International Journal of Colorectal Disease (2019) 34:629–639
https://doi.org/10.1007/s00384-019-03237-x

ORIGINAL ARTICLE

Oncologic outcomes after adjuvant chemotherapy with capecitabine compared to 5-fluorouracil/leucovorin for geriatric stage II colon cancer: a retrospective cohort study

Kil-yong Lee[1] · Ji Won Park[1,2] · Ki-young Lee[1] · Sangsik Cho[1] · Yoon-Hye Kwon[1] · Min Jung Kim[1] · Seung-Bum Ryoo[1] · Seung-Yong Jeong[1,2] · Kyu Joo Park[1]

Accepted: 4 January 2019 / Published online: 19 January 2019

Abstract

Purpose After curative resection of stage II colon cancer, adjuvant chemotherapy with 5-fluorouracil/leucovorin (FL) or capecitabine is selectively recommended. However, there is little evidence of the effect of capecitabine on oncologic outcome in geriatric patients with stage II colon cancer compared to that of FL. The aim of this study was to determine the difference in recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) in patients older than 70 years of age with stage II colon cancer receiving capecitabine and FL.

Methods Patients over 70 years of age diagnosed with primary pathologic stage II colon cancer at the Seoul National University Hospital from January 2005 to December 2015 were included. A prospectively collected database was analyzed retrospectively. Patients were separated into an FL group and a capecitabine group. The primary outcomes were RFS, CSS, and OS.

Results Of the 154 included patients, 96 patients received FL and 58 patients received capecitabine. There was no difference between the two groups in RFS, CSS, or OS ($p = 0.763$, $p = 0.221$, and $p = 0.470$, respectively) as measured by Kaplan–Meier analysis with log-rank test. Administration of capecitabine as compared to FL was not a factor affecting RFS (hazard ratio [HR] 0.503, 95% confidence interval [CI] 0.145–1.745), CSS (HR 1.519, 95% CI 0.348–6.629), or OS (HR 0.941, 95% CI 0.290–3.053) on multivariable analysis.

Conclusions Capecitabine is a safe regimen in terms of oncologic outcomes compared with FL in older patients with stage II colon cancer.

Keywords Geriatric patients · Colon cancer · Stage II · Capecitabine · 5-Fluorouracil/leucovorin

✉ Ji Won Park
sowisdom@gmail.com

Kil-yong Lee
cyboryee@hanmail.net

Ki-young Lee
canucome2me@gmail.com

Sangsik Cho
whtkdtlr@hanmail.net

Yoon-Hye Kwon
yoonhyekwon@naver.com

Min Jung Kim
surgeon.mjkim@gmail.com

Seung-Bum Ryoo
sbryoomd@gmail.com

Seung-Yong Jeong
syjeong@snu.ac.kr

Kyu Joo Park
kjparkmd@plaza.snu.ac.kr

[1] Department of Surgery, Seoul National University College of Medicine, 101, Daehak-ro, Jongno-gu, Seoul, South Korea

[2] Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea

Introduction

After curative resection for stage II colon cancer, either capecitabine or 5-fluorouracil (FU) and leucovorin (FL) is recommended for adjuvant chemotherapy [1]. The addition of oxaliplatin has not been proven to be effective in older patients (those over 70 years of age); therefore, capecitabine or FL is administered without oxaliplatin [2]. There is evidence that capecitabine and FL have an equivalent effect on disease-free survival in older patients with stage III colon cancer and that capecitabine is associated with fewer side effects [3]. However, there is little evidence on the effect of capecitabine on oncologic outcomes in geriatric patients with stage II colon cancer as compared to that of FL.

More evidence of adjuvant chemotherapy administration in older patients with colon cancer is needed, as there is a growing trend in the number of older patients treated for colon cancer, and patients with cancer continue to age [4]. Older patients also tend to have low-performance status, indicating the need for further study in this population. Additionally, patients who receive FL must be admitted to the hospital regularly, and FL is associated with more frequent side effects than capecitabine [3]. Therefore, capecitabine may be a better option for older patients. However, to the best of our knowledge, there is no study examining adjuvant therapy in older patients with stage II colon cancer. This is largely because it is difficult to enroll patients for a randomized controlled study in this population [5].

The aim of this study was to determine the difference in recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) between patients older than 70 years of age with stage II colon cancer receiving capecitabine and FL.

Materials and methods

This study was conducted with the approval of the institutional review board (IRB) of Seoul National University Hospital. Requirement for consent was waived with permission from the IRB. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patients

Patients older than 70 years who were diagnosed with primary pathologic stage II colon cancer at the Seoul National University Hospital from January 2005 to December 2015 were included. A prospectively collected database was analyzed retrospectively. Patients were excluded if they had a history of another malignancy, did not receive adjuvant chemotherapy, or received regimens other than capecitabine or FL. Since 2005, adjuvant chemotherapy has been administered to colon cancer patients with T4 primary tumors, inadequately sampled nodes (< 13), poorly differentiated tumors, perforation, lymphovascular invasion, or perineural invasion, based on the ASCO guidelines [6]. After 2012, colon cancer patients with obstruction or < 12 harvested lymph nodes were also indicated for adjuvant chemotherapy, and patients with high microsatellite instability (MSI-H) did not receive chemotherapy, based on the ESMO guidelines [7]. Furthermore, patients with suspected close radial margins from the operative findings were also administered adjuvant chemotherapy.

Adjuvant chemotherapy was administered to patients with a performance status of the Eastern Cooperative Oncology Group (ECOG) 0–1. Dose reduction was performed at the decision of the attending physician according to the patient's general condition.

Right-sided cancer was defined as colon cancer arising in the cecum to the T-colon, and left-sided cancer was defined as colon cancer arising in the splenic flexure to the sigmoid colon.

The data on death were obtained from the Statistics Korea database in order to analyze OS and CSS. The Statistics Korea database provided information on the cause of death and the date of death. The last update on the data in the Statistics Korea database occurred on December 31, 2016. Cause of death was determined by ICD code. CSS was identified in patients with the code C18-C19.

Recurrence was confirmed on physical examination, colonoscopy, computed tomography, or magnetic resonance imaging during regular follow-up.

Procedure

Capecitabine

Capecitabine was administered at a dose of 1000–1250 mg/m^2 twice a day as an intermittent regimen in 3-week cycles (2 weeks of treatment followed by 1 week of rest) for a total of eight cycles (24 weeks).

FL

5-Fluorouracil (FU) at a dose of 425 mg/m^2 and leucovorin at a dose of 20 mg/m^2 were intravenously administered for 5 days and performed six times every 4 weeks.

Primary and secondary outcomes

The primary end points were RFS, CSS, and OS. RFS was defined as the time between surgery and the diagnosis of recurrence or death from any cause. CSS was defined as the time

between surgery and death from colon cancer. OS was defined as the time between surgery and death from any cause.

The secondary end point was the incidence of side effects between the two groups. Furthermore, we evaluated the difference in side effects of grade 3 or higher. Side effects were categorized using the Common Terminology Criteria for Adverse Events version at the time of database collection.

Statistical analysis

To compare baseline characteristics between the two groups, categorical variables were compared by Pearson's χ^2 test and continuous variables were analyzed by Student's T test. Kaplan–Meier curves with log-rank test were used to compare RFS, CSS, and OS between the two groups. To analyze factors associated with RFS, CSS, and OS, Cox regression test was performed. Factors with $p < 0.2$ in univariable analysis were used in multivariable analysis.

The adjusted hazard ratio (HR) of the chemotherapy regimen was calculated with covariables of age, sex, body mass index (BMI), tumor sidedness, preoperative carcinoembryonic antigen (CEA), pathologic T stage, number of harvested lymph nodes (LNs), lymphatic invasion, venous invasion, and perineural invasion.

Statistical analysis was performed using SPSS version 25.0 for Windows (IBM Corp, Armonk, NY, USA). A $p < 0.05$ was considered statistically significant.

Results

A total of 583 patients were included from January 2005 to December 2015. One hundred fifty-four patients were analyzed after excluding 60 patients who had history of another malignancy, 291 patients who did not receive adjuvant chemotherapy, and 78 patients who were administered other regimens. Of the 154 included patients, 96 patients received FL and 58 patients were administered capecitabine (Fig. 1). The median follow-up period was 55.1 months (range 6–96 months).

Baseline characteristics

Baseline characteristics between the two groups are shown in Table 1. The mean age was higher in the capecitabine group (74.3 years vs 72.5 years, $p < 0.001$). There were no statistical differences in comorbidities between the two groups. In terms of pathologic results, the percentage of T4 tumors in the capecitabine group was higher than that in the FL group (19% vs 7.3%, $p = 0.029$), and lymphatic invasion (36.2% vs 9.4%, $p < 0.001$), venous invasion (15.5% vs 5.2%, $p = 0.031$), and perineural invasion (34.5% vs 12.5%, $p = 0.001$) were more frequent in the capecitabine group (Table 1). The rates of dose reduction in the capecitabine and FL groups were 44.8% and

Table 1 Baseline characteristics

	FL ($n = 96$)	Capecitabine ($n = 58$)	p value
Age (years)	72.5 ± 2.3	74.3 ± 3.2	< 0.001
Sex			0.413
Male	61 (63.5%)	33 (56.9%)	
Female	35 (36.5%)	25 (43.1%)	
BMI (kg/m^2)	23.6 ± 2.8	22.9 ± 3.3	0.175
ASA classification[a]			0.888
1	24 (25.5%)	11 (19.3%)	
2	62 (66.0%)	55 (77.2%)	
3	8 (8.5%)	2 (3.5%)	
Diabetes	17 (17.7%)	13 (22.4%)	0.475
Hypertension	43 (44.8%)	25 (43.1%)	0.838
Cardiac disease	4 (4.2%)	3(5.2%)	0.772
Pulmonary disease	2 (2.1%)	6 (10.3%)	0.053
Liver disease	4 (4.2%)	0 (0%)	0.298
Tumor sidedness			0.585
Right-sided	42 (43.8%)	28 (48.3%)	
Left-sided	54 (56.3%)	30 (51.7%)	
Preoperative CEA (ng/mL)	4.4 ± 6.8	7.0 ± 13.8	0.187
Operation type			0.155
Open	76 (79.2%)	40 (69.0%)	
Laparoscopy	20 (20.8%)	18 (31.0%)	
Tumor differentiation			0.189
WD	9 (9.4%)	2 (3.4%)	
MD	83 (86.5%)	53 (91.4%)	
Mucinous	4 (4.2%)	2 (3.4%)	
Adenosquamous	0 (0%)	1 (1.7%)	
Size (cm)	4.8 ± 2.2	4.8 ± 1.8	0.976
Pathologic T stage			0.029
3	89 (92.7%)	47 (81.1%)	
4	7 (7.3%)	11 (19.0%)	
Number of harvested LNs	22.5 ± 12.6	26.2 ± 11.7	0.071
Lymphatic invasion	9 (9.4%)	21 (36.2%)	< 0.001
Venous invasion	5 (5.2%)	9 (15.5%)	0.031
Perineural invasion	12 (12.5%)	20 (34.5%)	0.001
MSI[b]			0.513
MSS	79 (83.2%)	49 (89.1%)	
MSI-L	11 (11.6%)	3 (5.5%)	
MSI-H	5 (5.3%)	3 (5.5%)	
Dose reduction	45 (46.9%)	26 (44.8%)	0.805
Chemotherapy completion	74 (77.1%)	45 (77.6%)	0.942
Side effect	60 (62.5%)	42 (72.4%)	0.207

BMI body mass index, *ASA classification* the American Society of Anesthesiologists physical status classification, *CEA* carcinoembryonic antigen, *WD* well-differentiated, *MD* moderately differentiated, *LN* lymph node, *MSI* microsatellite instability, *MSS* microsatellite stable, *MSI-L* low microsatellite instability, *MSI-H* high microsatellite instability, *FL* 5-fluorouracil and leucovorin

[a] Missing data: 3

[b] Missing data: 4

46.9%, respectively ($p = 0.805$), and the rates of chemotherapy completion in the capecitabine and FL groups were 77.6% and 77.1%, respectively ($p = 0.942$).

Recurrence, CSS, and OS

During the follow-up period, recurrence was observed in ten patients (10.4%) in the FL group and in seven patients (12.1%) in the capecitabine group, and the mean time to recurrence among these patients was 18.2 months (range 3–33 months). The 5-year RFS were 89.0% in the FL group and 87.4% in the capecitabine group. Kaplan–Meier and log-rank analysis showed no difference in RFS between the two groups ($p = 0.763$) (Fig. 2).

The 5-year CSS were 96.7% in the FL group and 89.1% in the capecitabine group. Kaplan–Meier and log-rank analysis showed no difference in CSS between the two groups ($p = 0.221$) (Fig. 3). The 5-year OS were 94.4% for the FL group and 86.4% for the capecitabine group, and no difference was found between the two groups after Kaplan–Meier analysis with log-rank test ($p = 0.470$) (Fig. 4).

Risk factors for RFS, CSS, and OS

In univariable analysis of factors affecting RFS, age and perineural invasion were significant factors. In multivariable analysis, the number of harvested LNs (HR 0.940, 95% confidence interval (CI) 0.891–0.991, $p = 0.022$) and perineural invasion (HR 3.439, 95% CI 1.208–9.793, $p = 0.021$) were found to be statistically significant factors (Table 2). When patients were stratified by the number of harvested LNs (> 12 vs < 12), > 12 LNs harvested was an independent factor affecting RFS in multivariable analysis (HR 0.317, 95% CI 0.106–0.946, $p = 0.037$).

Perivascular invasion (HR 5.245, 95% CI 1.377–19.978, $p = 0.015$) and preoperative CEA level (HR 1.032, 95% CI 1.005–1.061, $p = 0.022$) were the factors associated with CSS; both were statistically significant in both univariable and multivariable analysis (Table 3).

In the analysis for OS, age, the presence of cardiac disease, and preoperative CEA level were statistically significant factors in univariable analysis. In multivariable analysis, only age (HR 1.189, 95% CI 1.007–1.404, $p = 0.041$) and CEA level (1.047, 95% CI 1.031–1.081, $p = 0.006$) were factors affecting OS (Table 4).

The type of chemotherapy regimen was not a factor affecting RFS, CSS, or OS in the univariable analysis. In multivariable analysis with covariables of age, sex, BMI, tumor sidedness, preoperative CEA, pathologic T stage, number of harvested LNs, lymphatic invasion, venous invasion, and perineural invasion, receiving either FL or capecitabine was not a factor affecting RFS, CSS, or OS (Table 5).

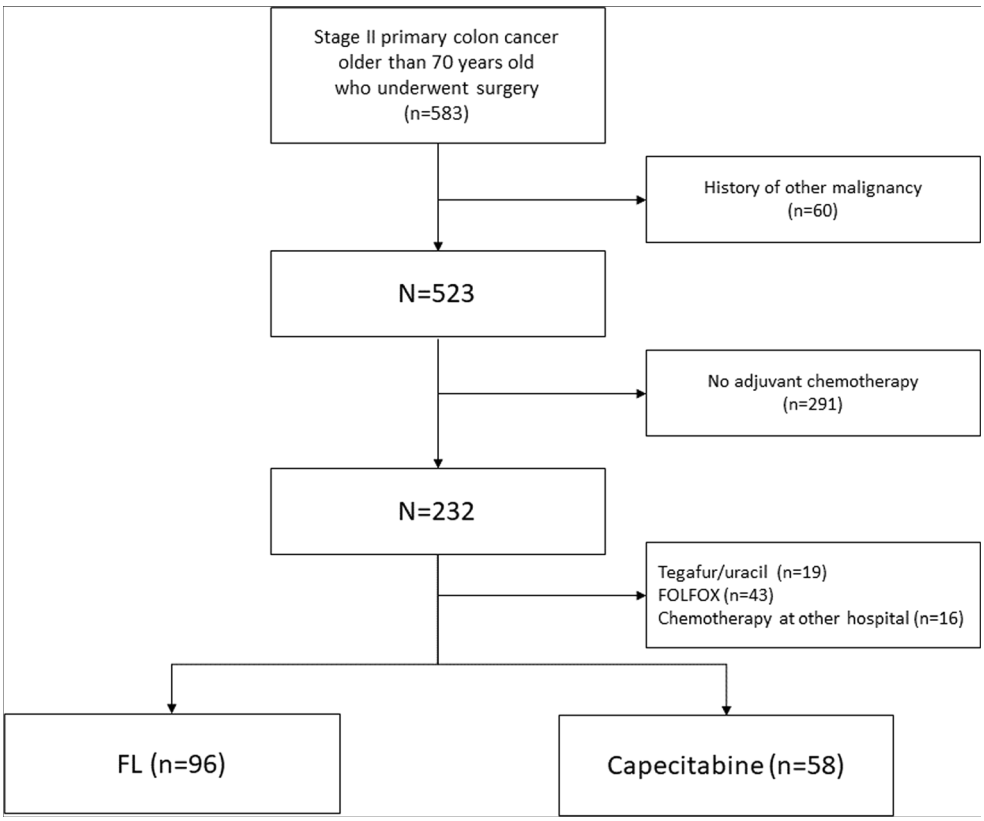

Fig. 1 Flow chart of patient selection

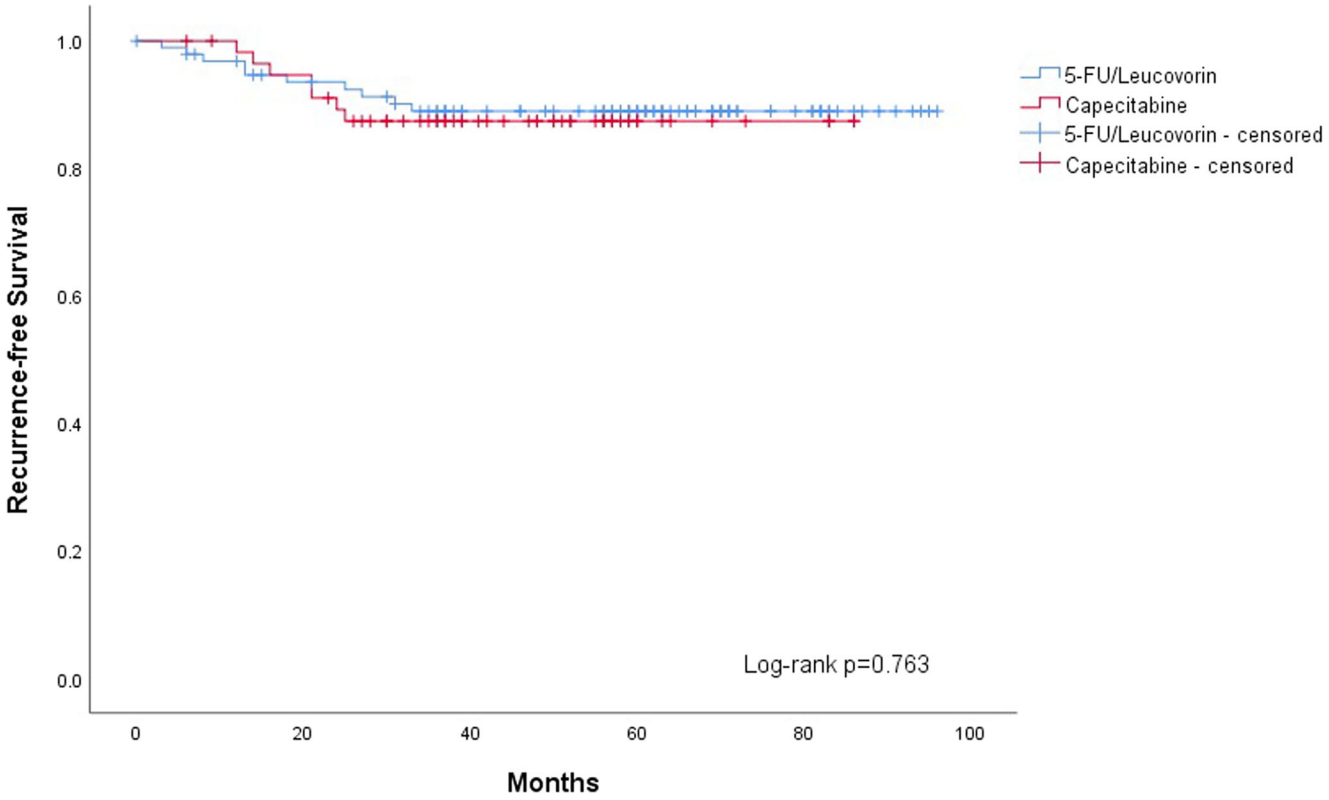

Fig. 2 Recurrence-free survival. There was no difference in recurrence-free survival between the capecitabine and 5-fluorouracil/leucovorin groups (log-rank $p = 0.763$)

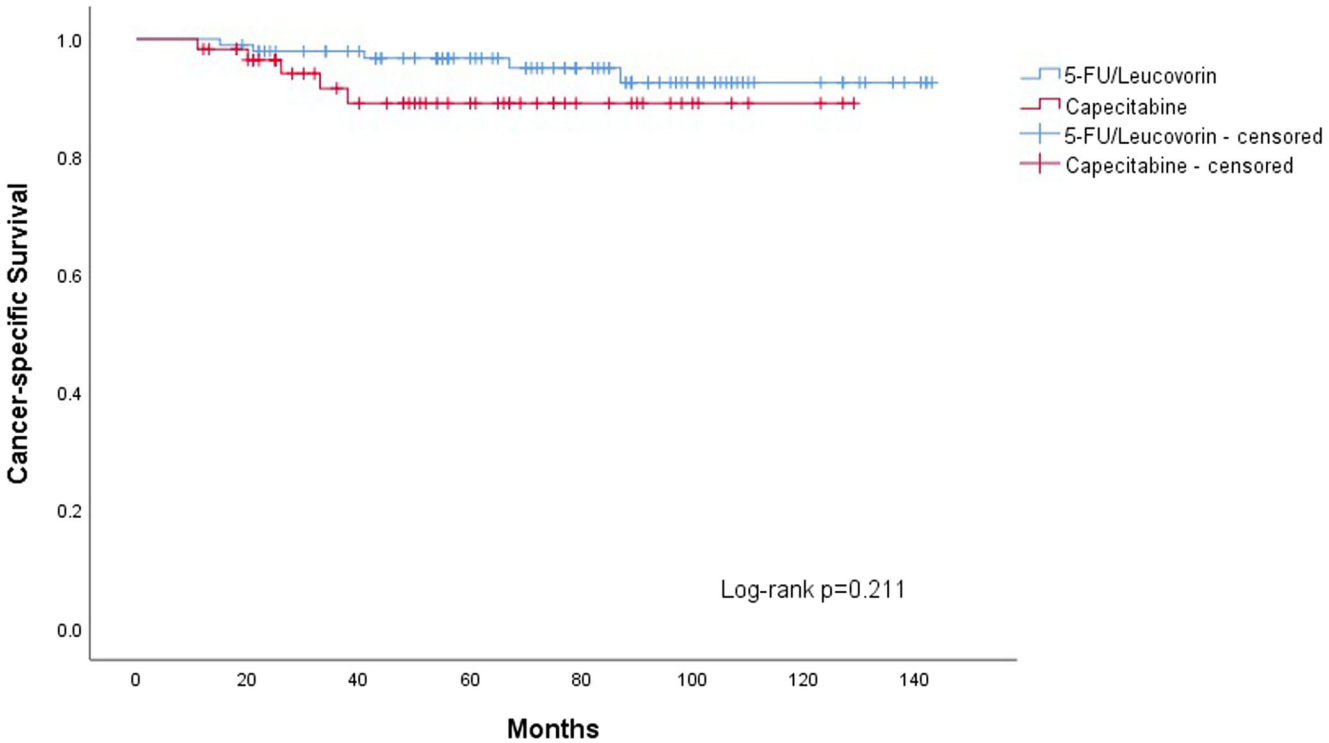

Fig. 3 Cancer-specific survival. There was no difference in cancer-specific survival between the capecitabine and 5-fluorouracil/leucovorin groups (log-rank $p = 0.211$)

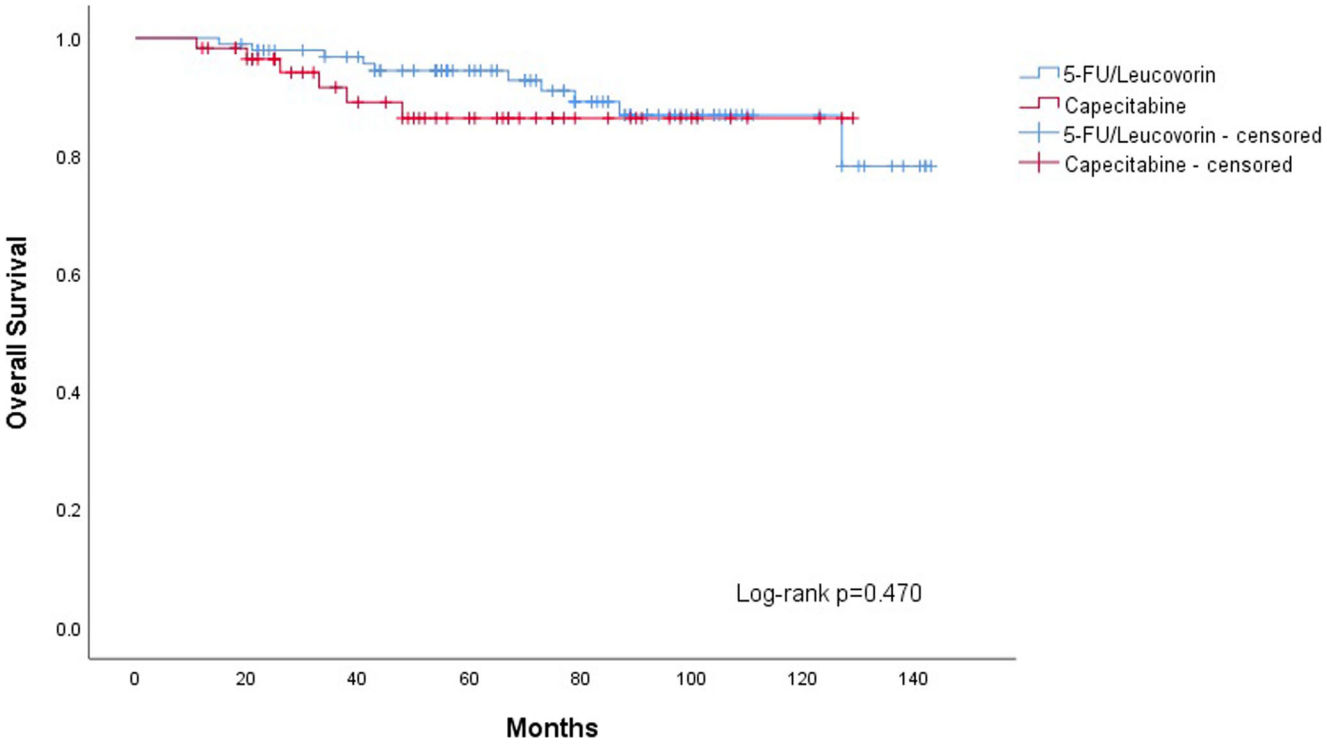

Fig. 4 Overall survival. There was no difference in overall survival between the capecitabine and 5-fluorouracil/leucovorin groups (log-rank $p = 0.470$)

Side effects

Side effects were observed in 60 patients (62.5%) in the FL group and 42 patients (72.4%) in the capecitabine group, but no statistical significance was observed ($p = 0.207$). However, the incidence of side effects of grade 3 or higher was lower in the capecitabine group than in the FL group (3.4% vs 12.5%, $p = 0.058$). When each type of side effect was analyzed, hand–foot syndrome was significantly more frequent in the capecitabine group than in the FL group (31% vs 2.1%, $p < 0.001$), but non-febrile neutropenia was significantly more frequent in the FL group than in the capecitabine group (34.4% vs 17.2%, $p = 0.022$) (Table 6).

Discussion

Our study showed that treatment with capecitabine, as opposed to FL, did not significantly affect RFS, CSS, or OS in patients over age 70 years with stage II colon cancer. Furthermore, in terms of side effects, the capecitabine group showed fewer grade 3 complications, although there was no statistical significance.

5-FU-based chemotherapy may be performed selectively in patients with stage II colon cancer. Many studies have reported that adjuvant chemotherapy has a survival benefit for patients with high-risk features, such as poorly differentiated histology, lymphovascular invasion, bowel obstruction, perineural invasion, localized perforation, positive margin, and number of positive LNs (< 12) after surgery, although they are less likely to benefit from adjuvant therapy if they show MSI-H [1]. In particular, there is no difference in disease-free survival or OS between stage III patients receiving FL and capecitabine, although patients receiving capecitabine experience fewer side effects [3]. However, there is a lack of research about the differences in oncological outcomes between patients with stage II colon cancer receiving FL and capecitabine. Especially in older patients, there is no study on which formulation is better, because patient enrollment in a randomized controlled study is difficult.

It has already been reported that a sufficient degree of LN harvesting is important to improve survival in older patients with stage II colon cancer [8]. Additionally, perineural invasion has already been shown to be an independent prognostic factor for stage II colon cancer in many studies [9–11]. Our results were similar to those of previous studies. In the analysis of factors affecting prognosis in stage II colon cancer, the number of harvested LNs and perineural invasion were independent factors in our study. Moreover, perineural invasion was a factor affecting RFS and CSS. This suggests that intensive follow-up is required for patients with perineural invasion.

In our study, the capecitabine group showed worse pathologic findings than the FL group. As a result, the 5-year CSS and OS rates were lower in the capecitabine group than in the FL group in our study, although there was no statistical significance. However, there was no difference in prognosis by

Table 2 Univariable and multivariable analysis for factors affecting recurrence-free survival

	Univariable analysis			Multivariable analysis[a]		
	Hazard ratio	95% Confidence interval	*p* value	Hazard ratio	95% Confidence interval	*p* value
Age	1.175	1.024–1.348	0.021	1.152	1.152–1.340	0.068
Sex			0.649			
Male	Reference					
Female	0.794	0.293–2.146				
BMI	1.019	0.875–1.188	0.805			
ASA classification			0.115			
1	Reference					
≥ 2	5.067	0.672–38.209				
Diabetes	0.858	0.246–2.984	0.809			
Hypertension	1.430	0.552–3.706	0.462			
Cardiac disease	2.929	0.670–12.810	0.154	3.695	0.828–16.483	0.087
Pulmonary disease	1.155	0.153–8.713	0.889			
Liver disease	2.122	0.281–16.005	0.466			
Tumor sidedness			0.303			
Right-sided	Reference					
Left-sided	0.602	0.229–1.582				
Preoperative CEA	1.023	0.999–1.048	0.058	1.025	0.998–1.053	0.066
Operation type			0.608			
Laparoscopy	Reference					
Open	0.761	0.268–2.160				
Tumor size	0.966	0.754–1.238	0.784			
Pathologic T stage			0.090			
3	Reference					
4	2.635	0.859–8.083				
Number of harvested LNs	0.961	0.916–1.007	0.095	0.940	0.891–0.991	0.022
Lymphatic invasion	1.278	0.417–3.921	0.668			
Venous invasion	1.365	0.312–5.970	0.679			
Perineural invasion	5.109	1.968–13.264	0.001	3.439	1.208–9.793	0.021
MSI			0.891			
MSS	Reference					
MSI-L	1.109	0.254–4.851				
Dose reduction	0.619	0.229–1.673	0.344			
Chemotherapy completion	0.632	0.223–1.795	0.389			
Chemotherapy regimen			0.763			
FL	Reference					
Capecitabine	1.160	0.441–3.049				

BMI body mass index, *ASA classification* the American Society of Anesthesiologists (ASA) physical status classification, *CEA* carcinoembryonic antigen, *LN* lymph node, *MSI* microsatellite instability, *MSS* microsatellite stable, *MSI-L* low microsatellite instability, *FL* 5-fluorouracil and leucovorin

[a] Multivariable analysis performed on factors with $p < 0.20$ in univariable analysis

regimen of adjuvant chemotherapy when factors that could affect prognosis were corrected for using multivariable analysis.

The American Society of Anesthesiologists classification was used in our study for severity of comorbidities because most of the patients underwent preoperative evaluation by anesthesiologists using this classification. Moreover, our database did not report the Charlson comorbidity index (CCI), and the CCI does not reflect the severity of the disease [12]. Most importantly, only patients with an ECOG performance status of 0–1 are administered adjuvant chemotherapy in our institution. Therefore, the severity of comorbidity in our study population was predictable.

In our study, the incidences of side effects of chemotherapy of any grade were 62.2% and 72.4% ($p = 0.207$) in the FL and capecitabine groups, respectively. However, there were fewer grade 3 and higher side effects in the capecitabine group, although it was not statistically significant (12.5% and 3.4% in the FL and capecitabine groups, respectively; $p = 0.058$).

Table 3 Univariable and multivariable analysis for factors affecting cancer-specific survival

	Univariable analysis			Multivariable analysis[a]		
	Hazard ratio	95% Confidence interval	*p* value	Hazard ratio	95% Confidence interval	*p* value
Age	1.203	0.997–1.451	0.054			
Sex			0.272			
Male	Reference					
Female	0.420	0.089–1.978				
BMI	0.917	0.739–1.138	0.432			
ASA classification			0.401			
1	Reference					
≥ 2	2.830	0.358–22.344				
Diabetes	1.705	0.440–6.615	0.440			
Hypertension	1.342	0.387–4.657	0.643			
Cardiac disease	3.502	0.440–27.899	0.236			
Pulmonary disease	2.619	0.330–20.754	0.362			
Liver disease	0.047	0.000–351,611.493	0.706			
Tumor sidedness			0.666			
Right-sided	Reference					
Left-sided	0.760	0.219–2.637				
Preoperative CEA	1.045	1.017–1.073	0.001	1.032	1.005–1.061	0.022
Operation type			0.403			
Laparoscopy	Reference					
Open	2.416	0.305–19.130				
Tumor size	1.045	0.767–1.425	0.778			
Pathologic T stage			0.061			
3	Reference					
4	3.656	0.943–14.177				
Number of harvested LNs	0.972	0.917–1.030	0.337			
Lymphatic invasion	1.122	0.238–5.297	0.884			
Venous invasion	3.178	0.669–15.101	0.146			
Perineural invasion	5.960	1.700–20.891	0.005	5.245	1.377–19.978	0.015
MSI			0.854			
MSS	Reference					
MSI-L	0.823	0.104–6.520				
Dose reduction	0.524	0.135–2.028	0.349			
Chemotherapy completion	0.351	0.135–2.040	0.351			
Chemotherapy regimen			0.223			
FL	Reference					
Capecitabine	2.172	0.625–7.553				

BMI body mass index, *ASA classification* the American Society of Anesthesiologists (ASA) physical status classification, *CEA* carcinoembryonic antigen, *LN* lymph node, *MSI* microsatellite instability, *MSS* microsatellite stable, *MSI-L* low microsatellite instability, *FL* 5-fluorouracil and leucovorin

[a] Multivariable analysis performed on factors with $p < 0.20$ in univariable analysis

This is similar to the results of the incidence of side effects in the capecitabine and FL groups in patients with stage III colon cancer reported by Twelves et al. [3]. For geriatric patients with a poorer general condition, the side effects of chemotherapy are an important factor in regimen selection. It is important to consider that capecitabine is an oral regimen and can be prescribed in an outpatient setting. In this respect, capecitabine is recommended for this population. However, our study also showed more hand-foot syndrome in the capecitabine group than in the FL group (31.0% vs 2.1%, $p < 0.001$). Therefore, the increased likelihood of hand–foot syndrome with capecitabine should be considered.

In our study, adjuvant chemotherapy was administered to patients who had MSI-H. All of the patients with MSI-H stage II colon cancer who received adjuvant chemotherapy were treated before 2010, i.e., before Sargent et al. reported that

Table 4 Univariable and multivariable analyses for factors affecting overall survival

	Univariable analysis			Multivariable analysis[a]		
	Hazard ratio	95% Confidence interval	*p* value	Hazard ratio	95% Confidence interval	*p* value
Age	1.181	1.009–1.383	0.039	1.189	1.007–1.404	0.041
Sex		0.113–1.392	0.149			
Male	Reference					
Female	0.396					
BMI	0.935	0.787–1.111	0.445			
ASA classification			0.306			
1	Reference					
≥2	2.172	0.492–9.586				
Diabetes	0.931	0.265–3.274	0.911			
Hypertension	1.504	0.557–4.064	0.421			
Cardiac disease	5.249	1.175–23.451	0.030	3.822	0.842–17.345	0.082
Pulmonary disease	3.379	0.761–14.997	0.109			
Liver disease	2.148	0.282–16.361	0.460			
Tumor sidedness			0.501			
Right-sided	Reference					
Left-sided	0.713	0.266–1.910				
Preoperative CEA	1.040	1.011–1.069	0.007	1.047	1.013–1.081	0.006
Operation type			0.494			
Laparoscopy	Reference					
Open	1.681	0.380–7.439				
Size	0.932	0.711–1.222	0.609			
Pathologic T stage			0.295			
3	Reference					
4	1.960	0.556–6.904				
The number of harvested LN	0.967	0.922–1.014	0.167	0.958	0.913–1.004	0.074
Lymphatic invasion	0.963	0.270–3.432	0.954			
Venous invasion	1.887	0.427–8.343	0.403			
Perineural invasion	2.803	0.959–8.191	0.060			
MSI			0.960			
MSS	Reference					
MSI-L	1.039	0.235–4.587				
Dose reduction	0.956	0.355–2.574	0.930			
Chemotherapy completion	0.434	0.148–1.276	0.129			
Chemotherapy regimen			0.472			
FL	Reference					
Capecitabine	1.454	0.524–4.037				

BMI body mass index, *ASA classification* the American Society of Anesthesiologists (ASA) physical status classification, *CEA* carcinoembryonic antigen, *LN* lymph node, *MSI* microsatellite instability, *MSS* microsatellite stable, *MSI-L* low microsatellite instability, *FL* 5-fluorouracil and leucovorin

[a] Multivariable analysis performed on factors with $p < 0.20$ in univariable analysis

Table 5 The effect of chemotherapy regimen on recurrence-free survival, cancer-specific survival, and overall survival

	Unadjusted HR (95% CI)	*p* value	Adjusted HR[a] (95% CI)	*p* value
	Recurrence-free survival			
FL	Reference	0.763	Reference	0.279
Capecitabine	1.160 (0.441–3.049)		0.503 (0.145–1.745)	
	Cancer-specific survival			
FL	Reference	0.223	1.519 (0.348–6.629)	0.578
Capecitabine	2.172 (0.625–7.553)			
	Overall survival			
FL	Reference	0.472	Reference	0.919
Capecitabine	1.454 (0.524–4.037)		0.941 (0.290–3.053)	

FL 5-fluorouracil and leucovorin, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *CEA* carcinoembryonic antigen

[a] Adjusted factors: age, sex, BMI, tumor sidedness, preoperative CEA, pathologic T stage, harvested lymph nodes, lymphatic invasion, venous invasion, and perineural invasion

Table 6 Comparison of side effects between FL and capecitabine

	FL ($n = 74$)	Capecitabine ($n = 44$)	p value
Side effect			
All	60 (62.5%)	42 (72.4%)	0.207
≥ Grade 3	12 (12.5%)	2 (3.4%)	0.058
Anorexia			
All	2 (2.1%)	4 (6.9%)	0.199
≥ Grade 3	0	0	
Nail loss			
All	0	1 (1.7%)	0.377
≥ Grade 3	0	0	
Abdominal pain			
All	0	1 (1.7%)	0.377
≥ Grade 3	0	1 (1.7%)	0.377
Rash			
All	1 (1.0%)	0	> 0.99
≥ Grade 3	0	0	
Gastritis			
All	10 (10.4%)	0	0.011
≥ Grade 3	1 (1.0%)	0	> 0.99
Mouth sore			
All	9 (9.4%)	4 (6.9%)	0.768
≥ Grade 3	1 (1.0%)	0	> 0.99
Hand foot syndrome			
All	2 (2.1%)	18 (31.0%)	< 0.001
≥ Grade 3	0	0	
Neurologic toxicity			
All	0	1 (1.7%)	0.377
≥ Grade 3	0	0	
Asthenia			
All	4 (4.2%)	3 (5.2%)	> 0.99
≥ Grade 3	1 (1.0%)	0	> 0.99
Nausea			
All	15 (15.6%)	5 (11.4%)	> 0.99
≥ Grade 3	1 (1.0%)	0	> 0.99
Diarrhea			
All	16 (16.7%)	5 (8.6%)	0.159
≥ Grade 3	2 (2.1%)	1 (1.7%)	> 0.99
Thrombocytopenia			
All	0	2 (3.4%)	0.140
≥ Grade 3	0	0	
Febrile neutropenia			
All	1 (1.0%)	0	> 0.99
≥ Grade 3	0	0	
Non-febrile neutropenia			
All	33 (34.4%)	10 (17.2%)	0.022
≥ Grade 3	7 (7.3%)	0	0.045

FL 5-fluorouracil and leucovorin

MSI-H patients do not benefit from adjuvant chemotherapy [13]. Thereafter, adjuvant chemotherapy was not administered to MSI-H patients.

Limitations

First, selection bias can occur during the collection of the database. However, since prospectively collected data were used, it is unlikely that the data were manipulated to obtain favorable results in one group. Second, the two groups were unbalanced because matching was not performed. However, propensity score matching requires a large number of patients and a large number of events. Because of the nature of stage II colon cancer, there are few recurrences, and enrollment of a large number of patients is difficult with older patients. Nevertheless, we found no difference in the prognosis according to the regimen by adjusted HR.

Conclusion

In geriatric patients with stage II colon cancer, capecitabine is a safe regimen and has similar oncologic outcomes to FL. Although capecitabine is more likely to cause hand–foot syndrome, the regimen can be safely administered because the rate of severe side effects of grade 3 or higher is relatively low. Above all, capecitabine is a drug that can be administered as an outpatient-based prescription in patients with relatively low-performance status. However, further study is necessary to confirm the safety of capecitabine through a randomized controlled study or multicenter case-matching study to compare well-balanced groups.

Funding information This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (No. NRF-2017R1D1A1B03036191).

Compliance with ethical standards

This study was conducted with the approval of the institutional review board (IRB) of Seoul National University Hospital. Requirement for consent was waived with permission from the IRB. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Benson AB 3rd, Venook AP, Cederquist L, Chan E, Chen YJ, Cooper HS et al (2009) Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 15: 370–398

2. Tournigand C, Andre T, Bonnetain F, Chibaudel B, Lledo G, Hickish T et al (2012) Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol 30: 3353–3360. https://doi.org/10.1200/JCO.2012.42.5645
3. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A et al (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704
4. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A (2017) Colorectal cancer statistics, 2017. CA Cancer J Clin 67:177–193. https://doi.org/10.3322/caac.21395
5. Hutchins LF, Unger JM, Crowley JJ, Coltman CA Jr, Albain KS (1999) Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 341:2061–2067
6. Benson AB 3rd, Schrag D, Somerfield MR, Cohen AM, Figueredo AT, Flynn PJ et al (2004) American Society of Clinical Oncology recommendations on adjuvant chemotherapy for stage II colon cancer. J Clin Oncol 22:3408–3419
7. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K et al (2012) ESMO Consensus Guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol 23(10):2479–2516. https://doi.org/10.1200/JCO.2004.05.063
8. Reha J, Mukkamalla SKR, Rathore R, Somasundar PS (2018) Adequate lymph node evaluation in the elderly is associated with improved survival in patients with stage I-III colon cancer: a validation study using the National Cancer Data Base. Eur J Surg Oncol 44:148–156. https://doi.org/10.1016/j.ejso.2017.11.005
9. Poeschl EM, Pollheimer MJ, Kornprat P, Lindtner RA, Schlemmer A, Rehak P et al (2010) Perineural invasion: correlation with aggressive phenotype and independent prognostic variable in both colon and rectum cancer. J Clin Oncol 28:e358–e360. https://doi.org/10.1200/JCO.2009.27.3581
10. Cienfuegos JA, Martinez P, Baixauli J, Beorlegui C, Rosenstone S, Sola JJ et al (2017) Perineural invasion is a major prognostic and predictive factor of response to adjuvant chemotherapy in stage I-II colon cancer. Ann Surg Oncol 24:1077–1084. https://doi.org/10.1245/s10434-016-5561-0
11. Huh JW, Kim HR, Kim YJ (2010) Prognostic value of perineural invasion in patients with stage II colorectal cancer. Ann Surg Oncol 17:2066–2072. https://doi.org/10.1245/s10434-010-0982-7
12. Tan WP, Talbott VA, Leong QQ, Isenberg GA, Goldstein SD (2013) American Society of Anesthesiologists class and Charlson's comorbidity index as predictors of postoperative colorectal anastomotic leak: a single-institution experience. J Surg Res 184:115–119. https://doi.org/10.1016/j.jss.2013.05.039
13. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR et al (2010) Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 28:3219–3226. https://doi.org/10.1200/JCO.2009.27.1825