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ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 477–488

www.jcma-online.com

Original Article

Adjuvant chemotherapy with tegafur/uracil for more than 1 year improves disease-free survival for low-risk Stage II colon cancer

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Received August 29, 2015; accepted February 1, 2016

Abstract

Background: It is uncertain whether adjuvant chemotherapy (CMT) improves survival in patients with low-risk Stage II colon cancer. We aimed to determine the disease-free survival (DFS) and 5-year overall survival (OS) of low-risk Stage II colon cancer patients treated with adjuvant tegafur/uracil (UFUR).

Methods: From January 2004 to December 2011, the follow-up status of 278 low-risk Stage II colon cancer patients who underwent surgery in a single medical center was retrospectively analyzed. These patients were divided into three groups based on whether they received adjuvant CMT with UFUR, adjuvant CMT with 5-fluorouracil, or surgery alone. DFS and 5-year OS curves were calculated using Kaplan–Meier survival analysis and Cox proportional hazards regression.

Results: In the study population, including 278 low-risk Stage II colon cancer patients with a mean age of 68.28 ± 13.01 years, 132 (47.5%) received adjuvant CMT with UFUR, 49 (17.6%) received adjuvant CMT with 5-fluorouracil, and 97 (34.9%) underwent radical surgery alone. At 5 years, the adjusted DFS and OS of low-risk Stage II colon cancer patients were 85.5% and 81.8%, respectively, in the surgery alone group and 97.9% and 96.2%, respectively, in the surgery plus UFUR > 12 months group ($p = 0.004$ and $p = 0.098$, respectively). In multivariate analysis, CMT with UFUR for more than 12 months increased DFS over surgery alone. There was no statistical difference in the 5-year OS.

Conclusion: Adjuvant CMT treatment of low-risk Stage II colon cancer patients with UFUR for more than 12 months following surgery improves DFS over surgery alone.

Keywords: adjuvant chemotherapy; disease-free survival; low-risk Stage II colon cancer; overall survival; tegafur/uracil

1. Introduction

Radical surgical resection is the primary treatment for patients with locoregional colon cancer [negative lymph node (LN) Stage I, II disease]; such patients have a good prognosis, with a 5-year overall survival (OS) of approximately 80% after radical surgery alone.[1,2] Chemotherapy (CMT) drugs are administered as systemic therapy for colon cancer patients with positive LNs and distal metastasis. However, there is no definite consensus on the role of adjuvant CMT for Stage II colon cancer, especially in low-risk patients. In our patient database, the routine consecutive administration of tegafur/uracil (UFUR) as adjuvant CMT has provided good disease-free survival (DFS) and 5-year OS in patients with low-risk Stage II colon cancer, especially with treatment for more

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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http://dx.doi.org/10.1016/j.jcma.2016.04.001

than 12 months; this strategy has resulted in improved DFS and 5-year OS rates for low-risk Stage II colon cancer patients after radical surgery.

The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) treatment guidelines do not recommend the routine use of adjuvant CMT for Stage II colon cancer patients. ASCO and NCCN guidelines state that adjuvant CMT can be considered for patients with high-risk factors, including T4 tumors leading to obstruction, perforation, and poor differentiation, and for patients with fewer than 12 positive LNs.[3,4] Some published studies support the use of adjuvant CMT following surgery, as it provides a survival benefit over surgery alone,[5–8] while others have supported adjuvant CMT only for high-risk Stage II colon cancer patients.[9–13] However, most of these studies included mixed-Stage II cancers (low-risk and high-risk Stage II colon cancer patients), and not all of these studies provide a separate analysis of survival benefit for patients with low-risk Stage II colon cancer treated with adjuvant UFUR CMT. Some studies have addressed the question of whether to use adjuvant CMT for low-risk Stage II colon cancer. However, clinical trials have not demonstrated that adjuvant CMT improves survival for patients with resected low-risk Stage II colon cancer. Thus, its routine use in these patients has been controversial.[3] The purpose of this study was to investigate the survival outcome with UFUR as adjuvant CMT for low-risk Stage II colon cancer patients.

2. Methods

2.1. Patient selection

From January 2004 to December 2011, a total of 2809 colon cancer patients underwent operation at our hospital (Tri-Service General Hospital, Taipei, Taiwan). Clinical data were extracted from the retrospectively collected Cancer Registry Group, Tri-Service General Hospital. The surgical and pathological findings were recorded according to the $6^{th}/7^{th}$ American Joint Committee on Cancer (AJCC)/Union for International Cancer Control tumor-node-metastasis (TNM) classification. All operations were performed by colorectal surgeons in our hospital.

There were 535 patients with Stage II colon cancer in our hospital based on the pathology, according to the $6^{th}/7^{th}$ AJCC staging system. Those who underwent curative surgical intervention alone or surgery plus adjuvant CMT [UFUR or 5-fluorouracil (5-FU)] were enrolled in this study. Patients with any of the following criteria were excluded: (1) rectal cancer; (2) pathological diagnosis of positive surgical margins; (3) synchronous or metachronous double cancer; (4) synchronous or metachronous multiple colon cancer; (5) inflammatory bowel disease or hereditary colon cancer syndromes; (6) previous history of malignancy; (7) lack of an entire treatment course in our hospital; (8) perioperative (<30 days post-operation) mortality; (9) lack of follow-up data; or (10) incomplete oral adjuvant therapy (<3 months). Data on approximately 9.5% of patients was incomplete, and hence, these data were removed from the database. A total of 403 patients with Stage II colon cancer were included in this retrospective analysis. They were divided into three non-randomized groups: those who underwent surgery alone, surgery plus adjuvant CMT with UFUR, and surgery plus adjuvant CMT with 5-FU. In total, 175 Stage II colon cancer patients received UFUR as adjuvant CMT following surgery, including 132 low-risk patients.

After a potentially curative operation, the decision of whether or not to administer adjuvant CMT depended on the patients decision, the clinical judgment of the attending physicians, and our multidisciplinary team meeting, which was based on the general performance of the patient, their pathologic features, and operative condition. All of the patients in this study agreed to receive oral UFUR or infusional 5-FU after a discussion on the potential morbidity and benefits after treatment.

Seventy-three Stage II colon cancer patients received infusional 5-FU-based adjuvant CMT over 6 months. The regimen of infusional 5-FU-based CMT included high-dose 5-FU (425 mg/m^2/d) plus leucovorin (30 mg/m^2/d), as either a monthly 5-day course or a weekly 1-day course for a period of 6 months. In the UFUR group, patients receiving 5-FU prodrug capsules (UFUR; 100 mg/capsule) administered at 4 capsules/d (2 capsules twice a day) within the 1-month postoperative period at the initial dose were considered adjuvant therapy recipients.

The protocol treatment was discontinued when the first recurrence was confirmed or when the side effects or toxicity were not tolerated. A dose reduction was implemented when the white blood cell count was <3000/mm^3, platelets were <100,000/mm^3, absolute neutrophil count was <1500, and aspartate aminotransferase and/or alanine transaminase levels were more than three times higher than the upper limit of the normal range. None of the patients received preoperative CMT or radiotherapy.

The database included: (1) patient demographic information, including their name, sex, age, family history, levels of tumor markers such as carcinoembryonic antigen (CEA), and carbohydrate-antigen 19-9 (CA19-9); and (2) characteristics of the tumor, including the location, gross appearance, TNM stage, and important pathologic prognostic features, such as the number of LNs examined, differentiation, lymphovascular space invasion (LSI), tumor size, and the invasion pattern of the cancerous tissue and mucinous component.

2.2. Follow up

According to the NCCN treatment guidelines, all patients had a regular follow up consisting of visits at 3-month intervals for the first 2 years, 6-month intervals for up to 4 years, and annually thereafter. The follow-up examinations included a physical examination, rectodigital examination, blood chemistry panel (such as complete blood cell count and CEA, CA19-9 levels, and liver function tests), radiographs of the thorax, and abdominal sonograms. A colonoscopy was performed annually. If recurrence was suspected, further testing, such as a chest computed tomography scan, whole-body bone scan, or even a whole-body positron emission tomography

Table 1
Clinicopathological distribution of total Stage II colon cancer patients included in the analyses stratified by their characteristics and treatment group.

	Surgery alone (n = 155)	Surgery plus UFUR (n = 175)	Surgery plus 5-FU (n = 73)	p
	n (%)	n (%)	n (%)	
Age (y), mean (SD)	74.17 (12.13)	67.69 (11.26)	57.14 (11.08)	<0.001
≤70 y	48 (30.97)	101 (57.71)	63 (86.30)	<0.001
>70 y	107 (69.03)	74 (42.29)	10 (13.70)	
Sex				0.858
Male	83 (53.55)	99 (56.57)	40 (54.79)	
Female	72 (46.45)	76 (43.43)	33 (45.21)	
Risk factor				0.149[a]
Without risk factor	97 (62.58)	132 (75.43)	49 (67.12)	
With 1 risk factor	46 (29.68)	35 (20.00)	19 (26.03)	
With >1 risk factor	12 (7.74)	8 (4.57)	5 (6.85)	
Location of primary tumor				0.178
Cecum	16 (10.32)	18 (10.29)	8 (10.96)	
Ascending colon	35 (22.58)	34 (19.43)	25 (34.25)	
Transverse colon	17 (10.97)	27 (15.43)	6 (8.22)	
Descending colon	14 (9.03)	19 (10.86)	12 (16.44)	
Sigmoid colon	56 (36.13)	62 (35.43)	18 (24.66)	
Rectosigmoid	17 (10.97)	15 (8.57)	4 (5.48)	
Location of primary tumor				0.985
Right	65 (41.94)	74 (42.29)	30 (41.10)	
Left	90 (58.06)	101 (57.71)	43 (58.90)	
Obstruction				0.249[a]
Without obstruction	146 (94.19)	170 (97.14)	68 (93.15)	
With obstruction	9 (5.81)	5 (2.86)	5 (6.85)	
NLR, mean (SD)	6.38 (7.23)	4.71 (8.31)	5.53 (5.22)	0.145
CRM				
Proximal (cm), mean (SD)	6.66 (5.06)	7.00 (5.01)	7.53 (7.25)	0.675
Distal (cm), mean (SD)	6.12 (5.52)	6.74 (5.88)	8.09 (7.23)	0.192
CEA (ng/mL), mean (SD)	5.21 (7.04)	6.21 (16.35)	13.55 (37.97)	0.034
≤5	83 (73.45)	139 (82.25)	31 (67.39)	0.054
>5	30 (26.55)	30 (17.75)	15 (32.61)	
CA19-9 (U/mL), mean (SD)	36.72 (97.15)	18.51 (21.98)	57.46 (136.88)	0.012
≤25	65 (70.65)	115 (75.66)	25 (67.57)	0.508
>25	27 (29.35)	37 (24.34)	12 (32.43)	
Tumor size (mm), mean (SD)	49.63 (20.54)	51.16 (25.17)	62.72 (27.79)	<0.001
≤49	82 (53.25)	94 (53.71)	23 (31.94)	0.004
>49	72 (46.75)	81 (46.29)	49 (68.06)	
Gross appearance				0.054
Polypoid	47 (36.72)	51 (31.48)	29 (49.15)	
Ulcerative	81 (63.28)	111 (68.52)	30 (50.85)	
Histopathological classification				0.893
Not poorly differentiated	143 (92.26)	160 (91.43)	66 (90.41)	
Poorly differentiated	12 (7.74)	15 (8.57)	7 (9.59)	
Lymphovascular space invasion (LSI)				0.024[a]
Without LSI	142 (97.93)	169 (98.83)	56 (91.80)	
With LSI	3 (2.07)	2 (1.17)	5 (8.20)	
LNs (Z), mean (SD)	15.30 (5.66)	16.03 (5.26)	18.70 (6.66)	<0.001
<12	37 (23.87)	22 (12.57)	2 (2.74)	<0.001
≥12	118 (76.13)	153 (87.43)	71 (97.26)	
Perineural invasion				0.186[a]
Without invasion	137 (96.48)	163 (98.79)	58 (95.08)	
With invasion	5 (3.52)	2 (1.21)	3 (4.92)	

Assessed by one-way analysis of variance or by Chi-square test.
CA = cancer antigen; CEA = carcinoembryonic antigen; CRM = circumferential resection margin; LN = lymph node; NLR ratio = neutrophil to lymphocyte ratio; SD = standard deviation; UFUR = tegafur/uracil; 5-FU = 5-fluorouracil.
[a] Fisher's exact test.

scan was performed to clarify the site of recurrence. The definition of recurrence included a recurrent lesion that was confirmed pathologically or that showed progressively increasing size in image studies.

The 5-year OS time was measured from the date of the operation to the date of last visit or death. DFS was counted from the date of the operation to the date of confirmation of recurrence.

2.3. Statistical analysis

The primary endpoint was to determine whether the addition of CMT to curative surgical resection conferred an improvement in 5-year DFS and OS for patients with AJCC Stage II colon cancer. Analyzed factors included age (≤70 years or >70 years), sex, presence of risk factors, location of primary tumor (cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectosigmoid), presence of an obstruction, histopathological classification (well, moderately, or poorly differentiated), tumor size (≤49 mm, or >49 mm), CEA level (≤5 ng/mL, or >5 ng/mL), CA19-9 level (≤25 U/mL, or >25 U/mL), presence of LSI, presence of perineural invasion, and the number of LNs examined (1–11 or >12).

IBM SPSS statistics software version 22 (IBM SPSS Statistics 22, Asia Analytics Taiwan Ltd., Taipei, Taiwan) was used for data entry and statistical analysis. Each variable factor of the 5-year OS and DFS rates was estimated using the Kaplan–Meier method. The significance of the differences between subgroups was calculated using the log-rank test. The variables that reached statistical significance ($p < 0.05$) were entered into multivariate analysis, which was performed using the Cox proportional hazard model. All statistical tests were two-tailed, and a p value < 0.05 was considered to be statistically significant.

2.4. Ethics statement

This retrospective study has been approved by the Institutional Review Board of Tri-Service General Hospital (Taiwan). No informed consent was given because the data were analyzed anonymously.

3. Results

3.1. Patient demographics

After the exclusion of 132 patients, 403 individuals with Stage II colon cancer were initially enrolled in our study and stratified into three subgroups: (1) 155 (38.5%) patients who underwent surgery alone; (2) 175 (43.4%) who underwent surgery and also received adjuvant CMT with oral UFUR; and (3) 73 (18.1%) who underwent surgery plus received adjuvant CMT with infusional 5-FU. The distribution of patients by their demographic characteristics is shown is Table 1. The patient population included 222 men (54.9%) and 181 women (45.1%). With regard to tumor location, 170 (42.1%) patients were right colon carcinomas and 233 (57.9%) were left colon carcinomas. In this series, the average number of examined LNs in each specimen was 16.24 ± 5.80 (range, 3–43). In 61 specimens (15.1%), the number of LNs examined was <12. Within the median 53-month follow-up period, recurrence developed in 36 patients (8.18%). When the three treatment groups (surgery alone, surgery plus UFUR, and surgery plus 5-FU) were compared, there were no differences in sex, with or without risk factors, location of primary tumor, primary tumor size (≤ 49mm, or >49 mm), presence of LSI, presence of perineural invasion, CEA or CA-199 level, histopathological classification, gross appearance, and the number of LNs examined. There was no postoperative mortality.

Patients with at least one risk factor (i.e., T4 lesion, LSI, obstruction at presentation, or the number of LNs examined was <12) were considered as the high-risk group. We further examined our data to see if patients who had more risk factors had poorer DFS. Three subgroups of risk factors (no risk factor, one risk factor, and more than one risk factor) significantly distinguished differences in the 5-year DFS and OS (DFS, 92.1%, 81.7%, and 79.2%, respectively, $p = 0.003$; and 5-year OS, 90.7%, 83.3%, and 80.8%, respectively, $p = 0.007$; Fig. 1).

Two hundred forty-eight patients (61.5%) received adjuvant CMT, either orally or intravenously. There was a significant difference in the 5-year DFS and 5-year OS between the Stage II colon cancer patients who did and did not receive adjuvant CMT (DFS, 91.0% and 84.2%, respectively, $p = 0.01$; and 5-year OS, 92.6% and 80.1%, respectively, $p < 0.001$; Figs. 2 and 3). The data for low-risk Stage II colon cancer patients showed the same results (DFS, 94.8% and 85.8%, respectively, $p = 0.013$; and 5-year OS, 94.8% and 81.8%, respectively, $p = 0.006$; Figs. 2 and 3).

These results demonstrate a significant survival benefit of adjuvant CMT for low-risk patients with Stage II colon cancer in terms of 5-year DFS (surgery alone vs. surgery plus UFUR vs. surgery plus 5-FU: 85.8% vs. 97.5% vs. 88.5%, respectively, $p = 0.004$; Fig. 4A) and 5-year OS (surgery alone vs. surgery plus UFUR vs. surgery plus 5-FU: 81.8% vs. 93.5% vs. 97.8%, respectively, $p < 0.017$; Fig. 4B).

Among the total Stage II colon cancer patients, we stratified them into three subgroups: surgery alone, surgery followed by adjuvant UFUR for less than <1 year, and surgery adjuvant UFUR for >1 year. All of the patients were followed up. The reasons for not reaching the initial prescribed dose included recurrence during the treatment period, adverse reactions, and complications. The duration of adjuvant CMT with UFUR was evaluated in the same manner as the survival benefits for 5-year DFS and 5-year OS for the low-risk patients. The subgroup of patients treated with adjuvant CMT with UFUR for more than 12 months had a significant benefit in terms of DFS over the surgery alone subgroup (surgery alone vs. surgery plus UFUR ≤ 12 months vs. surgery plus UFUR > 12 months: 85.8% vs. 97.0% vs. 97.9%, $p = 0.004$; Fig. 5B), but it was not statistically significant for 5-year OS (surgery alone vs. surgery with UFUR ≤ 12 months vs. surgery with UFUR > 12 months: 81.8% vs. 86.2% vs. 96.2%, $p = 0.098$; Fig. 6B).

The univariate and multivariate analyses for DFS and 5-year OS of low-risk Stage II colon cancer are shown in Tables 2 and 3, respectively. In univariate analysis, only adjuvant CMT with UFUR > 12 months [hazard ratio (HR) = 0.08, 95% confidence interval, 0.01–0.65, $p = 0.018$] were good prognostic factors that significantly influenced 5-year DFS over that of the surgery alone group (Table 2). Similarly, age ≤ 70 years, and adjuvant CMT with UFUR >

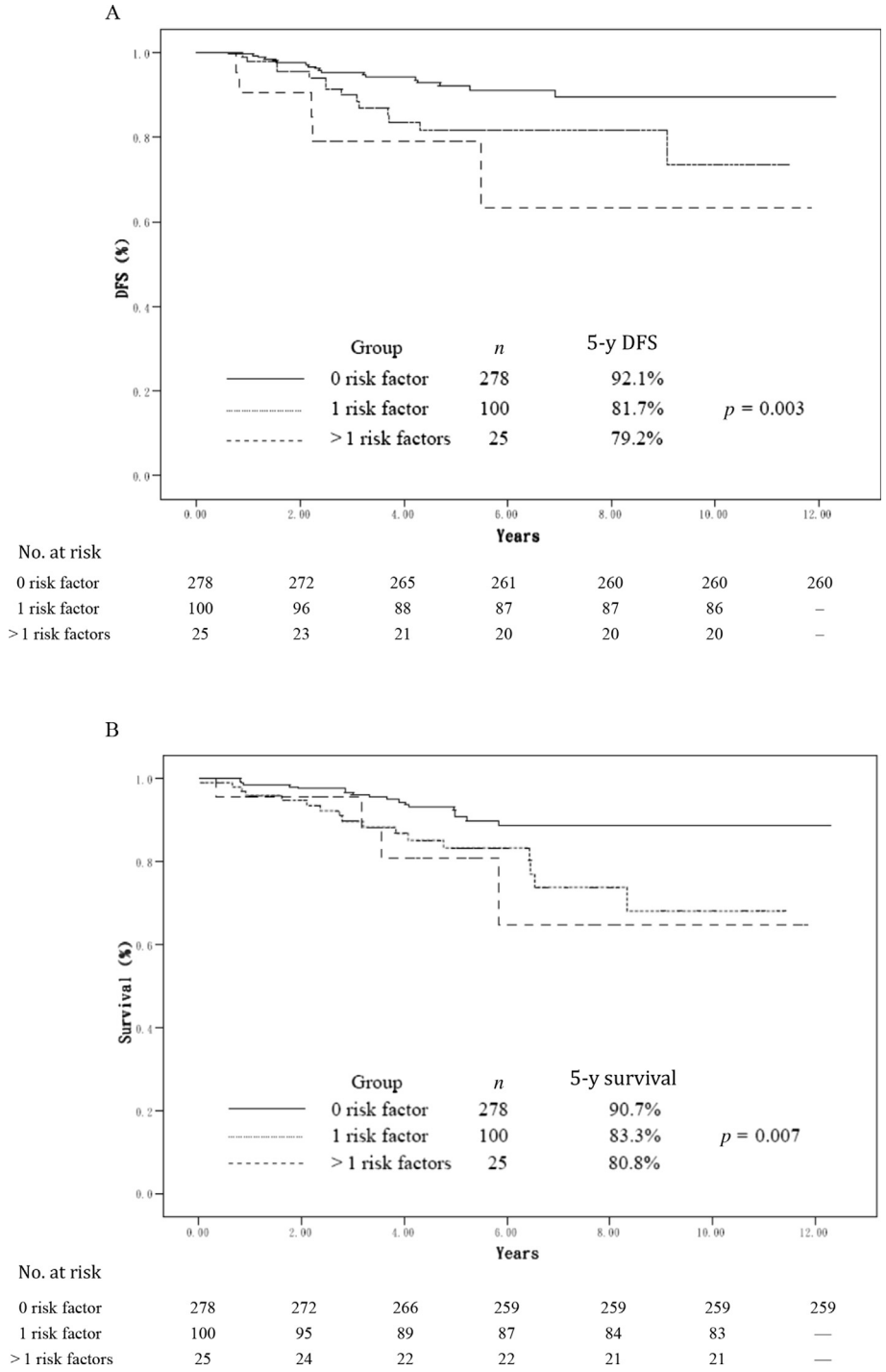


Fig. 1. Stage II colon cancer with more than one risk factor is associated with: (A) poorer disease-free survival (DFS; $p = 0.003$); and (B) 5-year overall survival ($p = 0.007$).

12 months (HR = 0.31, 95% confidence interval, 0.10–0.97, $p = 0.043$) were significantly associated with 5-year OS (Table 3). Multivariate analysis showed that only adjuvant CMT > 12 months (HR = 0.12, 95% confidence interval, 0.01–0.94; $p = 0.044$) was associated with better 5-year DFS. Moreover, age, sex, tumor size, gross appearance, and surgical margin were not associated with DFS for low-risk Stage II colon cancer patient (Tables 2 and 3).

3.2. Recurrence

Disease recurrence occurred in 36 patients (8.18%); most of these cases (31 patients, 86.1%) had distant metastases. Only five patients (13.8%) had a local recurrence around the anastomosis site. The distant metastases were mainly to the liver (18 patients, 50%) and the lungs (12 patients, 33.3%). In our study, the mean recurrence time was 28.9 months; 69% of

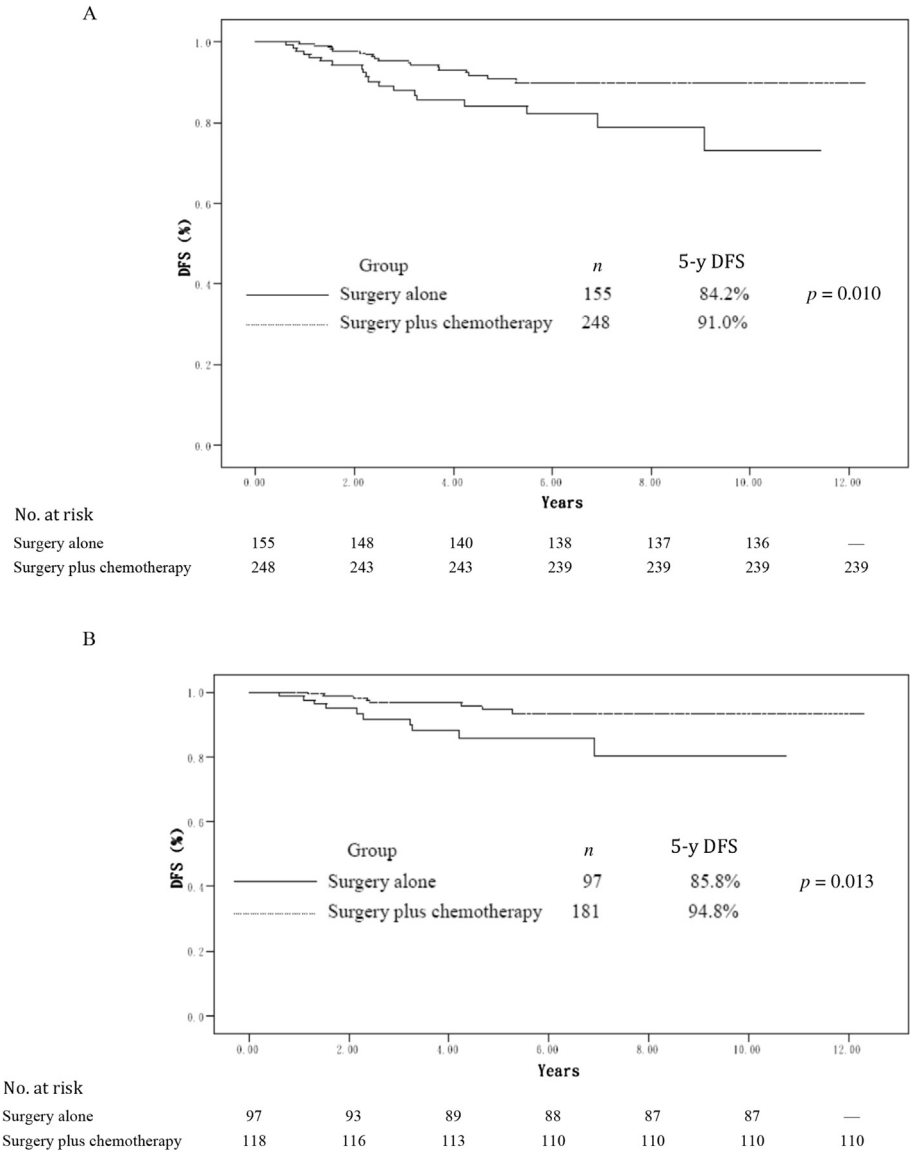


Fig. 2. Comparison of disease-free survival (DFS) between surgery alone and surgery with adjuvant chemotherapy. (A) Total Stage II colon cancer patients; (B) low-risk Stage II colon cancer patients.

recurrences after curative resection are known to develop within 3 years postoperation.

3.3. Toxicity

The incidence of nausea/vomiting, skin lesions, oral ulcers, and neutropenia was ≤4% in the surgery plus UFUR group, and there was no significant difference in the incidence of toxicities between the surgery alone and surgery plus UFUR groups. The most common side effects were severe nausea and anorexia.

4. Discussion

In Taiwan, colorectal cancer is the most common cancer and the third most frequent cause of cancer-related death,[14] accounting for an estimated 5698 deaths in 2012.[15] With the increase in the implementation of fecal occult blood test and screening colonoscopies performed in Taiwan, an increasing number of earlier Stage II colon cancer cases have been detected, representing an estimated 18–20% of the new colorectal cancer cases in our hospital database. From the Annual Cancer Report from Taiwan Cancer Registration System, 5-year OS for patients with Stage II approximates 71.3%.[15] To give the best possible care for more and more low-risk Stage II colon cancer patients, aggressive treatment guidelines are very important.

In this study, we set DFS and 5-year OS as the primary endpoints of evaluation to determine the effects conferred by adjuvant CMT on patients with Stage II colon cancer. Of these patients, multivariate analysis showed that adjuvant CMT with UFUR > 12 months was associated with improved DFS. Moreover, age ≤ 70 years and CMT with UFUR > 12 months were associated with improved 5-year OS. We

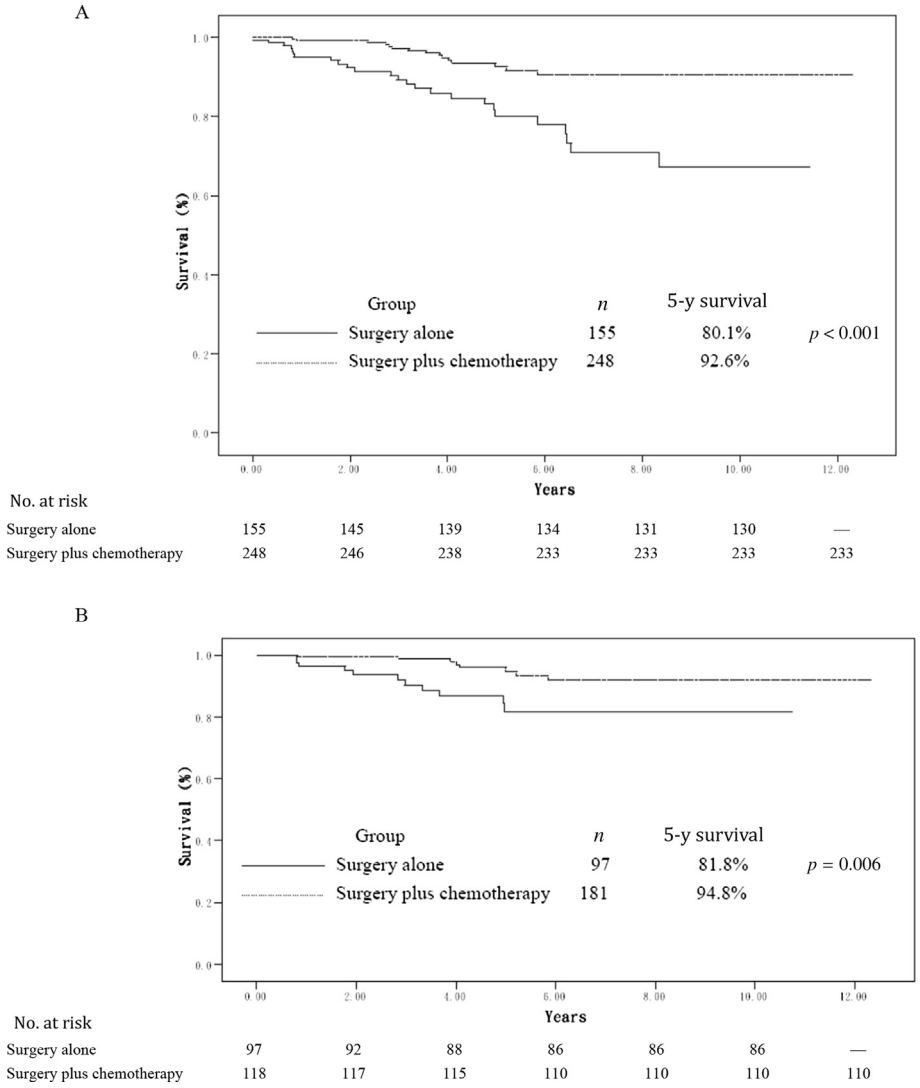


Fig. 3. Comparison of 5-year overall survival between surgery alone and surgery with adjuvant chemotherapy. (A) Total Stage II colon cancer patients; (B) low-risk Stage II colon cancer patients.

analyzed the prognostic value of risk factors recommended by the NCCN guidelines[16] and found that three subgroups of risk factors (no risk factor, 1 risk factor, and >1 risk factor) could distinguish significantly different DFS and 5-year OS rates. We further examined our database to see if patients who had more risk factors had poorer DFS and 5-year OS. For patients without any risk factors, the 5-year DFS could be more than 92.1%. However, the 5-year DFS for patients with one or more risk factors was only 79.2% ($p = 0.003$). The 5-year OS could be more than 90.7% for patients without any risk factors and only 80.8% for patients with one or more risk factors ($p = 0.003$). According to a report from an ASCO panel that reviewed the literature prior to May 2003, routine adjuvant CMT was not recommended as standard therapy for Stage II colon cancer, with the panel citing a possible 2−4% increase in absolute survival, which was not a statistically significant improvement.[3] Some studies also concluded that for Stage II colon cancer patients, either with or without poor prognostic features, there may be no survival benefit from adjuvant CMT.[17]

However, McKenzie et al[7] determined that adjuvant CMT improved OS in patients with Stage II colon cancer (HR = 0.88; 95% confidence interval, 0.78−0.99; $p = 0.031$). Later, another study reported that patients in a high-risk group ($n = 484$) with one or more risk factors who had received adjuvant CMT had a significantly improved prognosis compared with those in a high-risk group who did not receive adjuvant CMT (DFS with and without adjuvant therapy, 87.3% vs. 78.9%, $p = 0.028$), but not to low-risk patients.[8] Study of pooled analyses of more than 20,800 patients from 18 trials revealed that adjuvant CMT provided significant a DFS benefit, primarily by reducing the recurrence rate, within the first 2 years of adjuvant therapy, with some benefit in Years 3−4, translating into a long-term 5-year OS benefit.[18] Our results support the conclusions of these previous studies, as patients receiving adjuvant CMT showed improved DFS and

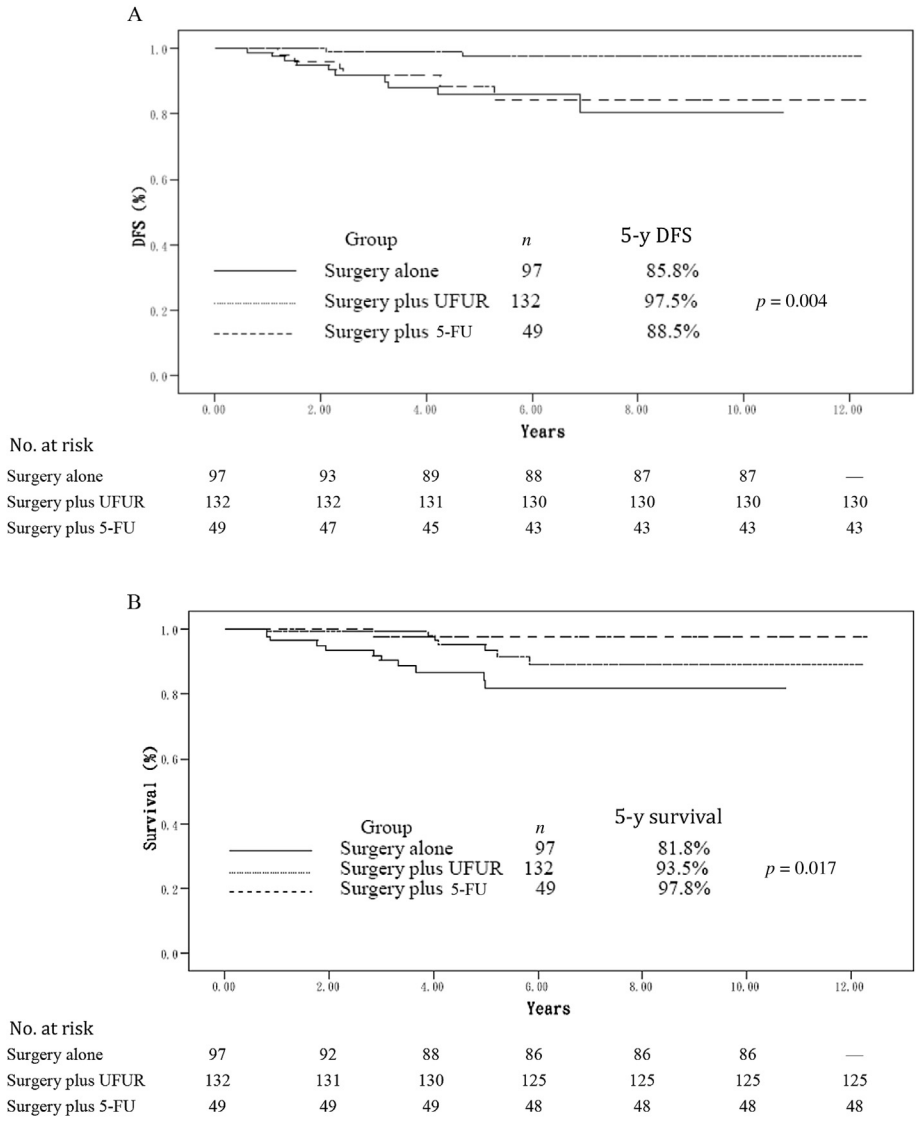


Fig. 4. Survival benefit of adjuvant chemotherapy for low-risk Stage II colon cancer patients compared between three subgroups of chemotherapy courses. (A) disease-free survival (DFS); (B) 5-year overall survival. UFUR = tegafur–uracil; 5-FU = 5-fluorouracil.

OS compared with those in the surgery-alone group, even in patients presenting without high-risk factors.

In several studies, bowel obstruction or tumor perforation at initial presentation have been identified as poor prognostic factors, because they enable the spread of tumor cells via the blood and the seeding of tumor cells in the peritoneal cavity.[19] The interpretation of these results, however, is complicated, as patients presenting with perforation or other complications of colon cancer tend to have a higher incidence of metastatic disease, higher disease stage, and greater residual tumor burden. According to our data, patients without obstruction had improved DFS but not 5-year OS. The ASCO guidelines indicate that a preoperative serum CEA level > 5 ng/mL is associated with a poor prognosis. However, our data did not confirm these results; this finding could be attributed to the small number of patients in this subgroup.

Most clinicians in Korea and Japan tend to prescribe adjuvant CMT for low-risk Stage II colon cancer patients. The aim of adjuvant CMT is to eradicate micrometastases and increase the 5-year OS; however, there seems to be no significant evidence to support the presence of micrometastases in low-risk Stage II colon cancer. Some reports have shown that survival is slightly superior for CMT-treated patients (range, 2–4%), but others have reported that the differences were not statistically significant.[2,20,21] A standard for postoperative adjuvant CMT in low-risk Stage II colon cancer has not yet been established.

To date, many genetic signature studies have important implications. Some geneticists recommended that patients with elevated microsatellite alterations at selected tetranucleotide repeats colorectal cancer (hMutSβ defective) had diminished response to adjuvant 5-FU chemotherapy.[22] However, the latest study concluded that adjuvant 5-FU-based chemotherapy has improved survival benefit for Stage II colorectal cancer patients regardless of elevated microsatellite alterations at selected tetranucleotide status. In terms of the

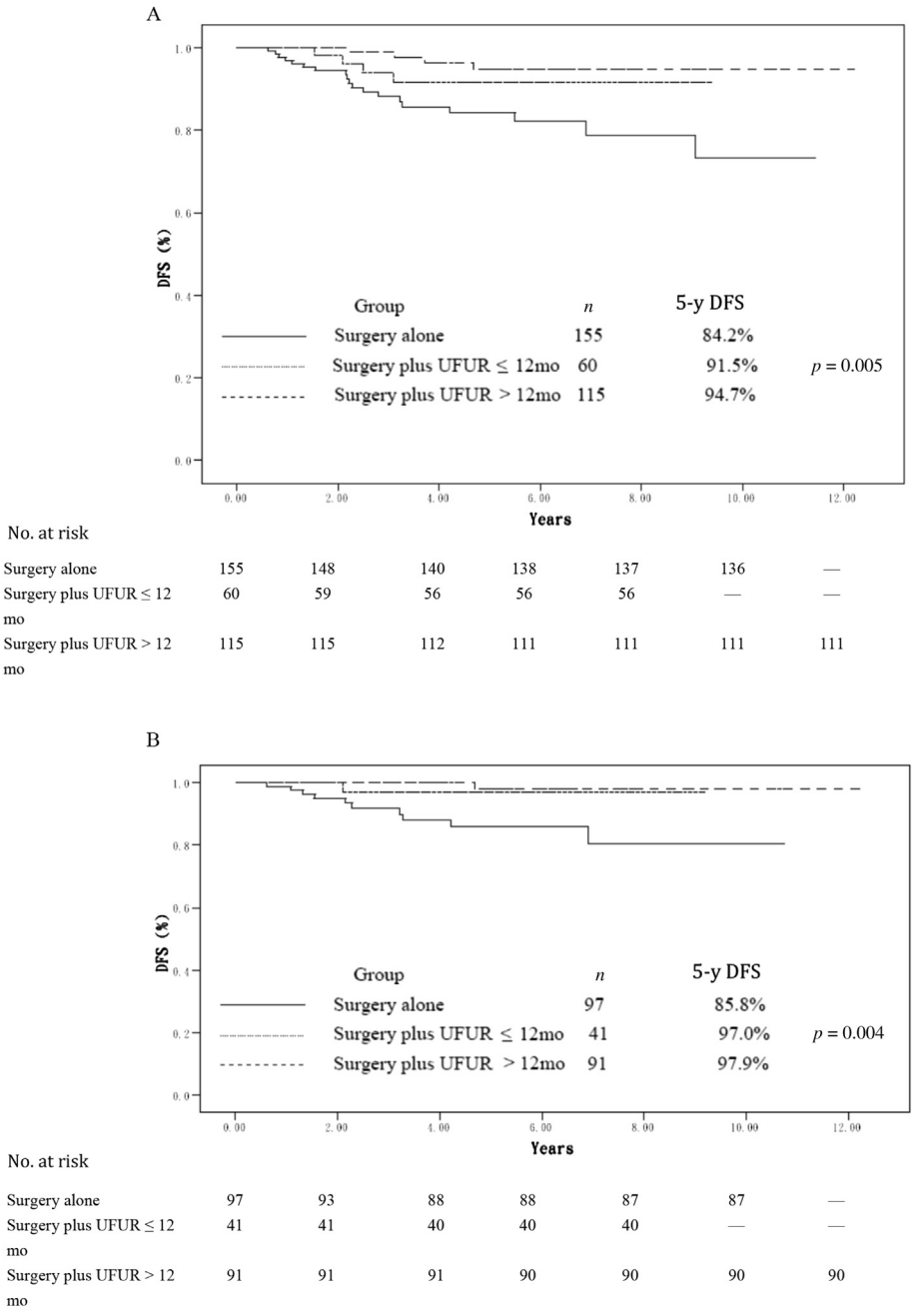
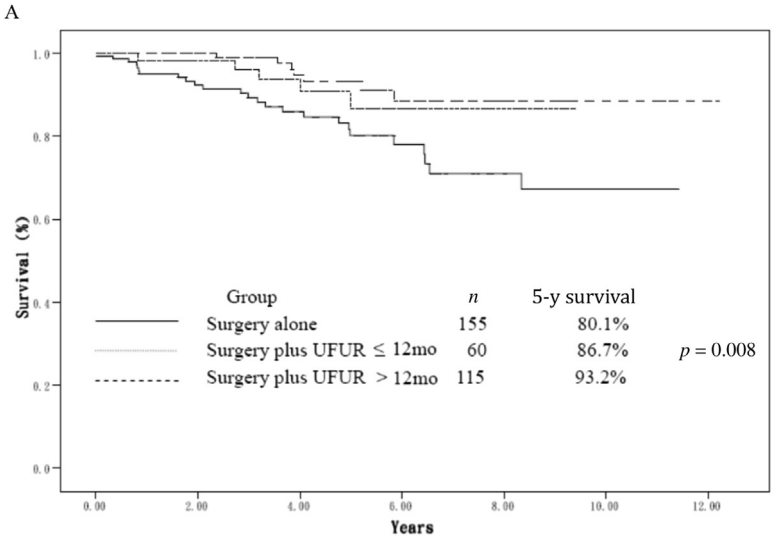


Fig. 5. Comparison of disease-free survival (DFS) between surgery alone and surgery with adjuvant chemotherapy with tegafur–uracil (UFUR) for less than and more than 1 year. (A) Total Stage II colon cancer patients; (B) low-risk Stage II colon cancer patients.

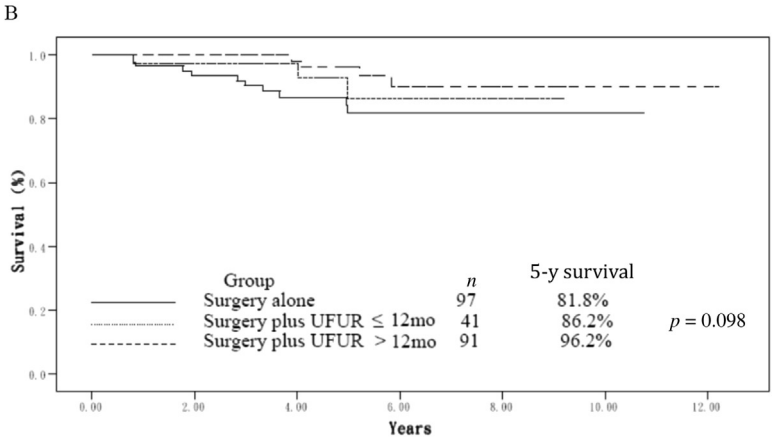
adjuvant CMT choice, since the 5-FU/UFUR era, we have reached a deadlock.[23,24] Lin et al[5] have shown similar therapeutic efficacies for 5-year OS and recurrence with infusional 5-FU and oral UFUR. A pooled analysis in our study, which included 278 low-risk Stage II colon cancer patients, indicated that adjuvant CMT with oral UFUR for low-risk Stage II colon cancer significantly improves DFS compared with 5-FU ($p = 0.004$), but not for 5-year OS ($p = 0.017$). It is possible that the use of long-term adjuvant CMT with UFUR and maintaining the serum concentration destroys microscopic deposits of cancer cells in the surgical field or hidden distant metastases, thereby decreasing the recurrence rate.[25]

Our results also illustrate the following important concept for the management of low-risk Stage II colon cancer: adjuvant UFUR treatment for more than 12 months actually eradicates colon cancer cells, thereby curing patients, prolonging survival, and reducing relapses. Analysis of our data, which included 132 low-risk patients who received adjuvant CMT with UFUR, indicates that treatment for more than 12 months significantly improves 5-year DFS over that of the surgery-alone group ($p = 0.004$); however, the results were not statistically significant for 5-year OS ($p = 0.098$). The 5-year DFS was 97.0% in the surgery plus UFUR $\leq$ 12 months group and 97.9% in the surgery plus UFUR $>$ 12 months



No. at risk

Surgery alone	155	145	139	134	131	130	—
Surgery plus UFUR ≤ 12 mo	60	59	57	55	55	—	—
Surgery plus UFUR > 12 mo	115	115	111	108	108	108	108



No. at risk

Surgery alone	97	92	88	86	86	86	—
Surgery plus UFUR ≤ 12 mo	41	40	40	38	38	—	—
Surgery plus UFUR > 12 mo	91	91	90	87	87	87	87

Fig. 6. Comparison of 5-year overall survival between surgery alone and surgery with adjuvant chemotherapy with tegafur–uracil (UFUR) for less than and more than 1 year. (A) Total Stage II colon cancer patients; (B) low-risk Stage II colon cancer patients.

group, and there was no statistical difference. According to our analysis, we believe that oral UFUR as adjuvant CMT provides 5-year OS benefits. However, our data did not confirm these results; this finding could be attributed to the small number of patients in this subgroup.

According to the national conditions and culture in Taiwan, oral adjuvant CMT with UFUR is preferable over the infusional form, and patients with low-risk Stage II colon cancer can easily be administered the therapy. The National Health Insurance Act in Taiwan has offered coverage for UFUR as adjuvant CMT for Stage II colon cancer since 2003. There are more and more patients receiving routine adjuvant CMT with UFUR after resection of low-risk Stage II colon cancer in Taiwan; according to our data, UFUR was administered to 47.5% (132/278) of the patients with low-risk Stage II colon cancer.

In the current study, no Grade 3 or greater toxicity attributable to the consecutive administration of UFUR was observed. A minority of the patients wished to discontinue treatment due to adverse reactions, and others suffered from complications. Although there is a possibility of experiencing side effects, it is still worth trying this therapy to reduce the risk of recurrence.

Table 2
Prognostic factors for disease-free survival in the low-risk Stage II colon cancer patients ($n = 278$).

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age						
≤70 y	1.00			1.00		
>70 y	1.50	0.61–3.70	0.378	2.07	0.54–8.04	0.292
Sex						
Male	1.00					
Female	0.59	0.22–1.56	0.285	–		
CEA						
≤5	1.00					
>5	0.43	0.06–3.40	0.425	–		
CA19-9						
≤25	1.00					
>25	0.03	0.00–18.46	0.287	–		
Tumor size (mm)						
≤49	1.00					
>49	1.27	0.48–3.35	0.624	–		
Gross appearance						
Polypoid	1.00					
Ulcerative	2.01	0.55–7.30	0.291	–		
CRM, proximal						
≤2 cm	1.00					
>2 cm	0.95	0.21–4.38	0.952	–		
CRM, distal						
≤2 cm	1.00					
>2 cm	2.53	0.33–19.60	0.375	–		
NLR	1.06	1.00–1.12	0.057	1.04	0.98–1.11	0.195
Chemotherapy						
No	1.00			1.00		
UFUR ≤ 12 mo	0.20	0.03–1.57	0.127	0.25	0.03–1.98	0.189
UFUR > 12 mo	0.08	0.01–0.65	0.018	0.12	0.01–0.94	0.044

CA = cancer antigen; CEA = carcinoembryonic antigen; CI = confidence interval; CRM = circumferential resection margin; HR = hazard ratio; NLR ratio = neutrophil-to-lymphocyte ratio; UFUR = tegafur/uracil.

Table 3
Prognostic factors for overall survival in the low-risk Stage II colon cancer patients ($n = 278$).

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p*	HR	95% CI	*p*
Age						
≤70 y	1.00			1.00		
>70 y	4.29	1.54–11.92	0.005	3.59	1.17–11.04	0.026
Sex						
Male	1.00					
Female	0.55	0.21–1.44	0.220	–		
CEA						
≤5	1.00					
>5	1.46	0.46–4.59	0.519	–		
CA19-9						
≤25	1.00					
>25	1.80	0.60–5.42	0.296	–		
Tumor size (mm)						
≤49	1.00					
>49	1.20	0.48–2.98	0.695	–		
Gross appearance						
Polypoid	1.00					
Ulcerative	1.05	0.39–2.84	0.923	–		
CRM, proximal						
≤2 cm	1.00					
>2 cm	1.13	0.25–5.15	0.871	–		
CRM, distal						
≤2 cm	1.00					
>2 cm	1.52	0.34–0.76	0.580	–		
NLR	1.04	0.98–1.11	0.198	–		
Chemotherapy						
No	1.00			1.00		
UFUR ≤12 mo	0.58	0.16–2.08	0.404	0.66	0.18–2.38	0.527
UFUR >12 mo	0.31	0.10–0.97	0.043	0.38	0.12–1.20	0.098

CA = cancer antigen; CEA = carcinoembryonic antigen; CI = confidence interval; CRM = circumferential resection margin; HR = hazard ratio; NLR ratio = neutrophil-to-lymphocyte ratio; UFUR = tegafur/uracil.

The results of this study suggest that: (1) only receiving adjuvant CMT with UFUR > 12 months is associated with improved DFS in low-risk Stage II colon cancer patients; and (2) age ≤ 70 years and adjuvant CMT with UFUR > 12 months may provide a survival benefit in low-risk Stage II colon cancer with improved OS. In this study, the effect of an oral UFUR course was examined, and although the number was small, an obvious improvement in DFS and a borderline improvement 5-year OS for low-risk Stage II colon cancer were observed in the >12 month treatment subgroup.

In conclusion, based on its improved survival profile, long-course oral UFUR has the potential to replace short-course infusional 5-FU/leucovorin as the standard adjuvant CMT for patients with low-risk Stage II colon cancer. Our results show that the routine consecutive administration of UFUR (400 mg/d) as adjuvant CMT after radical surgery provides improved DFS in patients with low-risk Stage II colon cancer, especially administration for more than 12 months. To achieve best DFS benefit, we suggest adjuvant CMT treatment of low-risk Stage II colon cancer patients with UFUR for more than 12 months following surgery over surgery alone. The present study had some limitations. It was conducted at a single center, had a retrospective design, and lacked randomization. Whether or not adjuvant CMT was administered after a potentially curative operation depended on the clinical judgment of the attending physicians. An additional randomized study is necessary to clarify the role of adjuvant therapy in low-risk Stage II colon cancer patients.

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