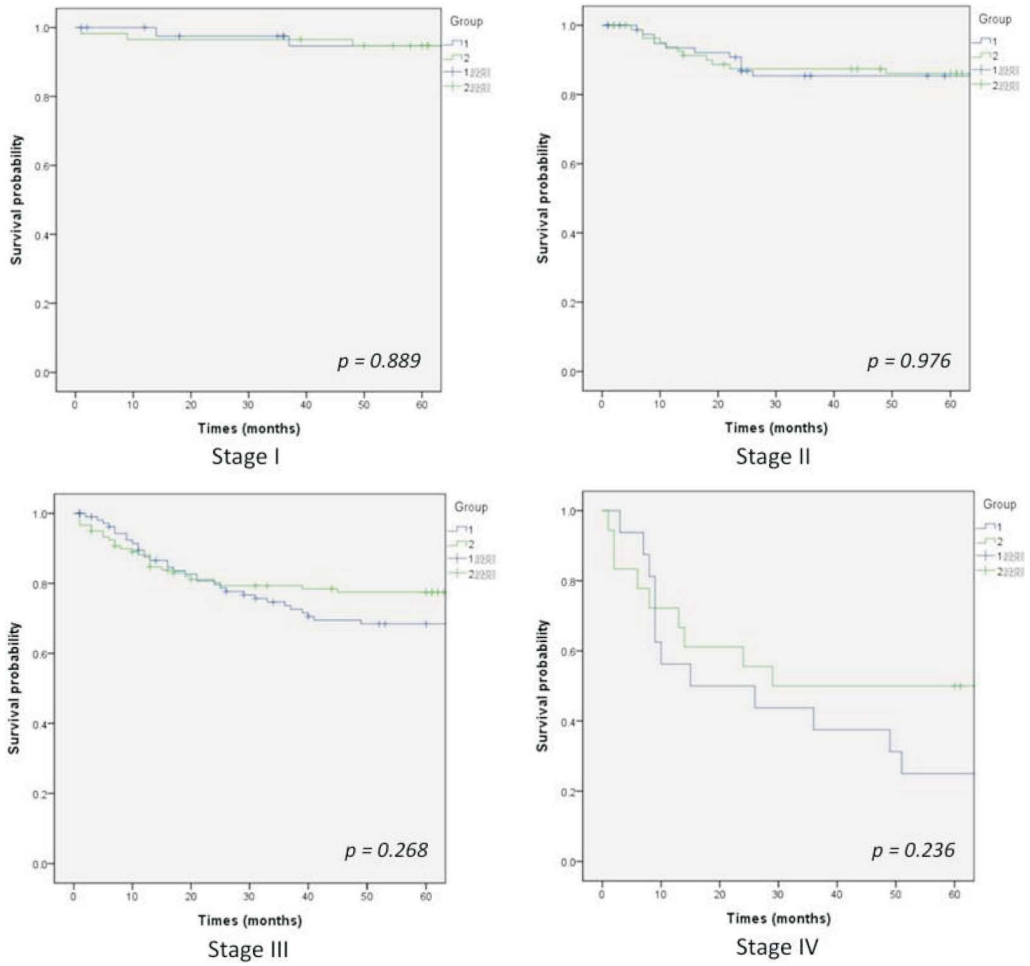

Fig. 4. Five-year disease-free survival rate in each cancer stage.

year relative survival rate for colon cancer patients has increased from 54% in 1999-2001 to 58% in 2005-2007.[11] In China, the age-standardized 5-year relative survival for CRC was reported 47.2% in 2003-2005, 52.7% in 2006-2011, and 56.9% in 2012-2015.[12] The population of these national-based studies, including all CRC patients who have undergone colorectal cancer surgery as well as those who receiving systemic treatments, differs from our study which focuses on patients underwent curative resection.

The improvement in cancer survival has been attributed to surgical techniques, increased availability of cancer treatments, and CRC screening.[13] The shift from conventional open procedures to laparoscopic and robotic procedures reflects ongoing advancements in CRC surgical techniques.[14] A propensity score-matched cohort study using nationwide hospital record database with total 531,536 patients, of which 65.6% patients underwent open surgeries, 32.9% underwent laparoscopic surgeries, and 1.5% underwent robotic surgeries, reported that patients undergoing open surgery had a higher mortality rate (OR 2.98, 95% CI 2.61-3.40), more general medical complications (OR 1.77, 95% CI 1.67-1.87), a longer length of hospital stay (6.60 vs. 4.36 days), and higher total cost, compared to those undergoing laparoscopic surgery. Mortality rate and general medical complications were equivalent in the laparoscopic and robotic surgery groups, but the median cost was lower in the laparoscopic group.[15] In the aspect of long-term oncological outcome, the RECOURSE Study, concluded from 1 randomized study (ROLARR trial) and 27 comparative studies, revealed significantly favored OS of robotic over laparoscopic (0.76, 95% CI 0.63-0.91, p =

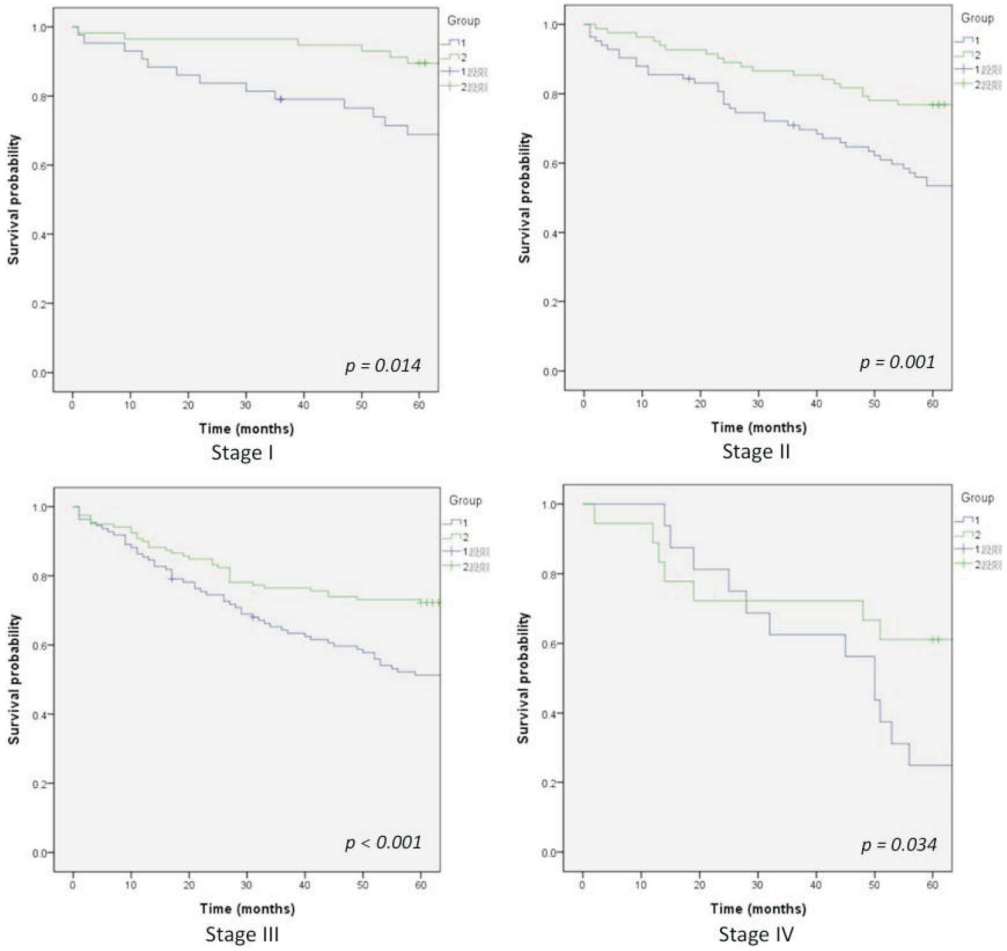

Fig. 5. Five-year overall survival rate in each cancer stage.

0.004) and open surgery (0.83, 95% CI 0.74-0.93, p = 0.001) in patients underwent low-anterior resection/ total mesorectal excision for rectal cancer.[16] No significant differences in rate of recurrence or DFS between robotic-assisted surgery and laparoscopic or open surgery was noted.[17]

For patients who have undergone curative resection, the accurate identification of lymph node metastasis is crucial for prognostic evaluation and treatment decision-making.[18] An adequate number of resected lymph nodes is needed to properly assess the regional lymph nodes status.[19] Currently, clinical guidelines recommend at least 12 negative lymph nodes to confirm the absence of nodal spread.[20,21] Importantly, comprehensive harvesting of lymph nodes in CRC cases enhances the precision of clinical staging, ultimately improving prognosis.[22-24] Advances in lymphadenectomy have increased the number of lymph node harvested. However, the lymph node count as a benchmark of quality in CRC remained controversial. On the one hand, Wang et al. concluded that the number of lymph nodes hospitals examined following colectomy for colon cancer is not associated with staging, use of adjuvant chemotherapy, or patient survival.[25] On the other hand, Jan H. et al. concluded that lymph node counts can have value as a benchmark of surgical/pathologic quality in node-negative CRC with a 12-node threshold, and warranted continued efforts to maximize node harvesting and examination.[26] In our experience, the development of surgical techniques performed in our hospital, such as laparoscopic complete mesocolic excision, laparoscopic total mesorectal excision, D3 lymph node dissection, transanal total mesorectal excision, and lateral pelvic lymph node dissection, showed significant increase in lymph node harvested amount. However, no significant dif-

ference was found in univariate logistic regression analysis of OS. We would only observe advance in lymphadenectomy, but the impact of surgical technique improvement on OS remained unclear. Further larger-scale and integrative studies may have the opportunity to clarify the relationships.

Chemotherapy for CRC has undergone considerable improvements over the last decade due to the understanding of the disease and its treatment developing.[27] Combination therapies, including FOLFOX (5-FU/leucovorin and oxaliplatin) and FOLFIRI (5-FU/leucovorin and irinotecan), have emerged as standard treatment options for metastatic CRC, with FOLFOX also serving as the gold standard of adjuvant therapy. The integration of biological agents such as bevacizumab and cetuximab/panitumumab has further enhanced these treatments.[28] The CRYSTAL trial revealed first-line treatment with cetuximab plus FOLFIRI, as compared with FOLFIRI alone, reduced the risk of progression of metastatic colorectal cancer (0.85, 95% CI 0.72-0.99; $p = 0.048$).[7] The FIRE-3 trial concluded that FOLFIRI plus cetuximab could be the preferred first-line regimen than FOLFIRI plus bevacizumab for patients with KRAS exon 2 wild-type metastatic colorectal cancer (0.77, 95% CI 0.62-0.96; $p = 0.017$).[29] The TRIBE study reported better median OS in the FOLFOXIRI plus bevacizumab group compared with the FOLFIRI plus bevacizumab group as first-line treatment of patients with metastatic colorectal cancer (0.80, 95% CI 0.65-0.98; $p = 0.03$).[30]

Similar to many other countries, Taiwan has experienced an evolution in its standard chemotherapy regimens for CRC. The use of combination regimens, has led to improved therapy response rates and survival outcomes in Taiwanese patients with CRC.[31,32] Agents such as bevacizumab and cetuximab/panitumumab have been introduced and have resulted in improved efficacy, enhanced survival benefits, and reduced toxicity compared with those of conventional chemotherapy.[33] However, the cost of cancer treatment, including chemotherapy, remains a key challenge. The adoption of novel therapies, particularly those involving targeted agents, has financial implications for both the health-care system and patients. This factor plays a crucial role in treatment decisions and the availability of certain therapies.[34]

In 2005-2010, Taiwan's National Health Insurance (NHI) started covering the cost of FOLFOX for CRC; in 2010-2015, the organization further expanded the coverage to FOLFOX with bevacizumab and cetuximab/panitumumab. Since then, the NHI has been progressively expanding its coverage to encompass other cancer treatment options, including immunotherapies and targeted therapies, in addition to traditional chemotherapy regimens. This expansion is part of Taiwan's ongoing efforts to provide comprehensive care and make advanced treatment options accessible to all patients with cancer.[35] In our study, the ratio of patients receiving chemotherapy significantly increased between the two groups. Also, receiving chemotherapy is a significant factor in univariate logistic regression analysis of DFS. However, we do not distinguish adjuvant or neoadjuvant chemotherapy, as well as initial CRC stage, regimen, and courses. Stage-specific chemotherapy regimen research of oncological outcome could be conducted in future studies.

As the saying, prevention is better than cure. The improvement in cancer survival has also been attributed to CRC screening techniques, which include endoscopic examinations (colonoscopy and flexible sigmoidoscopy), stool-based tests (FOBT and fecal DNA test), and novel screening tests in pipelines such as CT colonography, capsule endoscopy, and blood or urine biomarkers. Population-based evidence from the United States has demonstrated that the overall incidence of CRC has decreased by nearly 40% with the increased use of colonoscopy screening from 20% in 2000 to 61% in 2018 among individuals aged 50-64 years.[10] In Taiwan, CRC screening was first introduced since 2004 for residents between the age of 50-69, and became one of four major cancer screenings freely available under the NHI since 2010. The NHI coverage of CRC screening was further expanded to those aged 50-74 years since 2014.[36] In Asia, colonoscopy followed by CRC screening has been reported to be associated with a 56% reduction in incidence and a 68% reduction in mortality of CRC.[37] In Taiwan, Yang et al. conducted a retrospective study of 58,891 participants and concluded that CRC screen-

ing with fecal immunochemical test significantly increased the early detection rate (66.7% and 52.7%, $p = 0.0013$).[38] In our study, we found significant decrease in age of diagnosis in the decade. The trend might be due to CRC screening policies; yet the study did not collect patients' CRC screening profile for further analysis.

The Taiwan Society of Colon and Rectal Surgeons (TSCRS) has been pivotal in formulating consensus-based recommendations for the treatment of metastatic CRC in Taiwan.[39] The society suggests that treatment is a dynamic process and that patients receiving disease control therapy can undergo surgical resection as part of the care continuum.[40] The TSCRS consensus has provided guidance for clinical decision-making within multidisciplinary teams, optimizing the use of health-care resources in Taiwan.[41]

This study has some limitations. First, data loss might have affected the comprehensiveness and accuracy of our findings. Second, the single-center design might have limited the generalizability of our findings to broader populations. Third, we could not differentiate between open, laparoscopic, robotic-assisted surgeries and colon or rectal cancers; this prevented us from gaining deeper insights into the efficacies of specific treatment approaches. Fourth, because of limited digital records and consequent data loss, very few parameters were available for analysis, which affected the depth and breadth of our study. Finally, our statistical models were not extensively adjusted for variations in chemotherapy regimens and courses; this might have influenced the oncological outcomes. These factors collectively suggest the need for caution in interpreting our conclusions and underscore the importance of future research.

Conclusion

The observed improvement in overall survival in patients with colorectal cancer highlights the dynamic nature of cancer therapy and the importance of continual optimization of medical approaches. The advancements in surgical techniques, chemotherapy, and early screening methods might be relevant factors.

Acknowledgments

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Conflicts of Interest

The undersigned authors declare no financial (e.g., honoraria; educational grant; association with speakers' bureau; membership, employment, consultancy, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangement) or nonfinancial (e.g., personal or professional relationship, affiliation, and knowledge or belief) interestrelated to the work reported in the manuscript.

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原　著

台灣根治性手術後大腸癌結果趨勢：單一醫學中心 10 年資料分析研究中文摘要

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目的　大腸直腸癌是導致癌症相關死亡的主要原因之一。過去十年中，外科技術、化學治療和早期篩查的進步改善了患者的預後。

方法　本研究回顧了 2004 年 1 月至 2015 年 12 月間在單一醫學中心接受治療的結直腸腺癌患者的註冊資料。主要結果指標是 5 年總生存率和無病生存率。

結果　共有 528 名患者分為兩組。第一組 (2004-2008 年) 包含 252 例，第二組 (2011-2015 年) 有 276 例。兩組的 5 年無病生存率相似，但第二組觀察到了更好的 5 年總生存率，且收穫的淋巴結數量更多，接受術後輔助化療的比例更高，診斷時平均年齡也更低。

結論　本研究發現過去十年間大腸直腸癌患者總生存率的顯著提高，外科技術、化學治療和早期篩查方法的進步或許是相關原因。

關鍵詞　結直腸癌、腫瘤學成果改善、10 年追蹤。